Original Article

Comparison of Treatment Response Assessment for Stage IV NSCLC after Chemotherapy Between Non-Contrast and Contrast-Enhanced CT Scans of The Chest

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Abstract

Objective: To evaluate whether non-contrast chest CT (NCCT) images are as reliable as contrast-enhanced chest CT (CECT) images for the assessment of treatment response after chemotherapy in patients with stage IV non-small cell lung cancer (NSCLC).

Material and method: A total of 87 patients with the stage IV NSCLC underwent chest CT for the assessment of tumor response after chemotherapy at Thammasat University Hospital between January 2014 and December 2016. Tumor response after chemotherapy of each patient was evaluated by using follow-up NCCT and CECT in comparison with the baseline CECT before chemotherapy based on RECIST criteria (version 1.1).

Result: Eighty-six (99%) of the 87 patients had the same treatment response results from both imaging sets. Only one case (1%) had a different result that was caused by a minimal difference in the target lesions size. However, there was no change in the management of this patient. The statistical analysis showed almost perfect agreement between using follow-up NCCT and CECT in the assessment of tumor response after chemotherapy with a kappa value of 0.982 (95% confidence interval; 0.947, 1.017). There was no statistically significant difference in the target lesions size in the follow-up study obtained by NCCT and CECT (*P* - value = 0.350).

Conclusion: Using follow-up NCCT in comparison with the baseline CECT provides almost perfect agreement with follow-up CECT in the assessment of the tumor response after chemotherapy. Therefore, NCCT can be a reasonable alternative to CECT for follow-up tumor response after chemotherapy especially in a patient with impaired renal function.

Keywords: Non-contrast chest CT, Non-small cell lung cancer, Chemotherapy, Treatment response assessment

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.[1, 2, 3] In Thailand, lung cancer is one of the most common cancers in both male and female patients.[4] There are two major types of primary lung cancer comprising of non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The large majority of lung cancer that accounts for 80 - 85% of all lung cancer cases is NSCLC and two major histologic types are adenocarcinoma (40%) and squamous cell carcinoma (25 - 30%). About 40% of patients with NSCLC present with metastatic disease or stage IV disease at the time of diagnosis that is not curable.[1] The primary treatment option for patients with stage IV disease is chemotherapy to prolong survival and promote quality of life. However, some commonly used chemotherapy, particularly platinum-based chemotherapy regimens, have nephrotoxic side effects and may lead to kidney damage.[5, 6, 7]

Treatment response is commonly evaluated every 2 - 3 months during systemic therapy for stage IV NSCLC and usually relies on the repetitionof radiographic examinations, mainly by contrast-enhanced computed tomography (CECT). This group of patients is at high risk for kidney injury. In patients with impaired renal function, using iodinated contrast may further decrease renal function or cause contrast-induced nephropathy.[8-13] Although non-contrast computed tomography (NCCT) has inferior tissuecontrast, it has the advantage of avoiding contrast related allergic reaction and nephrotoxicity and also decreased radiation dose. This study aims to investigate whether NCCT images are comparable to CECT images in the assessment of treatment response after chemotherapy in stage IV NSCLC patients.

Materials and methods

Data collection

We retrospectively identified all patients with stage IV NSCLC who received palliative chemotherapy and underwent both baseline contrast-enhanced chest CT within 4 weeks before receiving chemotherapy and first follow-up chest CT that comprised of both non-contrast and contrast-enhanced CT images during chemotherapy at Thammasat University Hospital between January 2014 and December 2016. Patients who had a history of intrathoracic radiotherapy or incomplete imaging information were excluded from the study. All NSCLC cases were pathologically proven and staged by using the TNM staging system (8th edition).[14] Demographic data included age, gender, smoking status, and histologic type of the tumor were collected.

Imaging techniques

The images were acquired with either a 256-slice CT scanner (Brilliance iCT, Philips healthcare) or a 128-slice CT scanner (SOMATOM Definition AS, Siemens healthcare). Both non-contrast and contrast-enhanced images were obtained in the supine position from lung apices to adrenal glands with breath-hold after deep inspiration. Contrast-enhanced images were obtained by using 70 - 90 ml IV contrast material (300 mg iodine/ml) with a flow rate of 2.0 - 4.0 ml/sec and started scan at a fixed delayed time of 60 seconds from the beginning of contrast injection. The CT images in each set were displayed with both lung (window width, 1450 HU; window level, -500 HU) and soft-tissue windows (window width, 360 HU; window level, 60 HU). CT parameters were as follows: 0.5-second rotation time; 120 kVp; 100 - 250 mAs; 2.5 mm slice thickness.

Imaging interpretation

Chest CT images were retrospectively reviewed by two experienced radiologists in consensus. Treatment responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[15, 16] For the treatment response evaluation results, the first set we evaluated by using baseline contrast-enhanced chest CT before receiving chemotherapy compared with non-contrast chest CT images from the first follow up chest CT during chemotherapy. The second set we evaluated by using baseline contrast-enhanced chest CT before receiving chemotherapy compared with contrast-enhanced chest CT images from the first follow-up chest CT during chemotherapy (images from the same CT study as the first set).

Statistical analysis

The treatment responses obtained from NCCT and CECT were compared by using Kappa statistics. Agreement between two imaging sets

was categorized as followed: values < 0.00 = poor agreement, 0.00 - 0.20 = slight agreement, 0.21 - 0.40 = fair agreement, 0.41-0.60 = moderate agreement, 0.61 - 0.80 = substantial agreement and 0.81-1.00 = almost perfect agreement (Landis and Koch 1977).[17]

A paired Student's t-test was used to compare the sum of the longest diameters of the target lesions (cm) in the follow-up study obtained by NCCT and CECT of the chest. A *P* - value of less than 0.05 was considered to be significant.

Results

A total of 87 patients with stage IV NSCLC were eligible for this study. The population included 51% male (n = 44) and 49% female (n = 43). The age of the patients ranged between 34 and 89 years with a median age of 63.5 years. About 66% of the patients were a non-smoker. The most common histologic subtype of NSCLC in this study was adenocarcinoma (n = 85, 98%) (Table 1).

For the tumor response evaluation using RECIST criteria version 1.1, there were a total of 177 target lesions in 87 patients. The most common types of target lesions were lung nodules or masses followed by lymph nodes, liver, and adrenal metastases. The number and type of target lesions and distribution of non-target lesions were summarized in Table 2. Table 3 shows tumor response results that were assessed by using NCCT and CECT according to RECIST criteria version 1.1. Eighty-six patients (99%) had the same treatment response results obtained from both NCCT and CECT. Only one patient (1%) had a different result which was partial response of the disease assessed by using NCCT and stable of the disease assessed by using CECT. In this case, the sum of longest diameters of the target lesions assessed by using CECT was slightly higher than those assessed by using NCCT. There was almost perfect agreement between using NCCT and CECT of the chest in the assessment of tumor response after chemotherapy with a kappa value of 0.982 (95% confidence interval; 0.947, 1.017). The mean sum of longest diameters of the target lesions in the follow-up study obtained from NCCT (mean 6.38, SD 3.42) was slightly larger than that obtained from CECT (mean 6.33, SD 3.33). However, there was no statistically significant difference in the size of the target lesions that were assessed by NCCT and CECT, *P* - value = 0.350 (Table 4). In this study, there were a total of 28 cases of progressive disease. Twenty-three cases had new metastases included lung (n = 18), liver (n = 8), adrenal (n = 2), and pleural metastases (n = 1). There were no differences in the detection rate of new lesions among using NCCT and CECT. Only one patient with new liver metastases had an additional small liver lesion (size 2 mm) detected on contrast-enhanced CT, but this did not change metastatic status and tumor response result established at the non-contrast CT. For the evaluation of non-target lesions on the follow-up CT, which that defined as absent (n = 0), present (n = 69), and unequivocal progression (n = 18), there was no difference between the results assessed by NCCT and CECT. All 18 cases assigned as an unequivocal progression of non-target lesions had one or more new lesions.

Table 1 Demographic data

General characteristics		Number	Percentage
Sex	Male	44	51
	Female	43	49
Smoking status	Smoker	30	34
	Non-smoker	57	66
Histology of NSCLC	Adenocarcinoma	85	98
	Squamous cell carcinoma	1	1
	Large cell carcinoma	1	1

Table 2 Distribution of target and non-target lesions

Target lesions	Number	Non-target lesions	Cases
Lung lesions	93	Pulmonary nodules	55
Lymph nodes	60	Bone metastasis	28
Liver lesions	8	Lymph nodes	27
Adrenal lesions	8	Pleural metastasis	24
Pleural lesions	4	Adrenal metastasis	8
Splenic lesions	2	Liver metastasis	7
Pancreatic lesion	1	Renal metastasis	1
Pericardial lesion	1	Pancreatic metastasis	1

Table 3 Treatment responses assessed by using NCCT and CECT

CECT	NCCT				Total
	CR	PR	SD	PD	
CR	0	0	0	0	0
PR	0	17	0	0	17
SD	0	1	41	0	42
PD	0	0	0	28	28
Total	0	18	41	28	87

Note. CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease

Table 4 Sum of longest diameters (SLD) of the target lesions in follow up study obtained from NCCT and CECT

SLD of targets lesions obtained from NCCT (cm)		SLD of targets lesions obtained from CECT (cm)		*P*-value
Mean	**SD**	**Mean**	**SD**	
6.38	3.42	6.33	3.33	0.350

Note: A paired student t-test was used for statistical analysis.

Discussion

CECT is the main method for response assessment of solid tumor after chemotherapy. Patients with stage IV NSCLC that received palliative chemotherapy require sequential imaging to assess treatment response. This group of patients had a high risk of contrast-induced kidney injury. NCCT of the chest is a good method for evaluated anatomy, detecting, and measurement tumor and their metastasis, and has an advantage in avoiding contrast-induced kidney injury. There were few studies that evaluated the performance of NCCT in the staging of lung cancer and the evaluation of mediastinal lymph nodes. These studies show high agreement between non-contrast and contrast-enhanced chest CT in the staging of lung cancer and the detection of mediastinal lymph nodes which suggests that NCCT is a reliable tool in lung cancer evaluation.[18, 19] However, there was no previous study that evaluated the performance of non-contrast chest CT for response assessment after chemotherapy in a patient with stage IV lung cancer. In this study, we compared the diagnostic performance of NCCT and the routinely used CECT in treatment response assessment of stage IV NSCLC after chemotherapy and found that there was almost perfect agreement between using NCCT and CECT. Only one case (1%) had a different result caused by a minimal difference in the target lesions size. In this case, the result obtained by using NCCT was a partial response (about 32% decreased in the sum of longest diameters of target lesions as compared to the baseline study), while the result obtained by using CECT was stable of the disease (about 29% decreased in the sum of longest diameters of target lesions as compared to the baseline study). However, there was no change in the management of this patient.

Concerning the detection of new metastasis that is considered a progressive disease that can cause a substantial change in management, there was no difference in the detection rate of new metastasis between the two groups (Figure 1). The common sites of intra-abdominal metastasis from lung cancer were adrenal glands and the liver. In a recent study of Semaan H et al., they evaluated NCCT of the abdomen in the detection of cancer-related findings (CRFs) in patients with a known cancer diagnosis. They found that follow-up NCCT of the abdomen was highly accurate in the detection of CRFs with a non-detection rate of 3%.[20] The most common findings missed were vascular thrombosis, whereas the non-detection rate of adrenal nodules is 0%. In our study, the adrenal glands and adrenal nodules were well visualized on both NCCT and CECT. There was no difference in the detection of adrenal metastasis using NCCT and CECT. For the liver metastasis, one small new low attenuating lesion was missed by using NCCT (size = 2 mm) but the metastatic status of this patient did not change because of the detection of other new larger liver metastasis (Figure 2). For the purpose of detecting liver metastasis in other cases, there were not significant differences between NCCT and CECT.

Nazarian LN et al. investigated the measurement of hepatic metastasis from colorectal carcinoma by using NCCT and CECT.[21] They found that measurements of hepatic metastases on NCCT images are significantly larger than measurements on CECT images. In our study, the overall target lesions size measured by using NCCT was slightly larger than that measured by using CECT (Figure 3). It may be due to the poorly visualized border of the lesion. However, there were not significant differences in the summation of the longest diameters of target lesions obtained from NCCT and CECT.

Limitation, in this study, we did not evaluate the performance of NCCT and CECT in the measurement of the target lesions from each organ separately and its effect on the evaluation of treatment response. Another limitation is we have not conducted the evaluation of non-cancer-related findings that may have implications on treatment.

In conclusion, NCCT of the chest provides almost perfect agreement with CECT of the chest in the assessment of the tumor response in stage IV NSCLC patients treated with chemotherapy. Therefore, follow-up chest CT obtained without intravenous contrast administration can be used for the assessment of treatment response after chemotherapy, especially in patients with impaired renal function or acute kidney injury.

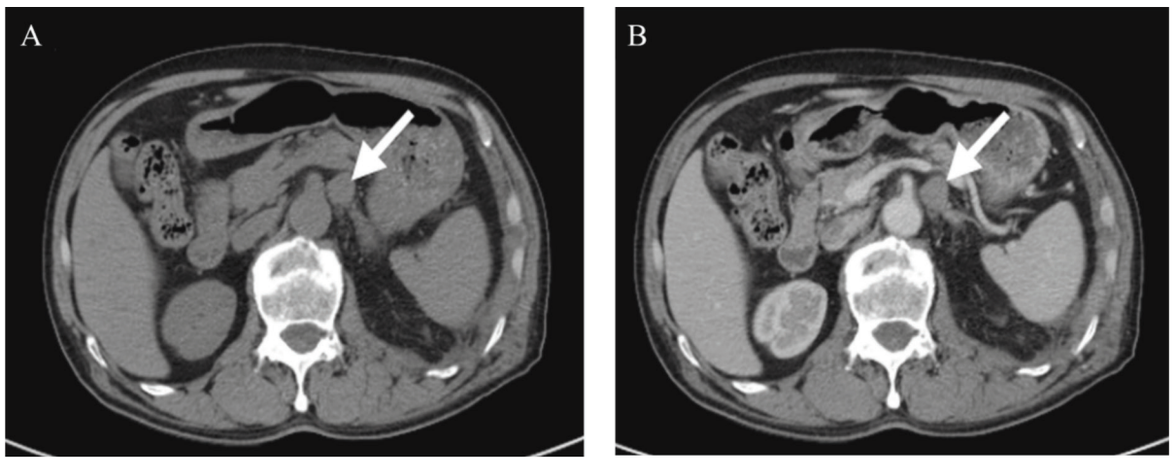

Figure 1 A 64-year-old man with stage IV NSCLC was sent to follow-up after chemotherapy. (A) Axial NCCT and (B) CECT show a new retroperitoneal lymph node metastasis (white arrow).

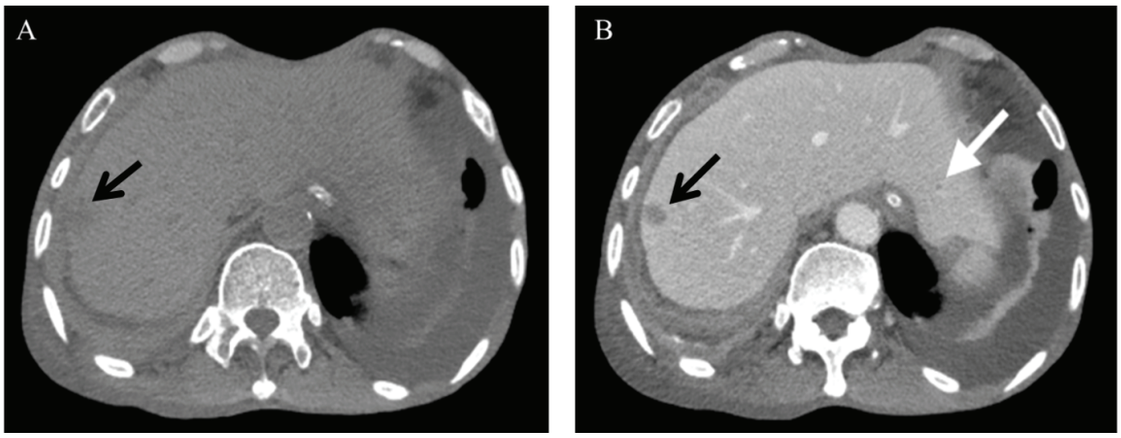

Figure 2 A 72-year-old man with stage IV NSCLC was sent to follow-up after chemotherapy. (A) Axial NCCT and (B) CECT show new liver metastasis (black arrow). The small hypodense lesion (size < 4mm) in the left hepatic lobe (white arrow) is seen only on the CECT image.

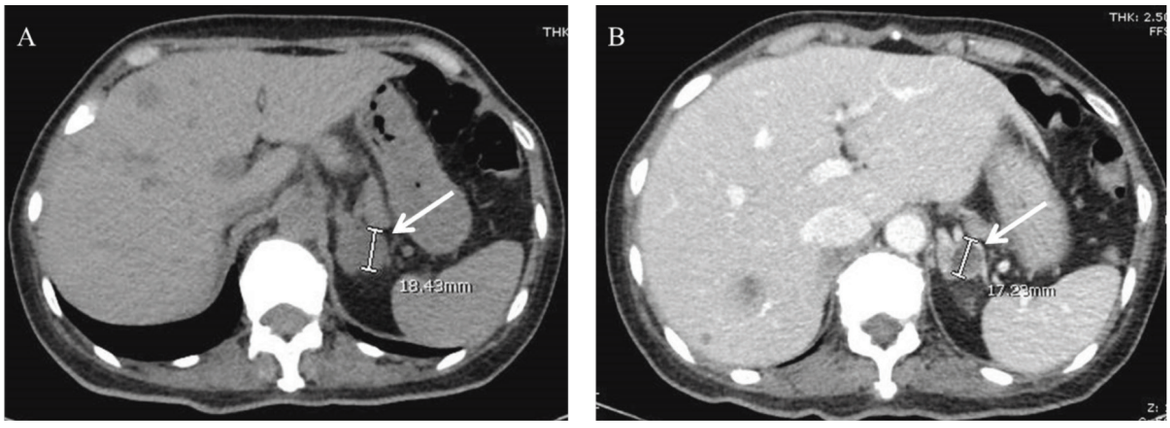

Figure 3 A 54-year-old woman with stage IV NSCLC was sent to follow-up after chemotherapy. (A) Axial NCCT and (B) CECT show left adrenal metastasis (white arrow). Note that the size of the left adrenal metastasis obtained from the NCCT image is slightly larger than that obtained from the CECT image because the measurement on the NCCT image includes surrounding normal soft tissue that is clearly delineated on the CECT image.

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