INTRODUCTION

Lung cancer continues to increase steadily around the world and remains the most common causes of death in cancer patients (1,2). Patients with unresectable lung cancer are primarily treated with chemotherapy with/without radiation therapy and are regularly followed with computed tomography (CT) scanning to evaluate treatment responses (3). A common method to evaluate treatment response is the Response Evaluation Criteria in Solid Tumor (RECIST) criteria, which depend largely on the longest diameter of the lesion seen on the CT images (4). It is assumed that the survival rates of patients who responded according to the RECIST criteria will be prolonged (5). However, conventional CT may be limited in the assessment of treatment responses because the changes in tumor size can be insignificant in the early follow-up stages of treatment (6,7).

18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) scanning offers the ability to visualize increased glucose metabolism in tumor cells compared with normal cells, with varying consequences for treatment outcome (8,9). Contrast-enhanced MRI can be useful for differentiating between malignant and benign lesions in solitary pulmonary nodules or monitoring of treatment response after chemotherapy (10-12). These new imaging modalities based on the pathophysiology of tumor growth are increasingly used in tumor evaluations. Dynamic contrast-enhanced CT (DCE-CT) scans have been used in monitoring tu-
Dynamic Contrast-Enhanced CT in Advanced Lung Cancer after Chemotherapy with/without Radiation Therapy

This method is useful due to its fast data acquisitions. However, there are some difficulties in evaluating early treatment responses in advanced lung cancer with the RECIST criteria because tumor shrinkage usually does not occur or is minimal until several cycles of chemotherapy have been completed (12). Therefore, the purpose of this study is to evaluate the enhancement pattern of tumors after chemotherapy with/without radiation therapy in patients with advanced lung cancer using dynamic contrast-enhanced CT, and to assess whether the enhancement pattern of tumors at early stages of treatment can predict treatment responses assessed by the RECIST criteria during follow-ups.

MATERIALS AND METHODS

Patients

Between April 2010 and November 2011, 42 patients who had residual tumors after chemotherapy with/without radiation therapy for advanced non-small cell lung cancer (NSCLC) (stage IIIIB/IV; unresectable) were retrospectively enrolled in this study. All patients underwent DCE-CT examinations within one month after each cycle of chemotherapy (a mean interval of 20 ± 7 days; range, 14 to 30 days). Additional follow-ups by using conventional CT scanning were performed with a time interval of 3 months between CT scans at our institute. During the follow-up period, patients who had metastatic lesions or lymph nodes in other sites were excluded in this study. Patients who had insufficient renal functions (creatinine level > 150 µmol/L) or an allergy to iodinated contrast materials were excluded. Of the 42 enrolled patients, 23 were male and 19 were female. The mean age at the time of examination was 66.0 ± 13.0 years (age range, 34-86 years). Institutional Review Board approval was gained for this study and written informed consent was obtained from all patients for DCE-CT scans.

Dynamic Contrast-Enhanced CT Imaging

CT scans were performed with a 64-slice multi-detector CT scanner (Somatom Sensation 64; Siemens Medical Solutions, Erlangen, Germany). Scanning was performed in a craniocaudal direction at end-inspiratory suspension with patients in the supine positions. After acquiring the scout images to localize the target lesions, we obtained pre-contrast CT images through the target lesions, with the field of view as small as possible in order to minimize patients’ radiation exposures. After the injection of contrast materials, subsequent DCE-CT series were obtained through the lesions at 30, 60, 90, 120 seconds, and 5 minutes. For injection of contrast media, an 18-gauge cannula was placed in the superficial vein of the antecubital fossa. A total of 100 mL of iopromide (Prosure® M300, LG Life Sciences, Seoul, Korea) was administered intravenously at a rate of 4 mL/sec using a power injector (Envision CT; Medrad, Pittsburgh, PA, USA) in all patients. The exposure parameters for CT scans were 100 kVp, 175 mA, 1.2 mm collimation, table pitch 1, 500 msec rotation time, 5 mm slice thickness, and a 5 mm reconstruction increment. CT scans at 120 seconds covered the whole thorax with 120 kVp and 175 mA for tumor re-staging, which might be changed. The dose-length product (DLP) in the CT units was used to evaluate the radiation doses received by the patient. The effective radiation dose was calculated by multiplying the DLP by the conversion coefficient (k = 0.014) for the chest, and was expressed as millisievert (mSV) (15).

Images were reconstructed on the scanner’s workstation using commercially available software (Syno, Somaris 5®; Siemens Medical Solutions, Germany), with a slice thickness of 5 mm by using a standard algorithm. All dynamic and staging CT data were transferred to our picture archiving and communication system (PACS) (Centricity 1.0; GE Medical Systems, Mt. Prospect, IL, USA), which displayed all images on monitors (1536 × 2048 image matrices, 60-foot-lambert luminescence).

DCE-CT Image Analysis

Images were evaluated in one image interpretation section by consensus of two radiologists (M.R.Y. and S.H.H.) who had 4 and 8 years of experience in chest imaging interpretations. All images were set up with a mediastinal window [width, 400 Hounsfield unit (HU); level, 20 HU] and lung window (width, 1500 HU; level, -700 HU) on the PACS monitors. Target tumor size was measured based on the longest diameter of the lesions on the DCE-CT images obtained at 90 seconds after injection of contrast material and the follow-up CT images.

Attenuation values for the lesion were measured on the serial DCE-CT images with a mediastinal window. The region of interest (ROI) was drawn as the largest possible circle to encom-
pass the lesions. Necrotic areas, cavities, and calcifications were avoided (13). We referred the PET images to differentiate between residual tumor and atelectasis or fibrosis in cases where they were available. We computed mean values based on two measurements obtained from two ROIs for each lesion on the dynamic series of images. We obtained tumor attenuation values (TAV\textsubscript{t}, in HU), where t represents each designed time point before and after the injection of contrast medium. Peak enhancement (PE) was defined as the attenuation value with the maximum TAV\textsubscript{t} during the entire dynamic period after injection of contrast medium. Time (in second) corresponding to PE during the early dynamic period was also recorded. Wash-in (WI) was calculated by subtracting the pre-enhancement attenuation value from the PE attenuation value (PE-TAV\textsubscript{0}) (16). Wash-out (WO) as absolute loss of enhancement was calculated by subtracting the attenuation value at 5 minutes (TAV\textsubscript{300}) from the PE value (PE-TAV\textsubscript{300}) (16).

In order to analyze the enhancement pattern on the dynamic CT images, we plotted the mean attenuation values of the lesions at each time point as a time-density curve (TDC). TDCs were classified as one of the following four types according to WI and WO patterns: type A, an early WI and early WO pattern; type B, an early WI and maintaining a plateau; type C, an early WI and then continuous acceleration during the dynamic period; and type D, net enhancement less than 15 HU without an early WI pattern during the dynamic period.

Evaluation of Treatment Response

On follow-up conventional CT scans, the treatment response was evaluated according to the RECIST criteria (RECIST 1.1) as follows: complete response, disappearance of the lesions; partial response (PR), at least a 30% decrease in the diameter of the lesion on the follow-up CT images; progressive disease (PD), a more than 20% and 5 mm absolute increase in lesion diameter; stable disease (SD), neither sufficient shrinkage of the lesion to qualify for PR nor sufficient increases in size to qualify for PD (4).

Statistical Analysis

All parameters were presented as mean ± standard deviations. We used Fisher’s exact test to evaluate differences of distribution of three groups formed based on the RECIST criteria between TDC type A and type B, C and D. And then, we used an analysis of variance to evaluate the statistical significance of differences in PE and NE values among the three groups in lesions with type A TDC pattern. Receiver operating characteristic (ROC) analysis was performed to evaluate cutoff values of WI and WO to predict the treatment response. A p-value less than 0.05 was considered statistically significant. SPSS software (version 19.0; Statistical Package for the Social Sciences, Chicago, IL, USA) was used for statistical evaluations.

RESULTS

A total of 61 lesions were detected on the dynamic CT images in 42 patients. The characteristics of the 42 patients with advanced NSCLC are summarized in Table 1. On the basis of treatment responses assessed by the RECIST criteria, there were 7 PR lesions (11.5%), 16 PD lesions (26.2%), and 38 SD lesions (62.3%). The mean longest diameter of all tumors was 2.9 ± 1.7 cm (range, 0.9 to 8.6 cm); 2.8 ± 1.0 cm in PR, 3.2 ± 2.0 cm in SD, and 2.2 ± 0.8 cm in PD (Table 2). The mean effective radia-

### Table 1. Patient Characteristics, Treatment Methods and Histologic Finding

| Characteristics          | Value |
|--------------------------|-------|
| Age                      | Year  |
| Mean                     | 66    |
| Range                    | 34-86 |
| Sex                      | n = 42|
| Man                      | 23    |
| Woman                    | 19    |
| Histologic finding       | n = 61|
| Adenocarcinoma           | 32    |
| Squamous cell carcinoma  | 19    |
| NSCLC, NOS*              | 10    |
| Treatment methods        |       |
| Chemotherapy only        | 46    |
| Chemoradiotherapy        | 15    |
| Chemotherapy agent       |       |
| Cisplatin based agent    | 29    |
| EGFR inhibitor           | 17    |
| Other agent†             | 15    |

Note.—Except for age and sex, values are number of the lesions (n = 61).

*Confirmed as NSCLC with needle aspiration biopsy but not categorized into any of the subtype of NSCLC on pathologic report.

†Cisplatin with gemcitabine, docetaxel, paclitaxel, pemetrexel or irinotecan.

‡Erlotinib or gefitinib.

§Non-cisplatin single agent such as gemcitabine, docetaxel, pemetrexed. EGFR = epidermal growth factor receptor, NOS = not otherwise specified, NSCLC = non-small cell lung cancer
tion dose for the dynamic CT scans in 42 patients was 3.5 mSV (dose range, 2.9-5.4 mSV).

Degree and Pattern of Contrast Enhancement

The mean NE values were 46.5 ± 14.9 HU in PR, 44.9 ± 18.2 HU in SD, and 63.1 ± 13.5 HU in PD group, respectively. The PE mean values were 83.0 ± 14.9 HU in PR, 81.9 ± 18.3 HU in SD, and 98.4 ± 12.5 HU in PD group, respectively (Table 2). Patterns of contrast enhancement according to the RECIST groups are summarized in Table 3. The TDCs showed that there were 36 type A lesions (Fig. 1), 7 type B, 16 type C (Fig. 2), and 2 type D lesions. There was statistically significant difference of distribution of RECIST groups between the type A lesions and the other types of the groups ($p < 0.05$). Most lesions that were type B (100%), type C (93.8%), or type D (100%) on the TDCs belonged to the PR and SD groups according to the RECIST criteria.

### Table 2. Size and Degree of Contrast Enhancement According to the Response Evaluation Criteria in Solid Tumor (RECIST) Classification after Chemotherapy (Mean Interval, 20 ± 7 days)

| RECIST | Diameter (cm) | NE (HU) | PE (HU) |
|--------|---------------|---------|---------|
| PR ($n = 7$) | 2.8 ± 1.0 | 46.5 ± 14.9 | 83.0 ± 14.9 |
| SD ($n = 38$) | 3.2 ± 2.0 | 44.9 ± 18.2 | 81.9 ± 18.3 |
| PD ($n = 16$) | 2.2 ± 0.8 | 63.1 ± 13.5 | 98.4 ± 12.5 |
| *p*-value | < 0.05 | < 0.05 |

**Note.**- Data are mean ± standard deviations. HU = Hounsfield unit, NE = net enhancement, PD = progressive disease, PE = peak enhancement, PR = partial response, SD = stable disease

### Table 3. Time-Density Curves (TDC) According to the Response Evaluation Criteria in Solid Tumor (RECIST) Groups

| RECIST | Types of Time-Density Curve (TDC)* | Total (n) |
|--------|-----------------------------------|-----------|
| PR | A | 1 | 3 | 3 | 0 | 7 |
| | B | 20 | 4 | 12 | 2 | 38 |
| | C | 15 | 0 | 1 | 0 | 16 |
| | Total ($n$) | 36 | 7 | 16 | 2 | 61 |

**Note.**- *A* = showing an early wash-in and early wash-out, *B* = showing an early wash-in and maintaining a plateau, *C* = showing an early wash-in and continuous acceleration, *D* = showing no early wash-in in the dynamic period. PD = progressive disease, PR = partial response, SD = stable disease

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**Fig. 1.** A 69-year-old men with stage IV non-small cell carcinoma in the left upper lobe with lung to lung metastasis. **A.** Dynamic contrast-enhanced CT images at pre-contrast, 30, 60, 90, 120 sec, and 5 minutes over the lesion after chemotherapy with a cisplatin regimen. **B.** The time-density curve shows early wash-in and wash-out pattern consistent with type A. Net enhancement and peak enhancement values were 44 HU and 81 HU, respectively. The lesion was categorized as progressive disease according to the Response Evaluation Criteria in Solid Tumor criteria. **Note.**- HU = Hounsfield unit, TAV = tumor attenuation value.
There were 35 lesions showing type A patterns on the TDCs that belonged to the SD or PD groups. The SD group comprised 20 (55.6%) and the PD group included 15 lesions (41.7%). Although the type A TDC pattern were exclusive to the SD or PD groups and thus could not be used to differentiate between the two groups, net and peak enhancement differed significantly among the SD and PD ($p < 0.05$) (Table 2, Fig. 3).

The mean values of NE and PE were significantly higher in the PD group than in the PR or SD groups according to the RECIST criteria (Fig. 3) ($p < 0.05$). The ROC curve analysis of net enhancement values indicated that the sensitivity and specificity were 62.5% and 82.2%, respectively, with a net enhancement value of 60.3 HU as a cutoff value to differentiate between the PD group and the PR or SD groups. When the cutoff value was set at 94.5 HU for the peak enhancement value, the sensitivity and specificity were 75.0% and 75.6%, respectively (Fig. 4).

**DISCUSSION**

In our study, we tried to demonstrate that the dynamic CT

![Fig. 2. An 83-year-old woman with stage IV adenocarcinoma in the left upper lobe.](image)

**A.** Dynamic contrast-enhanced CT images at pre-contrast, 30, 60, 90, 120 sec, and 5 minutes over the lesion after chemotherapy with agefinitib regimen.

**B.** The time-density curve shows early wash-in and continuous acceleration pattern consistent with type C. Net enhancement and peak enhancement values were 40 HU and 70 HU, respectively. The lesion was categorized as stable disease according to the Response Evaluation Criteria in Solid Tumor criteria.

**Note.** HU = Hounsfield unit, TAV = tumor attenuation value

![Fig. 3. Mean values of net and peak enhancement in 61 lesions among three groups according to the Response Evaluation Criteria in Solid Tumor criteria on the dynamic contrast-enhanced CT images in 41 patients with advanced lung cancer.](image)

**A.** Net enhancement (NE) differed significantly between the PD group and the PR or SD groups ($p < 0.05$).

**B.** Peak enhancement (PE) differed significantly between the PD group and the PR or SD groups ($p < 0.05$).

**Note.** HU = Hounsfield unit, PD = progressive disease, PR = partial response, SD = stable disease
differentiation of progressive disease from stable or responding disease is important. Most of the type A lesions which shows early WI and WO patterns on dynamic CT were included in SD and PD groups on the follow-up conventional CT. Although TDC patterns were not useful for differentiations between the SD and the PD groups in our study, the NE and PE of the lesions were significantly higher in the PD group as compared with the PR and SD groups.

The NE and PE of lesions have been used to differentiate between benign and malignant lung tumors on the DCE-CT images. Jeong et al. (16) reported that nodules showing persistent enhancements of ≥ 25 HU in 2 minutes and 5-31 HU WO on the delayed phase were usually malignant, and lesions with less than 25 HU WI and without WO greater than 31 HU were usually benign. Donmez et al. (18) demonstrated that all malignant lesions except one lung cancer had an early peak enhancement with rapid WO, and all benign lesions displayed early increasing enhancements with an early plateau within 2 minutes after contrast administration or with a late plateau in 4 minutes on dynamic MRI. On the perfusion CT images the sensitivity, specificity, and accuracy for differentiating between benign and malignant nodules were 96.4%, 69.6%, and 84.3%, respectively, for a cutoff NE value set at 20 HU (20). In our study, we demonstrated that when the cutoff values were set at 94.5 HU for PE and at 60.3 HU for NE, the sensitivities and specificities for differentiating between the PD group and PR or SD group were 75.0% and 75.6% in PE and were 62.5% and 82.2% in NE, respectively.

Generally, the tumor response to radiation therapy is believed to be a slow process with maximum response (minimum volume) an average of 5-11 months after radiation therapy completions (21, 22). In this study, 15 lesions were treated with chemo-radiotherapy but mean interval between termination of radiotherapy and time of dynamic CT taken were 292 days (range, 86 to 600 days), which might be explained that radiation itself may have little effects on acute microvascular damages.

Our study has a few obstacles which will be bridged in the future. First, the study population was too small to generalize the results, especially with respect to the PR group. Second, we did not compare directly the degree or pattern of contrast enhancements before and after treatment. We need to understand the pattern of contrast enhancement before treatment, and how it changes after treatment according to treatment response status.
Third, the delayed imaging time was slightly short at 5 minutes. In order to precisely evaluate the WO patterns of contrast media, it might be helpful to take the additional dynamic CT images after 5 minutes (16). Fourth, although we measured the attenuation values in the areas apart from tumor necrosis, cavities, it was sometimes difficult to differentiate between fibrosis by radiation therapy and residual tumor in the lesions. It will be necessary to further study the PET scan to evaluate the tumor viability. Finally, patients were exposed to extra radiations due to the routine scans for tumor staging plus the additional dynamic scans when compared with that of our other studies (3.3 mSV; dose range: 2.9-5.2 mSV).

In conclusion, the type A TDC pattern, defined as early WI and early WO of contrast enhancement, was observed mostly on the dynamic CT images in the SD and PD groups classified by the RECIST criteria. The SD and PD groups showing that type A TDC pattern of contrast enhancements can be differentiated according to PE or NE values, which are significantly higher in the PD group as compared with the SD group. Therefore, DCE-CT scans can be helpful for predicting treatment response outcomes according to the RECIST criteria in patients with advanced lung cancers after chemotherapy with/without radiation therapy.

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진행성폐암 환자에서 항암화학치료 또는 방사선치료 후 역동적조영증강 CT를 이용한 치료반응 평가에 대한 연구

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목적: 진행형폐암 환자에서 체화학요법 후 dynamic contrast-enhanced CT (DCE-CT)를 이용한 조영증강 양상을 평가하고, 치료 초기 단계의 조영증강 양상으로 치료반응을 예측할 수 있는지 알아보고자 하였다.

대상과 방법: 진행성폐암 환자 중에서 항암화학요법과 방사선치료 후 DCE-CT와 추적 CT를 시행한 환자 42명을 대상으로 하였다. DCE-CT 영상에서 최고 및 순수 조영증강(peak and net enhancement; PE, NE) 정도 및 시간-음영관성(time-density curve; TDC)에 따라 4가지 형태의 조영증강 양상(A, B, C, D형)을 평가하였다. 치료반응은 개정된 Response Evaluation Criteria in Solid Tumor로 평가하였다.

결과: NE와 PE 값은 진행형(progressive disease; PD)군이 안정형(stable disease; SD) 혹은 부분반응(partial response; PR)군보다 유의하게 높았다(\( p < 0.05 \)). TDC상에서 B, C, 그리고 D형은 PR과 SD군에서 대부분 관찰되었다(96.0%), 반면, A형은 SD와 PD군에서 대부분 관찰되었으며(97.2%), SD와 PD군 사이에 PE와 NE 값은 통계적으로 유의한 차이가 있었다(\( p < 0.05 \)).

결론: DCE-CT에서 조영증강 양상은 치료 결과에 따라 유의하게 달라졌다. 그러므로, DCE-CT는 진행성폐암에서 치료반응을 예측하는 데 도움이 될 수 있다.