Diffusion Weighted MR Imaging: Predictive Capability for Chemoradiotherapeutic Effect in Non-Small Cell Lung Cancer Patients as Compared with FDG-PET/CT

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INTRODUCTION: Although early stage non-small cell carcinoma (NSCLC) cases can be curatively treated by surgical treatment, advanced NSCLC cases are largely incurable. Therefore, in patients with unresectable, and/ or locally advanced stage III NSCLCs, combined modality therapy, involving chemotherapy and thoracic radiation therapy (i.e. chemoradiotherapy) is the treatment of choice. In the last decade, some investigators have suggested the promising results of FDG-PET or PET/CT for evaluation of therapeutic effect and prediction of prognosis after treatments based on the glucose metabolism of lung cancer. Recently, diffusion-weighted MR imaging (DWI) has been applied to the evaluation of tumors such as detection, diagnosis, staging, prediction and/ or evaluation of treatment response(1-6). One of the most interesting findings associated with the use of DWI in several cancer patients has been the potential of apparent diffusion coefficient (ADC) measurements for prediction of the tumor responser to chemotherapy and radiation therapy (4-6). To the best of our knowledge, the capability of DWI for prediction of therapeutic effect in advanced NSCLC patients with chemoradiotherapy has not yet been determined. In the present study, we hypothesized that quantitatively assessed DWI can be utilized for prediction of therapeutic effect after chemoradiotherapy in NSCLC patients as well as FDG-PET/CT. Thus, the purpose of the present study was to directly and prospectively compare the predictive capability for therapeutic effect of chemoradiotherapy between DWI and FDG-PET/CT in NSCLC patients.

MATERIALS AND METHODS: 64 consecutive patients with NSCLC including 38 men (age range: 42 to 81 years, mean age: 73 year old) and 24 women (age range 39 to 83 years, mean age: 71 year old) were enrolled in this study. In this 64 NSCLC patients, 35 were diagnosed as stage IIIA and 29 as stage IIIB. On pathological examination, 50 were diagnosed with adenocarcinoma, eight with squamous cell carcinoma, four with large cell carcinoma, and two with adenosquamous cell carcinoma. All subjects underwent FDG-PET/CT and whole-body DWI before treatment. All whole-body DWI (TR 5759ms/ TE 70 ms/ TI 180 ms/ ETL 141/ b=0, 1000 sec/mm^2) was obtained by using moving-table system and body coil on two 1.5 T MR scanners (Gyroscan Intera and Achieva, Philips Medical Systems) in each patient. All FDG-PET/CT examinations were performed by using standard whole-body PET/CT protocol on a PET/CT scanner (Discovery ST; GE Health Care). Then, all patients received concurrent chemotherapy during the period that they have thoracic radiotherapy. The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) criteria after treatment. For quantitative assessment of DWI and FDG-PET/CT, ADCs and maximum standard uptake values (SUV_{max}s) at all targeted regions were measured by using region of interest (ROI) measurements in each patient. To determine differences of ADC and SUV_{max} among PR, SD and PD groups, both indexes were compared by means of analysis of variance with Tukey's honest significance tests. To determine the usefulness of ADC and SUV_{max} as a marker for distinguish SD or PD group from PR groups, receiver operating characteristics (ROC) analyses were performed to determine feasible threshold. Then, sensitivities, specificities and accuracies of both indexes were compared each other by using McNemar's test. To determine utilities of DWI and PET/CT for prediction of prognosis after chemoradiotherapy, overall survival of two groups divided by the each adapted threshold value of both indexes were compared by using Kaplan-Meier methods followed by log-rank test. A p value less than 0.05 was considered significant in all statistical analyses.

RESULTS: Representative case is shown in Figure 1. Results of comparison of ADC and SUV_{max} among all groups are shown in Table 1. ADC of PR group had significant difference with those of SD and PD groups ($p<0.05$). SUV_{max}s of PR and SD groups had significant difference with that of PD group ($p<0.05$). Results of ROC analyses of ADC and SUV_{max} shows that area under the curve (Az) of ADC (Az=0.81) was significantly larger than that of SUV_{max} (Az=0.64, $p<0.05$). The feasible threshold value and diagnostic capability of each index are shown in Table 2. Feasible threshold value of ADC and SUVmax were determined as 2.1×10^{-3}mm^2/sec and 3.9. When these threshold values were adapted, specificity (44.4 %) and accuracy (76.6 %) of ADC were significantly higher than those of SUV_{max} (specificity: 11.1%, $p<0.05$; accuracy: 67.2%, $p<0.05$). The overall survival curves of patients with ADC more than or equal to 2.1×10^{-3}mm^2/sec and ADC smaller than 2.1×10^{-3}mm^2/sec and those with SUV_{max} more than or equal to 3.9 and SUV_{max} smaller than 3.9 are shown in Figure 2. Median overall survival period of patients with ADC smaller than 2.1×10-3mm2/sec was 38.2±4.6 months (mean±SD), and that of patients with ADC more than or equal to 2.1×10-3mm2/sec was 25.9±2.0 months. On the other hand median overall survival period of patients with SUV_{max} smaller than 3.9 was 30.8±3.1 months, and that of patients with SUVmax more than or equal to 3.9 was 30.0±2.1 months. There was significant difference of overall survival between two groups divided by the threshold value of ADC ($p<0.05$)

CONCLUSION: Whole-body DWI has potential for more specific and/or accurate method for therapeutic effect prediction of chemoradiotherapy than FDG-PET/CT in NSCLC patients. ADC has potential to play a new biomarker for chemoradiotherapy in NSCLC patients.

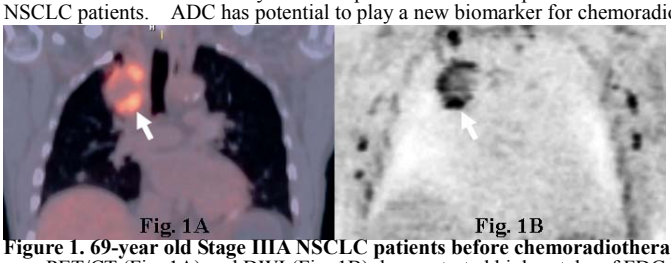

Figure 1. 69-year old Stage IIIA NSCLC patients before chemoradiotherapy.
PET/CT (Fig. 1A) and DWI (Fig. 1B) demonstrated high uptake of FDG and high signal intensity of tumor, especially in the periphery. SUV_{max} and ADC were assessed as 4.5 and 2.0×10^{-3}mm^2/sec. This case is PR case on RECIST criteria, and determined as false-negative on PET/CT and true-positive case on DWI.

Table 1. Differences of ADC and SUV_{max} among PR, SD and PD groups.

		Group		
		PR (n=18)	SD (n=40)	PD (n=6)
ADC ($\times10^{-3}$mm^2/sec)	Mean ± SD	2.05±0.40	2.68±0.60*	3.00±0.33*
SUV_{max}	Mean ± SD	5.54±1.77	6.77±2.73	13.88±4.28*, **

SD: Standard deviation; PR: Partial response; SD: Stable disease; PD: Progressive disease; *: Significant difference with PR group ($p<0.05$). **: Significant difference with SD group ($p<0.05$).

Table 2. Feasible threshold value and diagnostic Capability for Differentiation of PR from SD or PD groups on DWI and FDG-PET/CT.

	Feasible threshold value	SE (%)	SP (%)	PPV (%)	NPV (%)	AC (%)
ADC ($\times10^{-3}$mm^2/sec)	2.1	89.1	44.4	80.3	61.5	76.6
		(41/46)	(8/18)	(41/51)	(8/13)	(49/64)
SUV_{max}	3.9	89.1	11.1*	70.7	28.3	67.2*
		(41/46)	(2/18)	(41/58)	(2/7)	(43/64)

SE: Sensitivity; SP: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; AC: Accuracy; *: Significant difference with ADC ($p<0.05$).

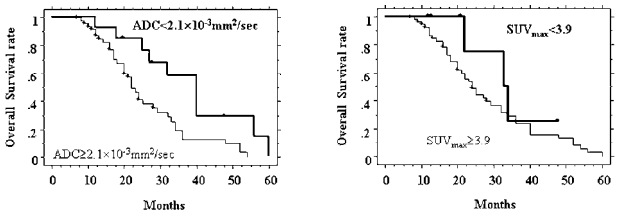

Figure 2. Overall survival periods of two groups divided by feasible threshold values of ADC and SUV_{max}.
ADC demonstrated significant difference of overall survival between two groups divided by the threshold value ($p<0.05$), although there were no significant difference between two groups on SUV_{max}.

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