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Diffusion-Weighted Magnetic Resonance Imaging for Early Detection of Chemotherapy Resistance in Non-Small Cell Lung Cancer

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Background: The aim of this study was to examine the role of magnetic resonance imaging-diffusion weighted imaging (MRI-DWI) in the early detection of chemotherapy resistance in non-small cell lung cancer (NSCLC) patients.

Material/Methods: MRI-DWI and computed tomography (CT) were carried out in 75 patients with newly diagnostic NSCLC before and after first, second, fourth, and sixth cycles of chemotherapy. Resistance to chemotherapy was assessed based on the change in the largest tumor diameter after chemotherapy. Diffusion of water molecule in each lesion was quantitatively measured by apparent diffusion coefficient (ADC). The diagnostic results of DWI after first and second cycle of chemotherapy were analyzed by the area under receiver operating characteristics curve (ROC).

Results: Among the patients, 43 patients were chemo-resistance while 32 patients were chemo-sensitive. The ADC changing rate between second and first cycle of chemotherapy was significantly higher in chemo-sensitive patients compared with chemo-resistance patients ($t=3.236$, $P=0.002$). The ROC showed cutoff values of the ADC changing rate after first and second cycles of chemotherapy for resistance/sensitive discrimination were 23.6% and 5.56%, respectively. DWI after first and second cycles of therapy showed sensitivities of 55.8% and 55.8%, specificities of 65.6% and 87.5%, and area under ROC of 0.568 and 0.733, respectively.

Conclusions: ADC changing rate between first and second cycles of chemotherapy could sensitively distinguish chemo-sensitive and chemo-resistant tumors at earlier stages, which may direct treatment adjustment and improve the prognosis of patients.

MeSH Keywords: **Carcinoma, Non-Small-Cell Lung • Diffusion Magnetic Resonance Imaging • Maintenance Chemotherapy**

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Background

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of newly diagnosed lung cancers and nearly one-third of patients have advanced/metastatic NSCLC at initial diagnosis [1]. Chemotherapy is still the most commonly used treatment for NSCLC. Most of the patients are sensitive to drugs at the early stage of chemotherapy, showing a significant reduction in tumor size and symptoms, but many patients are prone to drug resistance in the later period, resulting in poor outcomes [2,3]. Therefore, early detection of chemotherapy-resistance can guide the adjustment of clinical treatment programs in a timely manner, significantly improving the patient's prognosis. At present, the evaluation of treatment efficacy and drug resistance of chemotherapy in lung cancer generally conforms to the Response Evaluation Criteria in Solid Tumors (RECIST1.1) [4–6], which evaluates the changes in the maximum diameter of target lesions on computed tomography (CT). However, due to the late occurrence of morphological changes in tumors, at least 4 cycles of chemotherapy would typically be used before drug resistance would be determined, delaying the timing of treatment and wasting medical resources [4].

Diffusion-weighted imaging (DWI) is a functional imaging technique that quantitatively assesses the movement of water molecules in tissues. It is a radiation-free, non-invasive, and contrast-free examination method [7,8]. More and more studies show that DWI plays an increasingly important role in the early assessment and prediction of therapeutic efficacy of lung cancer [9–11]. However, there is no report on the application of DWI in determining resistance of lung cancer in the early stages of chemotherapy.

The apparent diffusion coefficient (ADC) can quantitatively reflect the ability of water diffusion. The degree of diffusion is related to cell density and cell membrane integrity in tissues. In tumors, the large cell density and increased internal structure density of cells results in limited diffusion of water molecules, leading to increased DWI signal and decreased ADC value. Effective anti-tumor therapy induces cell apoptosis, necrosis, and cell lysis, thus reducing tumor density and cell membrane damage. Therefore, water diffusion becomes easier, resulting in decreased DWI signal and increased ADC value. In this study, we dynamically monitored the changes of ADC values at multiple time points within 2 cycles of chemotherapy for NSCLC. Our study will help to make early judgments on drug resistance and guide clinical adjustments of treatment plans in a timely manner.

Material and Methods

Patients

Between July 2010 and October 2016, 75 newly diagnosed NSCLC patients (including 44 males and 31 females) from Taishan Medical University were treated for 4–6 cycles of chemotherapy. Among them, 30 cases were squamous cell carcinoma, 43 cases were adenocarcinoma, and 2 cases were adenosquamous carcinoma. Among these patients, 68 cases were TNM3 stage and 7 cases were TNM4 stage. Inclusion criteria were as follows: 1) patients with primary NSCLC; 2) patients did not receive any treatment before chemotherapy; and 3) patients without progression after 2 cycles of chemotherapy. The exclusion criteria were as follows: 1) patients with contraindications to magnetic resonance imaging (MRI); 2) chemotherapy history in other hospitals; 3) recurrent cancer after surgery; 4) disease progressed after 2 cycles of chemotherapy; 5) patients who dropped out of the study due to severe chemotherapy side effects; and 6) patients whose ADC values cannot be obtained. Informed consents were obtained from every patient and the study was approved by the ethics review board of Taishan Medical University.

MRI protocol

All examinations were performed using GE Signa HDe 1.5T MRI equipment (GE Healthcare, Chicago, IL, USA) and an 8-channel body array surface coil. Chest MRI and DWI images for all patients were performed. T2WI was performed based on fast relaxation fast spin-echo. MRI images were acquired using the following parameters: layer thickness of 6.0 mm without interval scanning; TR range, 3500–5000 ms; TE, 90–105 ms; number of excitations (NEX), 2; echo train length (ETL), 17; field of view (FOV), 36 cm; and, matrix, 320×224. DWI was conducted by applying a single-shot echo-planar imaging sequence in horizontal axis, using the following parameters: TR, 6000 ms; TE, 48.9 ms; NEX, 4; FOV, 36 cm; a slice thickness of 5 mm; an interval of 1 mm; scanning time, 64 s; matrix, 128×128; and, b value (diffusion sensitizing factor) of 0 and 500 s/mm². Array spatial sensitivity encoding technique was also used with the R value of 2.

DWI was acquired at 3 time points: one week before first chemotherapy cycle, the end of the first chemotherapy cycle (about 3 weeks after the start of chemotherapy), and the end of the second chemotherapy cycle (about 6 weeks after the start of chemotherapy).

MRI analysis

All MRI images were reviewed by 2 radiologists with 5 years of experience. DWI images and the ADC maps were generated by

Table 1. Clinical characteristics of non-small cell lung cancer patients.

Variables	Chemotherapy resistant (n=43)	Chemotherapy sensitive (n=32)	χ^2	P
Age	61.79±8.198	62.25±7.931	0.243	0.808
Sex (Female: Male)	20: 20	12: 23	0.296	0.586
Tumor size	4.095±2.100	3.922±1.378	0.406	0.686
Initial ADC value ($\times 10^{-3}$ mm ² /s)	1.11±0.329	1.12±0.338	0.034	0.973

ADC – apparent diffusion coefficient. The χ^2 test was used. The χ^2 value was the statistic value of χ^2 test.

Table 2. Change rate of ADC after first-round and second-round chemotherapy.

Variables	Chemotherapy resistant	Chemotherapy sensitive	Z	P
ADC change rate after first-round chemotherapy (%)	28.39±36.55	41.58±53.48	-1.007	0.314
ADC change rate between first- and second-round chemotherapy (%)	6.82±22.67	22.0±0.16	-3.433	0.001

ADC – apparent diffusion coefficient. Mann-Whitney U Test was used. The Z value was the statistic value of the Mann-Whitney U Test.

calculating the ADC value in each pixel of each slice, using the Functool software in an AW4.3 workstation (GE Healthcare). The criterion for NSCLC tissue was the absence of hyperintensity on the DWI sequence and absence of hypointensity on T2-weighted images in the peripheral zone at a site of biopsy-proven benign tissue. Regions-of-interest (ROIs) were drawn manually by the reviewing radiologist on ADC maps in the center of each visible tumor and at sites of biopsy-proven benign tissue. The ROIs were drawn to encompass the largest area of NSCLC or benign tissue without including the tumor margins. Mean signal intensity values (ADC) and SDs in the ROI were automatically determined by the Functool software. The ADC changing rate was calculated after first and second cycle of chemotherapy. ADC changing rate after first cycle=(ADC after first cycle chemotherapy-ADC before chemotherapy)/ADC before chemotherapy $\times 100\%$; ADC changing rate after second cycle=(ADC after second cycle chemotherapy-ADC after first cycle chemotherapy)/ADC after first cycle chemotherapy $\times 100\%$.

Assessment of chemotherapy resistance

Chest CT scan was used to evaluate the response to chemotherapy after 4–6 cycles of therapy protocol. Slice spiral CTs were carried out on all patients using Philips 256-slice Brilliance CT system (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA). Supine position was adopted using the following parameters: a slice thickness of 5 mm, slice spacing of 5 mm, tube voltage of 120-kVp, pitch of 1.0, and tube current of 250 mA. CT was performed at 4 time points: the end of second cycle, the end of fourth cycle, the end of sixth cycle, and 4 weeks after the end

of sixth cycle. For chemotherapy resistant patients, the largest diameter of lesion must have increased to 120% when comparing either pair of the latter and former time points. Otherwise, the patient was classified as sensitive.

Statistical analysis

Statistical analysis was performed using the SPSS software package version 17.0. The χ^2 test and Mann-Whitney U test were used to analyze clinical characteristics and the changes of ADC value, respectively. The receiver operating characteristics curve (ROC) curve was generated and z-test was used for comparing area under ROC (AUC). $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of patients

Of the 75 NSCLC patients, 43 were chemotherapy-resistant, whereas the other 32 were sensitive to chemotherapy. There were 15 patients who received 4 cycles of chemotherapy and the other 60 received 6 cycles of chemotherapy. No significant difference in age, sex, and tumor size was found between chemotherapy-resistant and chemotherapy-sensitive patients (Table 1). Importantly, the initial ADC values between the 2 groups of patients were similar (Table 1).

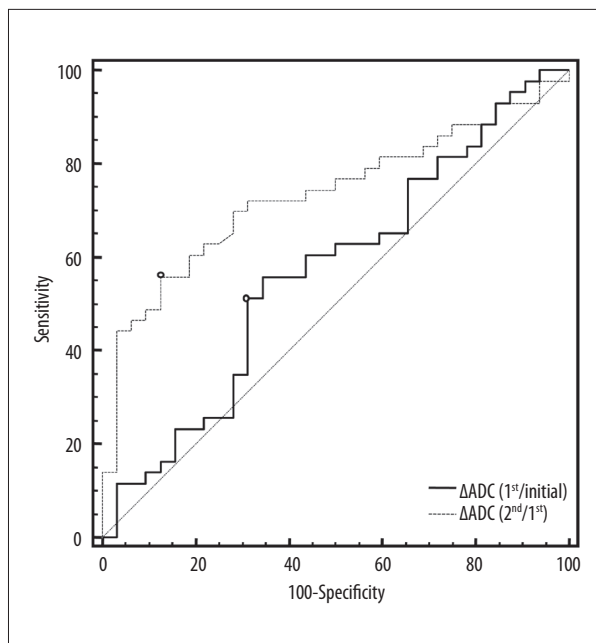


Figure 1. The receiver operating characteristics curve of ADC value for diagnosing chemotherapy resistance for NSCLC. The changing rate of ADC value after first and second cycle of chemotherapy was used. The small circles on the lines indicate the optimal cutoff values of ADC changing rate of first and second therapy. Area under curve: 0.568 for first cycle and 0.733 for second cycle ($z=1.672$, $P=0.095$). ADC – apparent diffusion coefficient; NSCLC – non-small cell lung cancer.

Diagnostic value of diffusion-weighted MRI for chemotherapy resistance in NSCLC

After the first cycle of chemotherapy, the ADC change rate of sensitive patients was higher than that of resistant patients, however, no statistical difference was found (Table 2). In contrast, the second cycle of chemotherapy significantly increased the ADC change rate of sensitive patients when compared with that of resistant patients (Table 2). After the first and second cycle of chemotherapy, the AUC of ADC changing rate on DWI for the sensitive/resistant discrimination was 0.568 and 0.733, respectively (Figure 1), showing no significant difference ($z=1.672$, $P=0.095$). The ROC curve showed optimal cutoff values of ADC changing rate on DWI to be 23.6% and 5.56% for the effect of first and second therapy, respectively (Figure 1). After first-cycle therapy, the sensitivity of DWI was 55.8%, the specificity was 65.6%, the positive predictive value (PPV) was 68.6%, and the negative predictive value (NPV) was 52.5% (Figure 1). After second-cycle therapy, the sensitivity of DWI was 55.8%, the specificity was 87.5%, the PPV was 85.7%, and the NPV was 59.6% (Figure 1). These results indicated the ADC changing rate between the second and first cycles of chemotherapy can be used for the predication of drug resistance.

Compared with that after first-cycle therapy, the ADC of all 32 chemotherapy-sensitive patients was increased after second-cycle therapy (Figure 2). In contrast, the ADC was decreased in 14 out of 43 chemotherapy-resistant patients (Figure 3).

Discussion

Lung cancer has the highest morbidity and mortality among all cancers worldwide [12]. Despite the significant advances in the molecular mechanisms of lung cancer and studies on lung cancer genomics in recent years, the 5-year overall survival rate is still as low as 16% (in the USA), with little improvement in the past 30 years [13]. Although low-dose chest CT screening has improved the early detection rate of lung cancer, about 70% of patients are diagnosed at late stages due to the lack of universal application of such screening [14,15]. Those patients thus lose the opportunity of surgery, rendering chemotherapy the main treatment for them. Drug resistance of lung cancer is one of the main reasons for tumor chemotherapy failure [13]. Therefore, if the drug resistance of lung cancer chemotherapy can be detected early, the treatment plan can be adjusted in time, leading to significantly improved treatment effect.

Until now, the evaluation of chemotherapy resistance in lung cancer mainly relies on RECIST system [16,17], which needs a long time before the morphology changes appears [18]. Clinically, CT images are used for the assessment of the efficacy firstly after the end of 2 cycles of chemotherapy [4]. The treatment would be continued for the effective and stable cases according to the original chemotherapy protocol, and reassessment is performed every 2 cycles thereafter [4–6]. Normally at least 4 cycles of chemotherapy would be administrated before drug resistance was determined, largely delaying the timing of treatment and wasting medical resources, as well as increasing the economic burden of patients [4]. Therefore, early detection of drug resistance of tumors to guide the adjustment of treatment programs in time can significantly improve the patient's prognosis.

As a non-invasive functional imaging technique, DWI can reflect changes in cell density and activity after treatment of tumors at the molecular level, far earlier than the conventional morphological changes, and evaluate the efficacy of treatment at the early stage [18]. The value of DWI in the early evaluation of the therapeutic effect of NSCLC has been studied intensively, which has been recognized by medical profession [19,20]. However, there is no study on the effect of DWI in early detection of drug resistance in lung cancer.

In a previous study, Yabuuchi et al. found that patients with significant elevated ADC value ($\Delta\text{ADC}\%$ threshold of 26%) at 3–4 weeks after chemotherapy had longer progression free

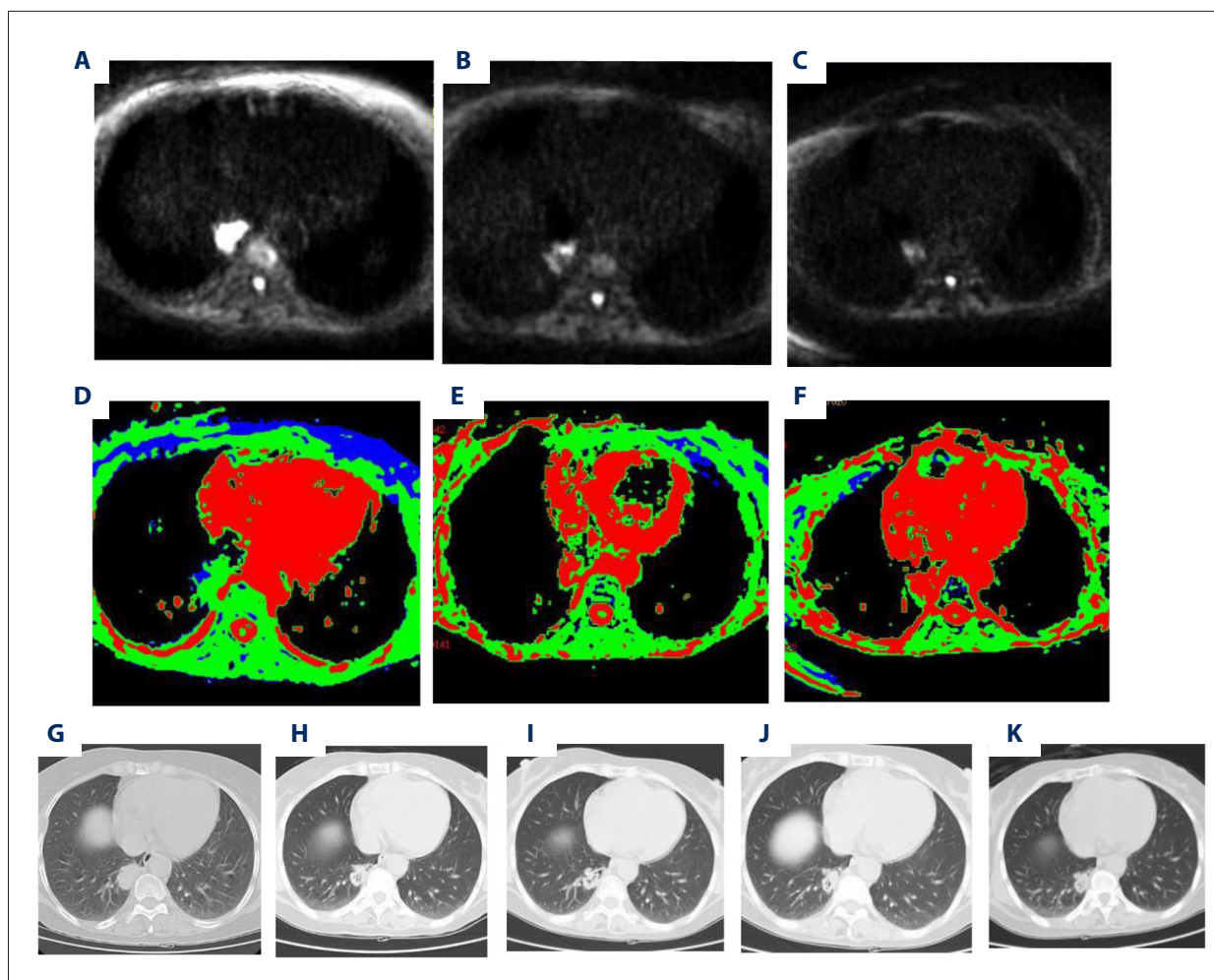


Figure 2. DWI and CT images of a typical chemotherapy sensitive patient. The images of a 57-year-old female patient with peripheral lung cancer in the lower lobe of right lung (moderately differentiated adenocarcinoma) were shown. (A–C) DWI images before (A), at the end of first chemotherapy cycle (B), and at the end of second chemotherapy cycle (C). (D–F) ADC values before (D, $1.12 \times 10^{-3} \text{ mm}^2/\text{s}$), at the end of first chemotherapy cycle (E, $1.83 \times 10^{-3} \text{ mm}^2/\text{s}$), and at the end of second chemotherapy cycle (F, $2.06 \times 10^{-3} \text{ mm}^2/\text{s}$). (G–K) CT images before chemotherapy (G) at the end of second cycle (H), the end of fourth cycle (I), the end of sixth cycle (J), and 4 weeks after the end of sixth cycle (K). DWI – diffusion weighted imaging; CT – computed tomography; ADC – apparent diffusion coefficient.

survival and overall survival time [11]. In addition, research by Tsuchida et al. showed similar results ($\Delta\text{ADC}\%$ threshold of 21.5%) [21], indicating that early changes in ADC values can predict a patient's long-term prognosis, and may provide an important reference for timely adjustment of treatment options for patients with poor responses. However, they did not evaluate the effect of ΔADC on drug resistance of tumors. In this study, the change rate of ADC value after 3 weeks of chemotherapy in the non-drug resistant group was higher than that in the resistant group. The $\Delta\text{ADC}\%=23.6\%$ was used as the critical value, which had higher sensitivity and specificity in monitoring the drug resistance of lung cancer. That is, if the ADC value is increased after 3 weeks of chemotherapy, it indicates that the tumor is less likely to be resistant and has

a good prognosis, which is consistent with the studies of Yabuuchi et al. [11] and Tsuchida et al. [21].

Here, we evaluated the usefulness of DWI by dynamically monitoring the changes of ADC during 2 cycles of chemotherapy. Our study found that the ADC change rate in chemo-sensitive patients versus chemo-resistant patients was similar after first cycle of chemotherapy. However, the ADC changing rate between the second and first cycles of chemotherapy was significantly higher in chemo-sensitive patients compared with chemo-resistant patients, indicating that the ADC changing rate between the second and first cycles of chemotherapy can be used for the predication of drug resistance. We also analyzed the diagnostic results of DWI after first and second cycle of

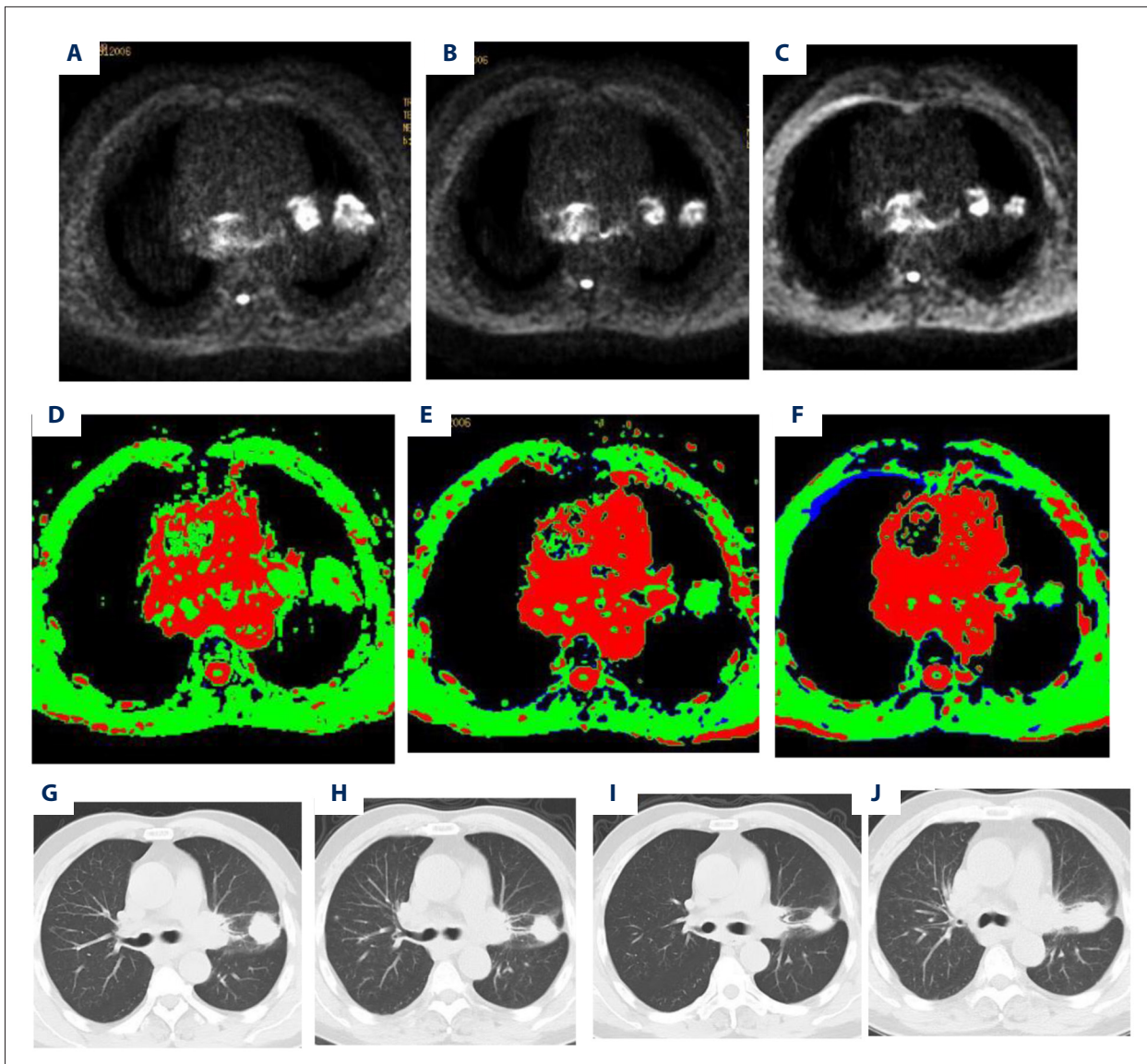


Figure 3. DWI and CT images of a typical chemotherapy resistant patient. The images of a 60-year-old male patient with poorly differentiated adenocarcinoma and adenosquamous carcinoma in left lung were shown. (A–C) DWI images before (A), at the end of first chemotherapy cycle (B), and at the end of second chemotherapy cycle (C). (D–F) ADC values before (D, $1.12 \times 10^{-3} \text{ mm}^2/\text{s}$), at the end of first chemotherapy cycle (E, $1.31 \times 10^{-3} \text{ mm}^2/\text{s}$), and at the end of second chemotherapy cycle (F, $1.09 \times 10^{-3} \text{ mm}^2/\text{s}$). (G–J) CT images before chemotherapy (G) at the end of second cycle (H), the end of fourth cycle (I), and the end of sixth cycle (J). DWI – diffusion weighted imaging; CT – computed tomography; ADC – apparent diffusion coefficient.

chemotherapy by calculating AUC, specificity and sensitivity. Although no significant change in ADC rate was found between second/first cycles and first cycle/initial time point, ADC changing rate between second and first cycles showed higher specificity and PPV, suggesting its higher predictive value. The reason may be that the rate of change in the ADC value after the first cycle reflects the microscopic changes of tumors before and after chemotherapy, while the rate of change of ADC values during the first and second cycles reflects the characteristics

of tumor between the 2 drug cycles. Therefore, the latter can better reflect the tumor response to different cycles of chemotherapeutic drugs and can be used to monitor drug resistance. Compared with that after first cycle, the ADC value after the second cycle was increased in all the 32 chemo-sensitive patients, whereas the ADC value after the second cycle was decreased to different extent in 14 out of 43 chemo-resistant patients. Thus, we speculate that drug resistance probably occurs if the ADC value after the second cycle of chemotherapy

decreases compared with that after first cycle, and it is the time to adjust treatment protocol.

There are still some limitations in this work. First, the number of cases was relatively small, and larger samples are needed to further demonstrate the results of the study. Second, we did not classify the NSCLC patients with different pathological types due to the small number of cases. Thus, the influence of histological differences on drug resistance cannot be excluded. Third, different equipment types, different b-values, and different parameter choices would affect the ADC value. Finally, the sensitivity and specificity are not high enough. In future studies, we will use MR perfusion imaging in combination with MRI-DWI to further improve the diagnostic sensitivity and specificity in predicting lung cancer resistance. Therefore, it is still necessary to conduct multi-center research to develop general standards.

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Conclusions

In summary, ADC changing rate between first and second cycles of chemotherapy could distinguish chemo-sensitive and chemo-resistant tumors at earlier stages in a relatively accurate way, which may direct treatment adjustment and improve the prognosis of patients.

Conflict of interest

None.