



Dynamic contrast-enhanced MRI for response evaluation of non-small cell lung cancer in therapy with epidermal growth factor receptor tyrosine kinase inhibitors: a pilot study

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Background: It is important to identify candidates who would benefit from target agent chemotherapy in advanced NSCLC patients. The purpose of this study is to evaluate the feasibility of DCE-MRI for early response evaluation in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) treatment in patients with NSCLC.

Methods: Seven patients were prospectively enrolled who have pathologically-proven NSCLC with EGFR mutations or at least 2 of the following factors; adenocarcinoma, female, or never-smokers. Patients were treated with gefitinib or erlotinib and the start of chemotherapy was denoted day 0. DCE-MRI was performed at day-1, day+7, and day+28. Longitudinal changes of perfusion parameters were quantified and compared to Response Evaluation Criteria in Solid Tumors (RECIST) results.

Results: Quantitative perfusion parameters; K^{trans} , v_e and v_p of the lung cancer showed a significant decrease at day+7 ($P=0.016$), but no further significant decrease between day+7 and day+28 ($P>0.05$). Semi-quantitative markers for tumor enhancement curve pattern; EA (enhancement amplitude), MS (maximum slope), and AUC (area under the curve) also showed a significant decrease at day+7 ($P=0.016$, 0.031 , and 0.016 , respectively), but no further significant decrease between day+7 and day+28 ($P>0.05$). When RECIST applied, all patient was in the stable disease at day+7 and three patients showed partial response (PR) at day+28. All seven patients showed PR by the 3-month follow-up.

Conclusions: Perfusion parameters may be used as an early non-invasive imaging biomarker for the response evaluation of target agent treatment in NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); perfusion magnetic resonance imaging (MRI); tumor angiogenesis

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Introduction

Tumor angiogenesis is one of the most important biomarkers in cancers. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) gives functional information on tumor angiogenesis and may reflect hemodynamic changes during treatment (1,2). Several techniques have been tested to characterize tumor angiogenesis by analyzing signal intensity-time or attenuation-time curve with semi-quantitative parameters including peak enhancement, wash out, maximum slope and time-to-peak (3-5). However, these semi-quantitative parameters are limited to quantify the physiologic changes of tumor angiogenesis like increased permeability, lack of differentiation between venule and arteriole, and abundant extravascular space in cancer tissue. Relatively complicated pharmacokinetic modeling is needed to quantify these physiologic characteristics and begin their evaluation in oncologic practice (6).

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI), such as gefitinib, erlotinib, afatinib, osimertinib, or dabrafenib, are well-known target agents for the treatment of non-small cell lung cancer (NSCLC). Epidermal growth factor receptors (EGFR) are involved in tumor growth in many steps including cellular proliferation, angiogenesis, metastasis, and inhibition of apoptosis (7,8). EGFR signaling up-regulates the expression of multiple angiogenic factors and indirectly regulates angiogenesis by increasing the synthesis and release of proangiogenic factors from tumor cells (9). EGFR-TKI therapy has showed dramatic responses in subsets of NSCLC patients. Clinical trials have demonstrated better responses to EGFR-TKI in association with somatic mutations in EGFR (10-12) and with the following clinical characteristics: adenocarcinoma, no history of smoking, female sex, and Asian ethnicity (13-15). However, there remains a great deal of variation in predicting the responsiveness to EGFR-TKI therapy due to many factors, including primary or acquired resistance caused by additional mutations in the *EGFR* gene or *KRAS* mutation (16,17). Therefore, non-invasive, repeatable, and early predictive parameters may benefit NSCLC patients by helping to determine a suitable treatment regimen, a practice revolutionized by the emergence of personalized therapy.

Although Response Evaluation Criteria in Solid Tumors (RECIST) is a well-established method for monitoring

response in solid tumors, it cannot measure early changes in functional parameters, but only measure the changes of tumor size as parameters of response evaluation (18,19). DCE-MRI is considered to measure tumor angiogenesis quantitatively with the perfusion parameters of a diffusible tracer, gadolinium chelates (6,20), and may generate parameters which respond earlier than changes in tumor size. DCE-MRI has been tested as a novel biomarker in assessing anti-angiogenic effects in several kinds of tumors, including renal cell carcinoma, pancreatic cancer, and hepatic metastasis from colorectal cancer (21-23); however it has not been tested for the response evaluation of the lung cancer after EGFR-TKI therapy. The purpose of this study is to prospectively quantify the anti-angiogenic effect of EGFR-TKI at multiple time points using perfusion parameters from DCE-MRI in patients with lung cancer.

We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/apm-19-622>).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of Samsung Medical center (IRB file number: SMC 2009-07-066). All patients were given written informed consents.

Patient selection

Figure 1 is a diagram showing patient selection. Patients with pathologically-proven recurrent or metastatic NSCLC, at more than 3 cm along longest diameter, were assessed for EGFR-TKI therapy. The criteria for EGFR-TKI therapy were either the presence of somatic mutation of EGFR or more than 2 among the following requirements: (I) adenocarcinoma, (II) female sex, or (III) no history of smoking. Exclusion criteria included the following: abnormal renal function and contraindications for MRI (claustrophobia, cardiac pacemaker, etc.). Seven patients were recruited between September 2009 and March 2010 and they were treated with gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE, USA) at a dose of 250 mg/day orally on a 4-week schedule or erlotinib (Tarceva®; Genentech, Inc., CA, USA or Hoffmann-LaRoche Ltd., Basel, Switzerland) at a dose of 150 mg/day orally on 4-week schedule. All patients who agreed to

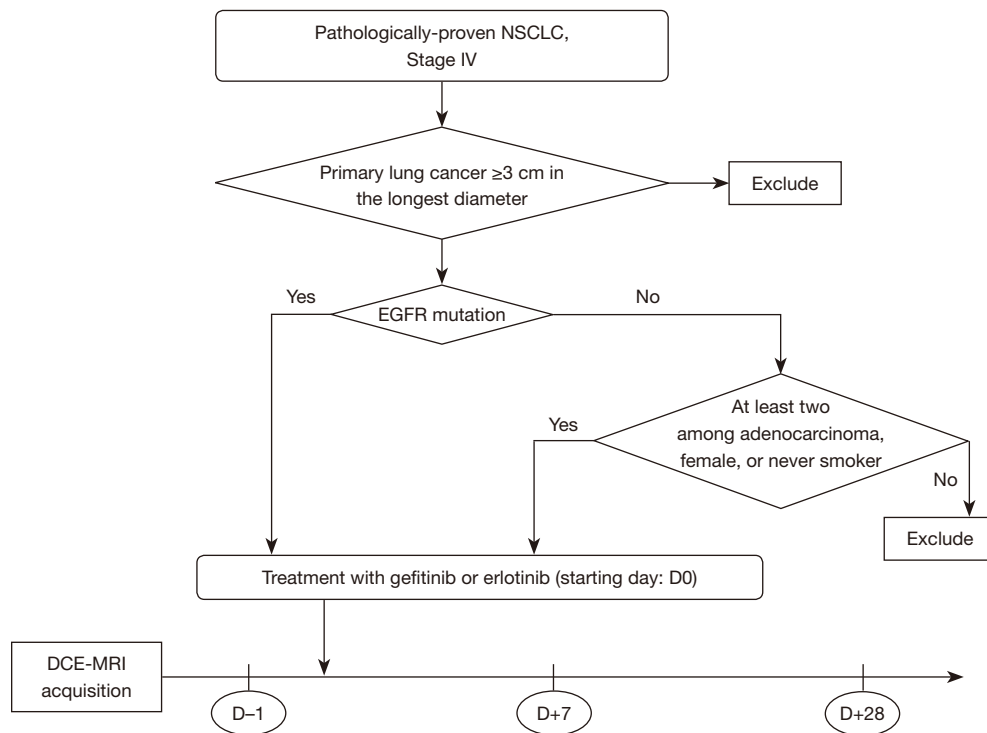


Figure 1 Flow diagram demonstrates patient selection algorithm.

participate in this study underwent a baseline DCE-MRI at day-1 (D-1). D0 denotes the starting date of chemotherapy. Follow-up DCE-MRI scans were scheduled at D+7 and D+28. The window period is ± 2 days.

DCE-MRI acquisition

DCE-MRI was performed with a 3-T MRI system (Achieva; Philips Medical Systems) equipped with a gradient system capable of ensuring maximum gradient amplitude of 80 mT/m, a rise time of 0.2 milliseconds, and a slew rate of 200 T/m/s. A sensitivity-encoding cardiac coil (SENSE, Philips Medical Systems) with a six-coil element was used for DCE-MRI covering the entire thorax.

The acquisition protocols are shown in *Table 1*. Transverse T2-weighted images with a multishot (MSH) spectral presaturation inversion recovery (SPIR) sequence was obtained for evaluation of the anatomy and the location of measurable disease. T1 mapping was done by multiple acquisitions using T1-weighted 3D spoiled gradient-recalled echo (SPGR) sequence of the thorax with different flip angles (5°, 15°, and 35°). DCE-MRI of the lung

parenchyma was optimized with the following acquisition parameters: TR, 5.6 ms; TE, 1.47 ms; flip angle, 35°; rectangular field of view, 350×448 mm; voxel size, 3×3 mm; reconstructed voxel size, 1.75×1.74 mm; reconstructed matrix, 256×256; coronal orientation. The slab thickness was 100 mm, and the slab was divided into 10 partitions to produce 10 images with 10 mm in section thickness. To increase acquisition speed, a sensitivity-encoding factor of 2 was applied in the phase-encoding direction. The temporal resolution was 3.0 seconds covering the whole thorax on coronal plane and a total of 60 dynamic scans were obtained. The entire DCE-MRI acquisition lasted up to 3 minutes imaging every 3 seconds. The patients were asked to breathe in as shallow a manner as possible during the MRI scanning. Gadolinium chelate (Dotarem; Guerbet, Aulnay-sous-Bois, France) was administered at a dose of 0.2 mL per kilogram of body weight by means of a power injector (Medrad, PA, USA) at a rate of 4 mL/s, followed by administration of 20 mL of normal saline in order to flush the tube.

All MR image data were directly interfaced to our PACS system (Pacspeed or Centricity 2.0, GE Healthcare),

Table 1 Parameters for MR imaging sequences

Parameter category	T2WI	T1 mapping	Dynamic scan
Acquisition parameters (unit)	MSH SPIR Sequence	T1-weighted 3D SPGR Sequence	T1-weighted 3D SPGR Sequence
Repetition time/echo time (msec/msec)	1,000/70	5.6/1.47	5.6/1.47
Flip angle (degrees)		5, 15, 35	35
Field of view (mm)	340×318	350×448	350×448
Voxel size (mm)	1.35×1.81	3×3	3×3
Reconstructed voxel size (mm)	0.66×0.66	1.75×1.74	1.75×1.74
Reconstructed matrix	512×512	256×256	256×256
Orientation	Transverse	Coronal	Coronal
Slice thickness (mm)	5		
Slab thickness (mm)		100	100
Section thickness (mm)		10	10
Respiratory compensation	Breath hold	Shallow breathing	Shallow breathing

MSH, multishot; SPIR, spectral presaturation with inversion recovery; SPGR, spoiled gradient-recalled echo.

which displayed all image data on 4 monitors (1,536×2,048 image matrices, 8-bit viewable gray-scale, 60-ft-lambert luminescence). Dynamic enhanced images were viewed on these monitors.

Data analyses

Concentration of contrast agent was estimated from MR signal intensity by computing the difference in longitudinal relaxation rate: $C(t) = (1/T_1(t) - 1/T_{10})/r_1$, where T_{10} is pre-contrast T_1 value and $T_1(t)$ is post-contrast T_1 value, and r_1 denotes the longitudinal relaxivity ($4.5 \text{ s}^{-1}\text{mM}^{-1}$ for blood) (24). The T_{10} value of each voxel was computed using the variable flip angle method (25). The general equation for signal intensity values at a given flip angle is $S = S_0\{\sin\alpha[1 - \exp(-TR/T_{10})]/[1 - \cos\alpha\exp(-TR/T_{10})]\}$, where TR is the repetition time, α is the flip angle, and S_0 is the equilibrium longitudinal magnetization. The S_0 and T_{10} parameter were estimated by a linear least-squares method using three sets of SPGR sequences with different flip angles (5° , 15° , and 35°). Following estimation of T_{10} from the precontrast images, postcontrast $T_1(t)$ can be estimated as $1/T_1(t) = -\ln\{1 - (S_{\text{post}}/S_{\text{pre}})[1 - \exp(-TR/T_{10})]\}/TR$.

DCE-MRI for lung cancers was analyzed using semi-quantitative and quantitative methods: the sigmoid fitting method for time-concentration curve pattern analysis and the pharmacokinetic modeling method, respectively.

For semi-quantitative analysis, a sigmoid equation was used (26):

$C(t) = A/[1 + (B/t)^C]$, where $C(t)$ is the time-concentration curve averaged across all voxels within the region-of-interests (ROIs) of the lung tumor, A is the asymptotic enhancement amplitude (EA), and B is time of half rising ($T_{1/2_{\text{max}}}$). Maximal slope (MS) was estimated as the first derivative of the above equation at $T_{1/2_{\text{max}}}$ time point. Area under the curve (AUC) was calculated after sigmoid fitting of the time-concentration curve.

For quantitative analysis, the extended Kety two-compartment model was used (6): $C_t(t) = K^{\text{trans}} C_p(t) \otimes \exp(-K^{\text{trans}} t/v_e) + v_p C_p(t)$, where C_t is the concentration of contrast agent in the observed tissue, C_p is the concentration in blood plasma, v_p is the fractional blood plasma volume per unit volume of tissue, K^{trans} is the volume transfer constant, and v_e is the fractional extravascular extracellular space (EES) per unit volume of tissue. The k_{ep} , flux rate constant between EES and blood plasma was calculated as K^{trans}/v_e .

The arterial input function (AIF) was determined semi-automatically by selecting an area within the pulmonary trunk or right ventricle among several candidates showing homogeneous Kendall's coefficients for time-concentration curves. The AIF at D-1 MRI was used as a baseline AIF and applied for analyzing data at D+7 and D+28 for each patient.

Response assessment

The longest diameters of the measurable diseases were measured using an electronic caliper of the PACS system. The measurement of size was performed on the T2-weighted axial images. The one-dimensional diameters were assessed by the RECIST criteria (27). If the sum of the diameters of target lesions showed a decrease of at least 30% on follow-up, it is considered as partial response (PR). Progressive disease was defined as an increase of at least 20% in the sum of diameters on follow-up. Stable disease was considered as having neither shrinkage sufficient to qualify for PR nor increase sufficient to qualify for PD on follow-up.

The longitudinal percentage change (% change) in each perfusion parameter was evaluated at D+7 and D+28. Increases in $T_{1/2_{max}}$ and decreases in EA, MS, K^{trans} , v_e and k_{ep} , were considered anti-angiogenic effects.

Statistical analysis

For the analysis of changes in time-concentration curves after EGFR-TKIs therapy, the difference in EA, MS, $T_{1/2_{max}}$, and AUC between two time points was compared using the Wilcoxon signed rank test.

For the analysis of changes in perfusion parameters after EGFR-TKIs therapy, the differences in K^{trans} , v_e , and v_p between two time points was compared using the Wilcoxon signed rank test.

A P value <0.05 indicated a statistical significance. Statistical analyses were performed using SAS (version 9.13, Cary, NC, USA).

Results

Patients' characteristics

All seven patients (four men and three women; median age, 53 years; age range, 46–67 years) underwent DCE-MRI before and after EGFR-TKIs therapy. The histological subtype of all patients was adenocarcinoma. Six out of the seven patients had EGFR mutations and the remaining one patient was a woman without a history of smoking. In terms of prior treatment: one patient had conventional chemotherapy and cyberknife surgery for brain metastasis; two patients had 1st line chemotherapy; four patients had 1st line plus another chemotherapy.

Longitudinal changes in perfusion parameters

The longitudinal changes in perfusion parameters (Figure 2) in the lung cancer were demonstrated with color changes on color map images. Lower scale colors were seen on perfusion map of the lung cancer on follow-up. Longitudinal parameter changes were demonstrated by changes in distribution of each voxel value of the whole lung cancer region. A bar graph of perfusion parameters depicts a shift toward the lower range of values on follow-up. Longitudinal changes of curve patterns were also quantitatively evaluated by sigmoid fitting of time-concentration curve. These curves showed lower EA and maximum slope on follow-up, decreasing the AUC as a result.

Perfusion parameter and curve pattern analysis suggested anti-angiogenic effects after chemotherapy by showing a decrease in K^{trans} , v_e , v_p , EA, MS, and AUC and an increase in $T_{1/2_{max}}$ (Table 2). The distribution of K^{trans} and v_e were significantly decreased at D+28 after EGFR-TKI treatment on voxel based analysis (P=0.04 and <0.00, respectively, Kolmogorov-Smirnov with Bonferroni's correction) (Figure 3). Concerning parameters from the curve pattern analysis, EA and MS were reduced and $T_{1/2_{max}}$ was increased after the start of EGFR-TKI therapy, but the statistical significance of this finding was not proven (Table 2).

Response assessment

All seven patients who were clinically eligible for the EGFR-TKI treatment were responsive to EGFR-TKI treatment according to the traditional response evaluation method of RECIST in 3-month follow-up, but their responsiveness to EGFR-TKI treatment cannot be seen with RECIST in three patients on the 28th day of follow-up and none on the 7th day of follow-up. However, the perfusion parameters from DCE-MRI showed significant changes at an early date on the 7th day of follow-up in this study, being an early indication of responsiveness of EGFR-TKI treatment.

Discussion

Changes in DCE-MRI parameters have been investigated to demonstrate efficacy of monoclonal antibodies targeting VEGF, TKIs and vascular-targeting agents for various kinds of tumors (28), but the lung cancers were rarely evaluated

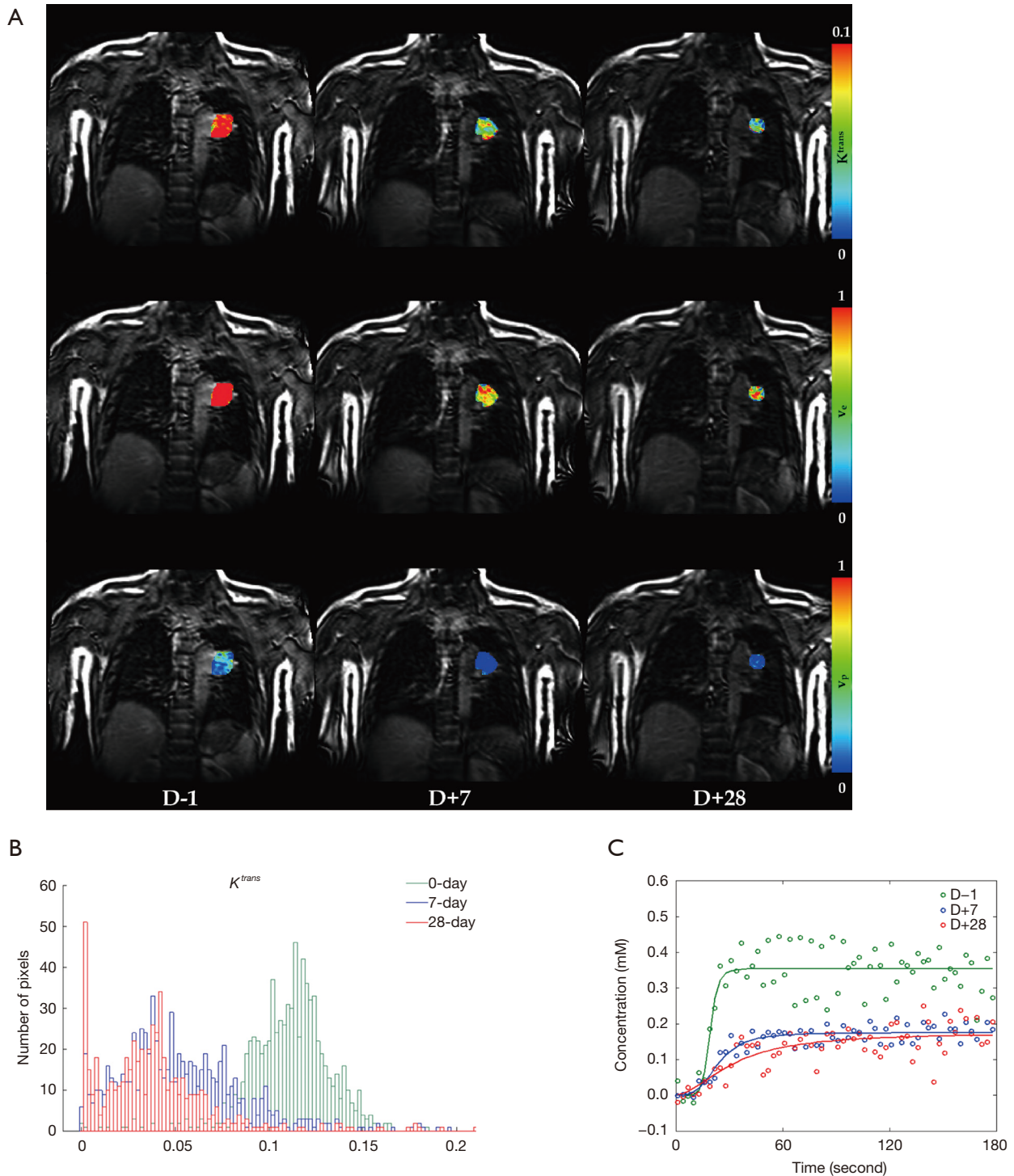


Figure 2 Longitudinal changes of perfusion parameters in a 46-year-old male patient with adenocarcinoma in the left upper lobe. The patient had an EGFR mutation and was treated with gefitinib. (A) Color maps visualize the decrease of K^{trans} , v_e and v_p in the lung cancer by showing color changes toward lower scale colors, especially striking changes between baseline and D+7. (B) Histogram demonstrates the voxel values of K^{trans} of the whole tumor at each time point. The distribution of K^{trans} shifts to the left, showing a decrease in K^{trans} value after chemotherapy. (C) The pattern of time-concentration curves change after chemotherapy with interval decrease in EA and MS, especially between baseline and D+7.

Table 2 Longitudinal changes of perfusion parameters (n=7)

Parameter category	Mean			P values*	
	D-1	D+7	D+28	D-1 and D+7	D-7 and D+28
Perfusion parameters					
K^{trans}	0.096	0.038	0.042	0.016	0.375
v_e	0.724	0.399	0.389	0.016	0.813
v_p	0.190	0.031	0.069	0.016	0.469
Curve pattern analysis					
EA	0.322	0.144	0.144	0.016	1.000
MS	0.043	0.010	0.020	0.031	0.578
$T^{1/2}_{max}$	8.576	9.188	9.340	0.688	0.813
AUC	16.466	6.959	7.042	0.016	0.813

*, Wilcoxon's signed rank test.

with DCE-MRI probably due to intrinsic difficulties to obtain enough signal from the air-filled organ and motion artifacts. There was only one published report about DCE-MRI for the response evaluation of the lung cancer, which was treated with inhibitor of VEGF in combination with cytotoxic agent (29). However, to the best of our knowledge, there have been no studies regarding EGFR-TKIs as monotherapy. EGFR-TKIs are one of the most commonly used target agent for the NSCLCs, but their survival benefit outweighed only in subsets of NSCLC patients (30). Although clinical and molecular characteristics helped to screen NSCLC patients who can benefit from EGFR TKI treatment, there still remained a great deal of variation in predicting the responsiveness to EGFR-TKI therapy mainly due to primary or acquired resistance caused by additional mutations in the EGFR gene or KRAS mutation (16,17). Therefore, non-invasive, repeatable, and early changing parameters are needed to guide EGFR-TKI treatment. DCE-MRI in our study visualized the longitudinal changes in perfusion parameters of the lung cancer on a voxel-by-voxel basis and quantified the early antivasular effects of EGFR-TKIs before these cytostatic agents make changes in volume of the tumor. We selected patients who were expected to show good response to EGFR-TKI therapy and all seven patients showed PR according to RECIST by the 3 months since the start of the chemotherapy. At the 7th day of follow-up after treatment, no patient met the criteria of PR without significant changes in tumor volume,

but perfusion parameters indicated anti-angiogenic effect of chemotherapy by showing significant decrease in extent of perfusion parameters named K^{trans} , v_e , and v_p and curve pattern parameters named EA, MS, and AUC.

Perfusion parameters of the whole lung cancer were calculated and displayed on a voxel-by-voxel basis and we could observe the heterogeneous characteristics of tumor angiogenesis in the lung cancer before and after the chemotherapy. In our analysis, longitudinal changes of K^{trans} , v_e , and v_p were calculated for all voxel values within the tumor and the changes of distribution of pixels of lung cancer could be demonstrated on perfusion maps. This helped to understand the decreasing or increasing trend of perfusion parameters and how significant they were, although the spectrum of parameter values was wide. In the evaluation of treatment response of the brain tumors, these perfusion parametric maps could be correlated voxel-by-voxel before and after therapy and quantified treatment response on voxel basis by showing parametric response map (31). For the lung cancer, each perfusion parametric maps also could be generated before and after chemotherapy, but significant misregistration was expected in correlation of two longitudinal parametric maps.

Although EGFR-TKIs do not have direct anti-angiogenic effect, they are known to have many indirect effects in diminishing angiogenesis. Our results demonstrated early and large percentage changes in perfusion parameters and in curve pattern parameters, which preceded changes in tumor size after EGFR-TKI treatment. This may suggest early anti-angiogenic effects of EGFR-TKIs decreasing permeability and EES volume in the lung cancer on treatment before shrinkage in the tumor volume. Perfusion parameters may be early and objective biomarkers for response evaluation in patients treated with anti-angiogenic drugs.

There are several limitations to our study. First, the number of patients was small since this was a feasibility study. Second, the correlation between perfusion parameters and long-term clinical outcome was not investigated. Third, patients who had tumors less than 3 cm were excluded from this study in order to measure a decrease in perfusion parameters and volume on follow-up image.

In conclusion, perfusion parameters from DCE-MRI can be quantified in patients with lung cancer. Quantitative biomarkers from DCE-MRI may play a role as objective parameters for tumor angiogenesis and early indicators for response evaluation of target agent treatment in NSCLC.

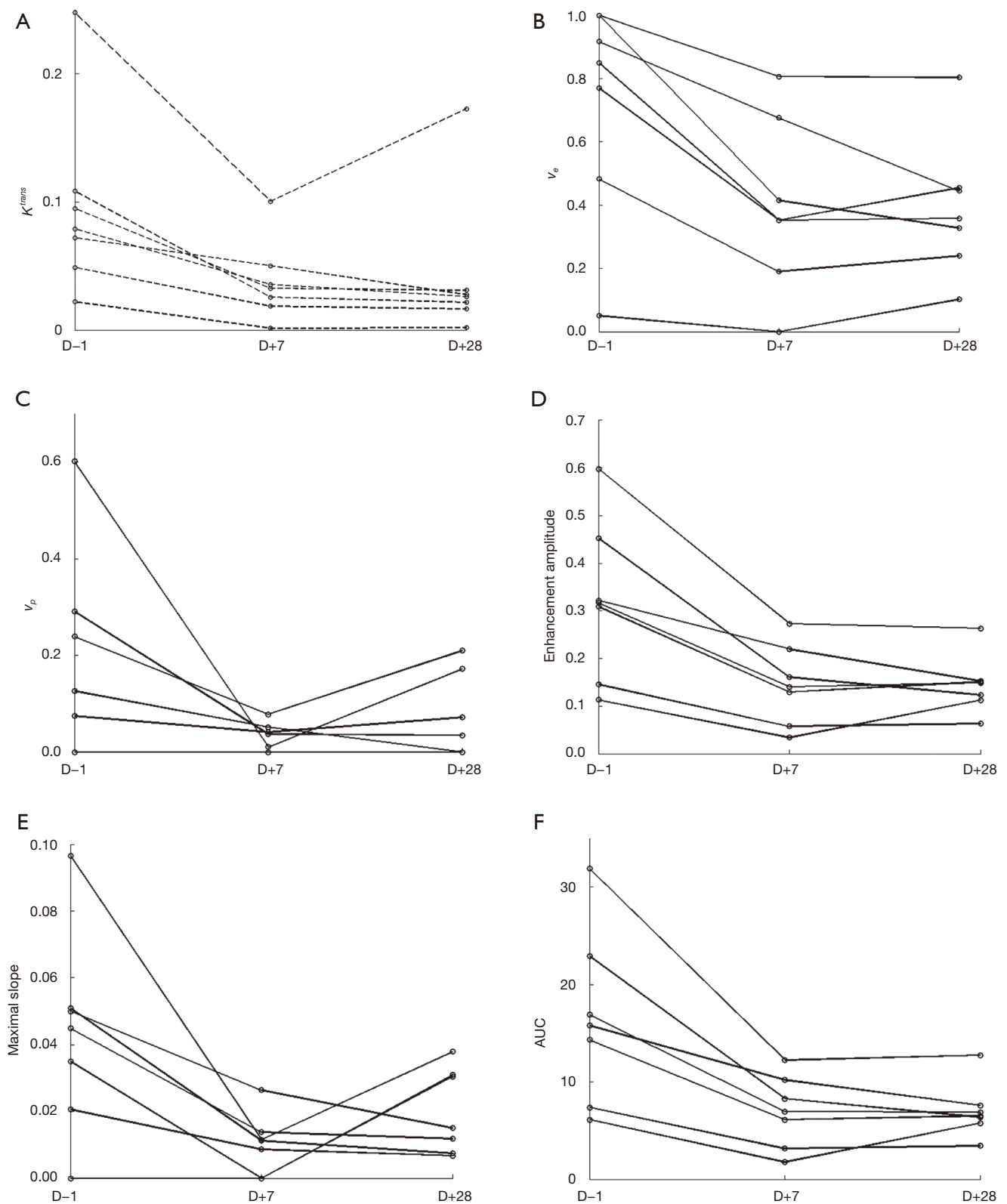


Figure 3 Changes in the following perfusion parameters in all seven patients: (A) K^{trans} , (B) v_e , (C) v_p , (D) EA, (E) MS, (F) AUC. Changes between D-1 and D+7 show significant drop for all these parameters. ($P < 0.05$ Wilcoxon's signed rank test).

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Footnote

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Data Sharing Statement: Available at <http://dx.doi.org/10.21037/apm-19-622>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-19-622>). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of Samsung Medical center (IRB file number: SMC 2009-07-066). All patients were given written informed consents. The study outcomes will not affect the future management of the patients.

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