Assessment of the feeding arteries by three-dimensional computed tomography angiography prior to multi-arterial infusion chemotherapy for lung cancer

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Abstract. The aim of this study was to evaluate the efficacy of multi-detector row helical computed tomography (MDCT) angiography in the detection of feeding arteries prior to multi-arterial infusion for lung cancer. A total of 59 consecutive patients (44 males and 15 females; age range, 27-86 years; median age, 62 years) with non-small cell lung cancer underwent MDCT angiography of the thorax prior to multi-arterial infusion for lung cancer. Findings on CT angiograms, including CT scans, maximum intensity projections and three-dimensional volume-rendered images, were used to evaluate the depiction of bronchial and non-bronchial systemic arteries. The results of detecting the feeding arteries for lung cancer by MDCT angiography and conventional angiography were compared. Among the 59 patients treated with multi-arterial infusion chemotherapy, a total of 80 feeding arteries (62 bronchial feeding arteries and 18 non-bronchial systemic arteries) were detected by conventional angiography and/or MDCT angiography. In 56 (70%) feeding arteries (including 44 bronchial feeding arteries and 12 non-bronchial systemic arteries) for lung cancers, concordant findings were observed with the two modalities. In 23 (29%) cases, MDCT angiography could not be used to define feeding arteries, but was used to identify the ostia of these feeding arteries. In one (1/80, 1.3%) case, the CT-defined feeding artery was not selectively catheterized. MDCT angiography of the chest is able to provide an overview for successful catheterization in multi-arterial infusion chemotherapy for lung cancer.

Introduction

Lung cancer was one of the most commonly diagnosed cancers as well as the leading cause of cancer mortality in 2008 globally, particularly in males (1). Bronchial arterial infusion (BAI) chemotherapy for lung cancer was introduced over 40 years ago (2,3) and reductions in tumor size and symptoms as well as in the incidence of adverse effects of anticancer drugs were predicted due to the direct infusion of high density chemotherapeutics into tumors. However, these outcomes have not been confirmed and severe side-effects, including esophageal ulceration and spinal cord damage, have been reported following these therapies (4,5). Thus, BAI has not achieved wide acceptance as a standard clinical therapy for lung cancer. Arterial infusion chemotherapy for lung cancer utilizing only the bronchial artery is not effective as feeding arteries for lung cancer other than the bronchial artery are involved (6). The former studies indicated that sufficient detection of feeding arteries may increase the effectiveness of the local control of lung cancer by arterial infusion chemotherapy (7,8). However, the disadvantage of this method is the complexity of the extensive angiographic examinations.

The efficacy of three-dimensional imaging using multi-detector row helical computed tomography (MDCT) in the preoperative assessment of the branching pattern of the pulmonary artery (PA) prior to complete video-assisted thoracoscopic lobectomy for lung cancer has been reported, particularly in the superselective segmentectomy of deep and small pulmonary nodules under the guidance of three-dimensional reconstructed computed tomographic angiography (9-11). Several studies have evaluated bronchial and non-bronchial systemic arteries using MDCT angiography in patients with pulmonary disorders (12-15).

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The purpose of this study was to evaluate the effective use of chest MDCT angiography for detecting lung cancer feeding arteries (bronchial and nonbronchial systemic arteries) and tumor staining.

Materials and methods

Patients. The research protocol in our study was approved by the Shanghai Chest Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China. Written consent was obtained from all patients prior to commencement of the study.

This study involved 59 patients (44 males and 15 females; age range, 27-86 years; median age, 62 years) with 59 non-small cell lung cancers (NSCLCs; mean diameter, 4.2±1.3 cm; diameter range, 1.5-7.0 cm), who underwent arterial infusion chemotherapy. All patients were difficult to treat with standard chemotherapy and thoracic radiotherapy due to poor performance status (PS ≥2), advanced age (≥75 years old), severe hepatic failure, severe respiratory failure or refusal of chemotherapy.

MDCT angiography examination. All patients were imaged using a 64-row MDCT scanner (LightSpeed VCT, GE Medical Systems, Milwaukee, WI, USA) or a dual-source CT scanner (Somatom Definition; Siemens AG, Medical Solutions, Forchheim, Germany). The main imaging parameters were 0.625 mm collimation, 0.5 sec gantry rotation time and 250 mA with a pitch of 0.938 in fast mode. The whole chest was scanned in ~10 sec. The craniocaudal scan ranged from the mandible angle level to the upper abdomen level. A power injector was used to administer iopamidol (370 mg I/ml, Bracco, Milan, Italy) at a rate of 4 ml/sec to provide a dose of 420 mg/kg body weight, followed by 20 ml saline solution at the same rate. Imaging commenced after a 20-25 sec delay and lasted 6-12 sec. Axial images were reconstructed with a thickness of 0.8 mm at 0.5 mm intervals.

From each data set, three series of images were systematically reconstructed as follows: contiguous 1-mm thick transverse CT scans viewed at mediastinal and lung window settings, oblique coronal and sagittal maximum intensity projections (MIPs), multi-planar reconstructions (MPRs) and three-dimensional volume-rendered (VR) images of the thoracic vascular structures.

Analysis of lung cancer feeding arteries by MDCT angiography. CT angiograms were interpreted in consensus by two faculty radiologists (X.Y. and X.X, with 8 and 25 years of experience with CT, respectively), who were blinded to the conventional angiography results but not to clinical information. The CT images were reviewed as hard-copy images with the option of a cine-mode display on the workstation, if needed. After several weeks, the two readers reviewed the conventional angiographic studies in consensus; subsequently, the degree of concordance between the results of CT angiography and those of conventional angiography was evaluated.

CT interpretation focused on the evaluation of bronchial arteries ipsilateral to the side of the lesion by recording the following parameters: a) the site of the ostium of the bronchial artery (or arteries) and b) the total number of bronchial arteries per patient. For each bronchial artery, the images of its ostium and its mediastinal and hilar course were analyzed on transverse CT scans and three-dimensional images to determine the ability of CT angiography to depict the vessel. Non-bronchial systemic arteries were defined as arteries that enter the parenchyma through the inferior pulmonary ligament or through the adherent pleura; their course is not parallel to that of the bronchi (16). The lung cancer feeding arteries detected by MDCT angiography were defined as those which had an increased arterial diameter, entered the lesion, had disorganized branches and varying degrees of angiogenesis. When these criteria were met, CT angiography was considered to provide an accurate identification of the feeding artery of interest. When CT angiography was able to aid the depiction of the ostium of the artery and recognize its course toward the adjacent lung parenchymal zone, CT angiography was coded as suboptimal for the depiction of this feeding artery. The numbers of lung cancer feeding arteries detected by MDCT angiography were recorded.

Detection of lung cancer feeding arteries by conventional angiography. Conventional angiography was performed with a digital substraction technique within 1 week after CT. Angiography was performed with a transfemoral approach and the Seldinger technique. Various types of angiographic catheters were used to selectively inject different systemic arteries. For the benefit of each patient, angiographic procedures were performed with the knowledge of the CT findings. We examined the bronchial arteries based on the assumption that two bronchial arteries usually arise from the thoracic aorta or that variants occasionally arise from the internal thoracic, superior intercostal or thyro-cervical trunk (17). When tumors had invaded the pleura, thoracic wall or mediastinum, we examined the feeding arteries according to tumor site and the extent of invasion into the surrounding tissues as effectively as possible. We manually applied angiography and infusion to avoid occluding the corresponding feeding arteries with the catheter. To detect feeding arteries, we observed tumor staining that was enhanced by filling the tumor with contrast medium. Arteries with tumor staining revealed by angiography were regarded as feeding arteries. Multi-arterial infusion was based on gemcitabine and cisplatin as a first-line therapy (8,18). We divided the total dose among the detected feeding arteries according to the degree of tumor staining in each artery. No complications were encountered following the angiography and the infusion of bronchial and non-bronchial systemic arteries in the studied population. The numbers of lung cancer feeding arteries detected by conventional angiography were recorded.

Evaluating tumor staining grades in all detected feeding arteries by MDCT and conventional angiography. Tumor staining of lung cancers was arbitrarily graded by the consensus of several physicians on a scale of I to IV, which represented a percentage (%) of the tumor stained area to the entire lesion on the chest X-ray or CT scan of: 0-25%, 26-50%, 51-75% and >75%, respectively (8). The tumor staining grades in all feeding arteries detected by MDCT angiography and conventional angiography were recorded and the results of conventional angiography and MDCT angiography were compared.

Statistical analysis. The χ^2 test or Fisher's exact text were used to investigate the statistical significance of the feeding artery and tumor staining grades detected by MDCT angiography and conventional angiography. P<0.05 was considered to indicate a statistically significant result. All statistical analysis was performed using SPSS software (version 10.0; SPSS, Inc., Chicago, IL, USA).

Results

Comparison of lung cancer feeding arteries detected by MDCT and conventional angiography. By conventional angiography and/or CT angiography, we detected 80 feeding arteries (62 bronchial feeding arteries and 18 non-bronchial systemic arteries) for 59 lung cancers. The number of feeding arteries detected in each lung cancer ranged from one to four (mean±SD, 1.4±0.6), and we identified one bronchial feeding artery for the lung tumor by conventional angiography/or CT angiography in 56 of the 59 patients, 2 bronchial feeding arteries in 3 patients, an intercostal feeding artery in 7 patients, 2 intercostal feeding arteries in one patient, an internal thoracic feeding artery in 4 patients, as well as an inferior phrenic feeding artery in 5 patients.

Among those 59 patients, CT angiography accurately depicted 56 (56/80, 70%) feeding arteries (including 44 bronchial feeding arteries, 3 intercostal feeding arteries, 4 internal thoracic feeding arteries and 5 inferior phrenic feeding arteries) for the lung cancers (Fig. 1). A total of 23 (23/80, 28.8%) feeding arteries defined by conventional angiography also had clearly displayed origins and courses of the major branches in the MDCT angiographic images, but no display of their distal branches extending down to the lesions (Fig. 2). They were graded as suboptimal. In one (1/80, 28.8%) case, the CT-defined feeding artery was not selectively catheterized.

Table I compares the results of MDCT angiography and conventional angiography in the depiction of feeding arteries in the 59 patients who underwent multi-arterial infusion chemotherapy.

CT angiography accurately depicted the bronchial artery as a feeding artery in all 21 patients with central lesions (21/21, 100%). However, for the other 38 patients who had peripheral lesions, CT angiography accurately depicted it in only 20 patients (20/38, 52.6%; P<0.05, χ^2 test).

Evaluation of tumor staining grades in all detected feeding arteries by MDCT and conventional angiography. Table II summarizes the tumor staining grades results evaluated by MDCT angiography and conventional angiography. The results showed that tumor staining grades were underestimated by CTA (P<0.001).

Discussion

Although BAI therapy is not a new therapy and has not achieved wide acceptance as a standard clinical therapy for lung cancer due to its unconfirmed outcomes and severe side-effects, including esophageal ulceration and spinal cord damage, several studies have indicated that it should be reappraised as a preoperative adjuvant therapy for advanced lung cancer as it has been observed histopathologically to
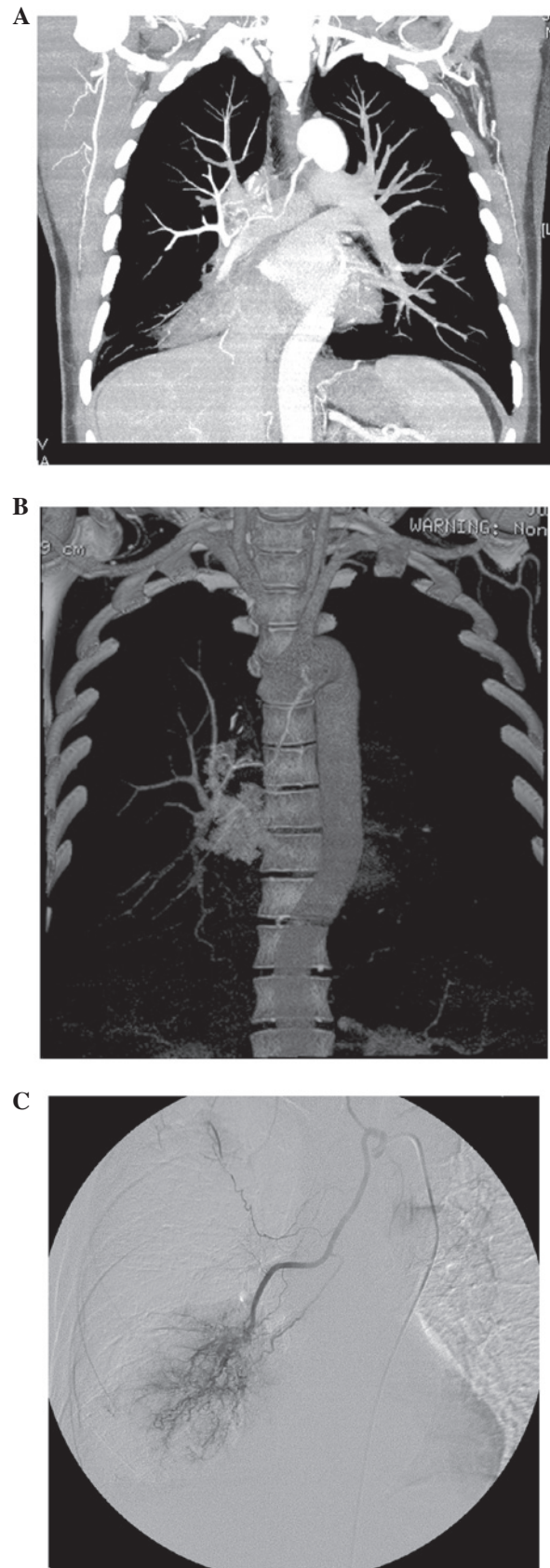

Figure 1. A squamous cell carcinoma located on the right hilum of the lung in a 55-year-old male patient. (A) The coronal maximum intensity projection (MIP) image shows the enhanced dotted and striped vessels in the lesion and the dilated, tortuous bronchial artery extends down to the lesion. (B) Volumetric three-dimensional computed tomography (CT) arteriography accurately depicted the bronchial artery arising from the aortic arch as a tumor feeding artery. (C) Conventional angiogram of the bronchial artery showing grade IV staining.
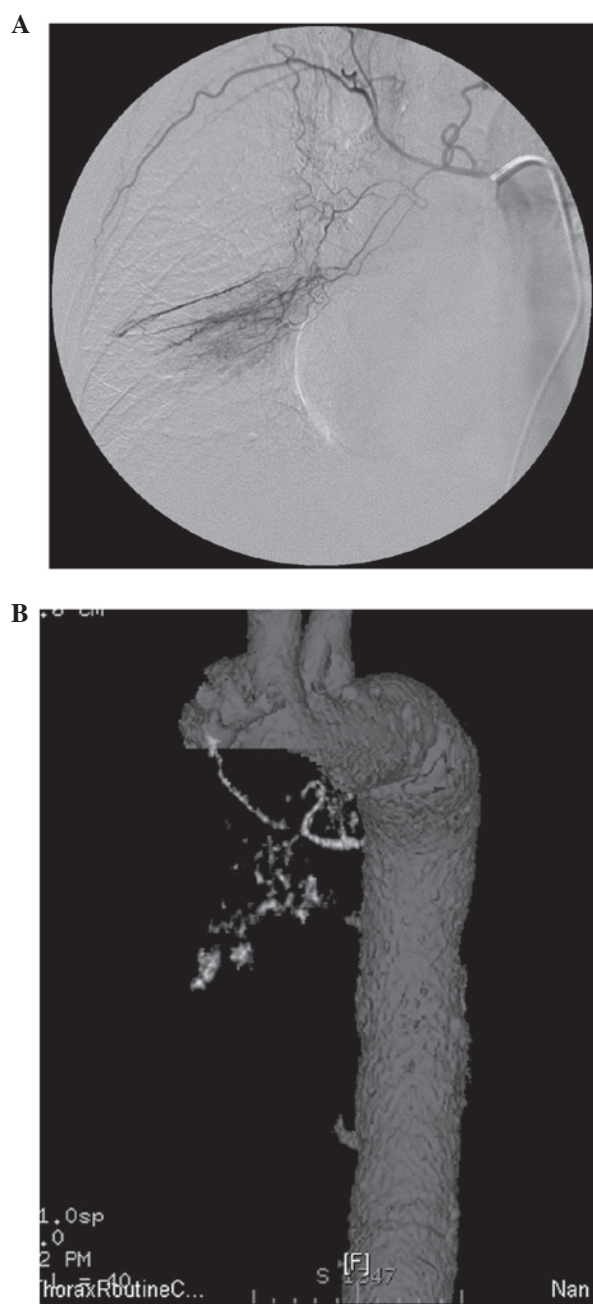
A

B

Figure 2. An adenocarcinoma located on the right lower lobe of the lung in a 71-year-old female patient. (A) Conventional angiogram showing tumor and one bronchial artery as a feeding artery on the right that presents as an intercostobronchial trunk (ICBT). (B) Volumetric three-dimensional CT arteriography suboptimal depiction of the feeding artery.

Table I. Depiction of feeding artery by MDCT angiography and conventional angiography in 59 patients treated with multi-arterial infusion chemotherapy.

| | Conventional angiography | |
	Selective catheterization	Failure of catheterization
MDCT angiography		
Adequate depiction	55	1
Suboptimal depiction	24	0

MDCT, multi-detector row helical computed tomography. Adequate depiction of feeding artery consisted of simultaneous depiction of its ostium, recognition of its course and showing increased arteries diameter, disorganization of the branches on CT angiograms. When there was only depiction of its ostium and recognition of its course, CT angiography was coded as suboptimal in the depiction of this bronchial artery.

Table II. Depiction of the grade of tumor staining by MDCT angiography and conventional angiography in 59 patients treated with multi-arterial infusion chemotherapy.

Tumor staining	Conventional angiography (n)	MDCT angiography (n)	P-value[a]
I	3	34	<0.001
II	15	17	
III	19	5	
IV	22	3	

MDCT, multi-detector row helical computed tomography. [a]Determined by χ^2 test.

have a high response (7,8,18,19). In the studies carried out by Nakanishi *et al*, many feeding arteries (including bronchial and nonbronchial systemic arteries) in patients with NSCLC were detected and the grade of total tumor staining was significantly higher than that of tumor staining supplied by the bronchial artery. Furthermore, the number of NSCLCs that responded to multi-arterial infusion chemotherapy was significantly increased among those with a higher grade of total tumor staining (7,8). Therefore, we consider that the precise definition of feeding arteries and sufficient tumor staining are vital to ensure a successful outcome of arterial infusion chemotherapy for patients with NSCLC. One point that should

be emphasized is the usefulness of their depiction with CT angiography prior to a multi-artery infusion chemotherapy session. Of particular importance are the subclavian artery and its branches (most commonly, the internal mammary artery) for tumor-invaded mediastinum, the inferior phrenic artery for lower lobe tumors, and the intercostal artery for tumors which have invaded the pleura as well as the thoracic wall. The time required to successfully cannulate the appropriate vasculature may take hours or the procedure may be ultimately unsuccessful for a number of technical reasons. Therefore, the ability to concentrate on the relevant vasculature reduces the procedure time and the potential iatrogenic risks of a selective hunt for abnormal nonbronchial systemic arteries. Based on this conclusion, we evaluated the feasibility of detecting the feeding arteries and evaluating the grade of total tumor staining by chest MDCT angiography. We detected 80 feeding arteries (62 bronchial feeding arteries and 18 nonbronchial systemic arteries) in 59 lesions by conventional angiography. These 80 feeding arteries detected by conventional angiography were also clearly displayed with their origins, courses and main branches on the MDCT angiographic images. However, only 56 of these arteries were defined as lung cancer feeding arteries by MDCT angiography (P<0.001). Similar

results were also found when evaluating the grade of total tumor staining by MDCT angiography (P<0.001). By analysis of the patients who had no display of feeding arteries by MDCT angiography, we estimated that the factors affecting the detection rate of the lung cancer feeding arteries by MDCT angiography are as follows. Firstly, the site of the tumor and the extent of its invasion into the surrounding tissues may take responsibility. In this study, the feeding arteries of centrally located lung cancers were accurately depicted by MDCT angiography according to conventional angiography (21/21, 100%). Conversely, of the 38 patients with peripheral NSCLC, only 20 bronchial arteries were accurately depicted as feeding arteries (20/38, 52.6%) (P<0.05, χ^2 test). The second factor is the diameter of the tumor. In our study, we found that when the diameter of tumor was smaller, the calibers of the feeding arteries were less clearly enlarged. The size of the bronchial arteries greatly affected their depiction on the CT image. This may be a limitation of the spatial resolution of MDCT. The advent of high-spatial resolution MDCT may allow radiologists to overcome the technical limitation of displaying small feeding arteries such as bronchial arteries.

From our results, we also identified that the grade of total tumor staining was underestimated by MDCT angiography. In this study, we started CT angiography examination 20-25 sec after administration of the contrast medium to optimize the quality of the CT angiography image. The transport of contrast medium through the lung involves the intravascular interstitial spaces and the washout phase from the interstitial spaces (20). The mean time to CT peak enhancement for malignant pulmonary nodules is 3.2 min (ranging from 30 sec to 15 min) (21). At a 20-25 sec delay after injecting the contrast medium, the transport of the contrast medium only involves an intravascular phase. By allowing an adequate delay for the contrast medium to penetrate into the interstitial spaces, results closer to the tumor staining grade evaluated by conventional angiography may be obtained. Therefore, it could be explained that the grade of the tumor staining was underestimated by MDCT angiography.

There were several limitations to our study. Firstly, our analysis was based on small groups of patients and the sensitivity of the imaging techniques might be under- or overestimated. Therefore, our results are only preliminary results and further studies with a larger number of patients would be beneficial. Secondly, in this study, most of the MDCT angiography was performed using a 64-row MDCT scanner which has a lower spatial resolution than 256- or 320-row MDCT and so the ability to detect feeding arteries by MDCT angiography may be underestimated. Thirdly, we did not quantitatively measure the artery caliber. It may be a predictive factor for the lung cancer feeding artery. Finally, we did not evaluate the correlation between the CT peak enhancement value to the grade of tumor staining by conventional angiography.

In conclusion, although MDCT angiography is not able to precisely or completely evaluate the lung cancer feeding arteries and the grade of total tumor staining in this preliminary study, it clearly displayed all feeding artery origins, courses and main branches, which were defined by conventional angiography. Therefore, chest MDCT angiography may provide an overview for successful catheterization in multi-arterial infusion chemotherapy for lung cancer.

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