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Magnetic resonance (MR) imaging for tumor staging and definition of tumor volumes on radiation treatment planning in nonsmall cell lung cancer

A prospective radiographic cohort study of single center clinical outcome

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Abstract

We investigate the impact of magnetic resonance (MR) on the staging and radiotherapy planning for patients with nonsmall cell lung cancer (NSCLC).

A total of 24 patients with NSCLC underwent MRI, which was fused with radiotherapy planning CT using rigid registration. Gross tumor volume (GTV) was delineated not only according to CT image alone (GTV_{CT}), but also based on both CT and MR image ($GTV_{CT/MR}$). For each patient, 2 conformal treatment plans were made according to GTV_{CT} and $GTV_{CT/MR}$, respectively. Dose-volume histograms (DVH) for lesion and normal organs were generated using both GTV_{CT} and $GTV_{CT/MR}$ treatment plans. All patients were irradiated according to $GTV_{CT/MR}$ plan.

Median volume of the $GTV_{CT/MR}$ and GTV_{CT} were 105.42 cm^3 and 124.45 cm^3, respectively, and the mean value of $GTV_{CT/MR}$ was significantly smaller than that of GTV_{CT} (145.71 ± 145.04 vs 174.30 ± 150.34, $P < 0.01$). Clinical stage was modified in 9 patients (37.5%). The objective response rate (ORR) was 83.3% and the l-year overall survival (OS) was 87.5%.

MR is a useful tool in radiotherapy treatment planning for NSCLC, which improves the definition of tumor volume, reduces organs at risk dose and does not increase the local recurrence rate.

Abbreviations: CT = computed tomography, CTV = clinical target volume, DVH = dose-volume histograms, DWI = diffusion-weighted imaging, GTV = gross tumor volume, MR = magnetic resonance, NSCLC = nonsmall cell lung cancer, ORR = objective response rate, OS = overall survival, PET/CT = positron emission tomography/computed tomography, PFS = Progression-Free-Survival, PTV = planning target volume, RT = radiation therapy.

Keywords: magnetic resonance, nonsmall cell lung cancer, radiation plan

1. Introduction

Patients with locally advanced nonsmall cell lung cancer (NSCLC) receive external beam radiation therapy as a part of their treatment. When defining target volumes, radiation oncologists must rely heavily on images because in most cases there are no other ways to know the scope of original tumor and the true status of individual lymph nodes, which makes it difficult to determine the appropriate target volume. Radiation therapy (RT) commonly uses computed tomography (CT) to delineate the target lesion and normal tissues. Unfortunately, CT is not always accurate when complicated by atelectasis,[1] Also, the sensitivity of CT imaging is low for determining the benign or malignant lymph nodes.[2,3] Therefore, it is urgent to supplement some other measures to make up for the deficiencies of CT in the definition of the gross target volume (GTV). Positron emission tomography/computed tomography (PET/CT) offer a better indication of the actual extent of metabolic active tumor, at present, PET/CT is the gold standard for staging and treatment planning in lung cancer. However, some study has provided that the accuracy (96.2%) for lymph node stations by magnetic resonance (MR) was significantly higher than that (94.3%) by PET/CT.[4] Furthermore, it costs more to take the PET/CT examination.

Clinical studies indicate that MR is a useful imaging tool to differentiate between inflammation and malignance, such as lung atelectasis and status of mediastinal lymph node.[5] MR is superior to CT in defining local extent of tumors, possible brachial plexus involvement, and chest wall or mediastinal invasion.[6] Recent researches have proved that T2-weighted MR with diffusion-weighted imaging (DWI) might have complemen-

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tary roles in staging, treatment response assessment, and radiation planning.[7] MR can allow the tumor margin to be accurately delineated.[8] Therefore, as a new simulator, MR has many potential advantages in radiotherapy planning, because it can decrease the interobserver variability amongst thoracic radiation oncologists. In addition to accurate staging, MR has the potential to improve radiotherapy planning by its precise delineation of primary tumor and lymph nodes. As for, MR imaging has been increasingly used for target volume delineation in radiotherapy planning to deliver the optimal radiation dose to tumors and to decrease radiation exposure to dose-limiting normal organs such as lungs and esophagus.[9] In this study, we focus on the role of MR-simulator in radiotherapy for NSCLC.

2. Materials and methods

2.1. Study design

This was a single center pilot study in patients with local advanced NSCLC who received radiotherapy simulated with CT and MR at Peking University Cancer Hospital & Institute according to standard guidelines between March 2014 and September 2014. This study was approved by the Peking University School of Oncology, Beijing Cancer Hospital & Institute Review Board for the Study of Human Subjects, written consents have been obtained from all the participants. Twenty-four consecutive patients were enrolled in this prospective study. Criteria for enrollment include (1) ages >18 years; (2) locally unresectable stage III NSCLC; (3) life expectancy $\geq$6 months; (4) Karnofsky performance status (KPS) $\geq$80; (5) good pulmonary function tests.

2.2. CT simulation

Immobilization and CT simulation were performed with a 40-row spiral Sim-CT scanner (Siemens AG, Germany) 30 seconds after intravenous administration of contrast agent (1.0 mL/kg; 320 mg/100 mL iodine) at an injection rate of 3.0 mL/s using an auto-bolus injector (MEDRAD VISTRON CT injection system) if the patient was not allergic to contrast agent. Before the CT simulation, patients were immobilized in the customized radiation body membrane. The treatment position is supine with both arms above the head and on a dedicated immobilization and laser marker system. The patients were scanned using 3-mm slice thickness. The GTV delineation included the primary tumor on lung window (W = 1600, L = –600) and lymph nodes larger than 1 cm on mediastinal setting (W = 400, L = 20), according to the radiologists. The clinical target volume (CTV) was defined as the GTV plus a margin of 6 to 8 mm, and the planning target volume (PTV) as the CTV plus a margin of 5 to 10 mm according to motion variation.

2.3. MR simulation

For MR images, a 3.0T scanner (Magnetom Skyra, Siemens AG, Germany) was used, which was equipped with a gradient system with a slew rate of 160 mT/m/ms and amplitude of 45 mT/m/ms. Patients were scanned at the same position as CT simulation using the same fixation device. MR images were under the free-breathing condition without externally administered contrast. Respiratory triggering was used to compensate for motion artifacts. The scan time for DWI was approximately 4 minutes. According our previous study, we choose 600 s/mm^2 as the reference value, DWI was acquired in the transverse plane with b values of 600 s/mm^2 during breath-holding. Prior to DWI, T1- and T2-weighted images were obtained in the transverse plane in each patient. T1-weighted fast spin echo images (repetition time/echo time, 600–900 ms/5.8 ms) and respiratory-gated T2-weighted fast spin echo images (repetition time/echo time, 6000–8000 ms/91 ms) were obtained with FOV of 360 to 380 mm, section thickness of 3 mm routinely. The metastatic lymph nodes were decided according to different images from MR. $GTV_{CT/MR}$ was performed according to simulating CT and coregistered simulating MR. The CTV was defined as the GTV plus a margin of 6 to 8 mm, and the PTV as the CTV plus a margin of 5 to 10 mm according to motion variation.

2.4. Image fusion and target volume delineation

Following image acquisition, MR images were registered with the CT acquired for treatment planning system (Pinnacle system, Philips Medical Systems, Milpitas, CA). The MR (including DWI, T1- and T2-weighted image) and CT images were subsequently fused by means of a dedicated RT planning system image fusion tool based on a mutual information algorithm.

The pathological lymph nodes were specified by an experienced MR specialist without knowledge of the CT scan data, and by an experienced CT specialist without knowledge of the MR scan data, respectively. After separate reading of CT and MR images, fusion image sets were read according to CT and MR information. A final conclusion was reached in agreement between both readers. If the MR scan was negative in the mediastinum and the CT scan positive, the mediastinum was considered negative and was hence not included in the $GTV_{CT/MR}$. On the other hand, if the lymph nodes were positive on MR scan but negative on CT scan, the whole pathological anatomical region of the mediastinum was taken as $GTV_{CT/MR}$. If patients were complicated by atelectasis, $GTV_{CT/MR}$ were delineated on DWI CT/MR maps.

2.5. Treatment

All patients received conventional fractionated radiotherapy (2 Gy per fraction,5 days per week). The total irradiation dose ranged from 60 to 66 Gy, with a median 64 Gy. All patients were treated with concomitant chemotherapy, 2 cycle paclitaxel (145 mg/m^2) and cisplatin (70 mg/m^2) every 3 weeks during radiotherapy followed by 2 cycles consolidation therapy.

2.6. Follow-up

The follow-up results served as the gold standard. All patients underwent follow-up office visits at 4 weeks after completing radiation therapy and monthly for the first half year, and then at 3 months intervals. At each follow-up, evaluations included a complete history, physical examination, blood routine, renal and hepatic function, and a CT and MRI scan of the thorax. Compared with previous images, estimates of local control, progression-free survival (PFS), and overall survival (OS) were calculated from the initiation of treatment. All the evaluations were performed by radiologists who were blinded to the treatment given, using the same guidelines.

2.7. Statistical methods

Statistical analysis was performed using an SPSS statistical package (Version 16.0, Chicago) and $P < 0.05$ was considered statistically significant. Continuous data were expressed as mean

±standard deviation and category data were presented as frequency and percentage. Continuous data were analyzed using paired-samples T test. PFS was calculated from the initiation of treatment to demonstrated radiological progression or death from any cause. OS was calculated from the diagnosis of disease to death from any cause. PFS and OS were estimated using the Kaplan–Meier curves.

3. Results

3.1. Patient characteristics

As a result, a total of 24 patients were included in this study. The detailed characteristics of all patients are shown in Table 1. However, 17 patients were complicated by atelectasis.

3.2. MR and CT correlations in lymph node status

All but 4 of the 24 patients had N2 or N3 disease on CT scan. CT-stage distribution was stage IIIA: 12 patients and stage IIIB: 12 patients. The MR staging was stage IIIA: 16 patients and stage IIIB: 8 patients. The lymph node involvement based on CT vs MR is given in Table 2. The metastatic lymph nodes were first determined according to CT image, then after MR diagnosis, 14 patients were ruled out and 2 patients were involved.

3.3. Comparison of radiotherapy plans on CT and CT/MR

The median volume of the $GTV_{CT/MR}$ and GTV_{CT} were 105.42 cm^3 and 124.45 cm^3 respectively, the mean value of $GTV_{CT/MR}$ was significantly smaller than that of GTV_{CT} (145.71±145.04 vs 174.30±150.34, $P<0.01$). The clinical stage was modified in 9 patients (37.5%), among which 7 patients were due to under staging and 2 patients were because of over staging.

Compared with GTV_{CT}, $GTV_{CT/MR}$ decreased by 0% to 25% in 15 cases, by 25% to 52% in 7 cases and increased from 0% to 17% in 2 patients. In all, GTV volumes changed more than 20% in 9 patients (37.5%). Examples of the GTV differences between CT and CT/MR are depicted in Fig. 1.

Table 1

Patient characteristics.

	Adenocancinoma	Squamous cell cancinoma
	N (%)	N (%)
Patients	4 (16.7)	20 (83.3)
Age	59.5±9.3	61.9±10.16
Gender		
Male	4 (16.7)	18 (75)
Female	0	2 (8.3)
Stage		
IIIA	2 (8.3)	10 (41.7)
IIIB	2 (8.3)	10 (41.7)
Site		
LUL	1 (4.1)	7 (29.2)
LLL	0	0
RUL	1 (4.1)	5 (20.8)
RML	0	4 (16.7)
RLL	2 (8.3)	4 (16.7)
Atelectasis	3 (12.5)	14 (58.3)

LLL = left lower lobe, LUL = left upper lobe, RLL = right lower lobe, RML = right mean lobe, RUL = right upper lobe.

Table 2

Involved lymph node stations on CT vs MR scan.

Patient	Involved lymph node station	
	CT scan	MR scan
1	2R, 4R, 4L, 7, 10L	2R, 4R, 4L, 7, 10L
2	–	10R, 7
3	1R, 4R, 5, 7, 10R	1R, 4R, 7, 10R
4	4, 7, 10R	4, 7, 10R
5	–	4R, 10R
6	4R, 4L, 5, 7, 10L, SLN	4R, 5, 7, 10L, SLN
7	4R, 7, 10R,	7, 10R
8	4R, 10L, SLN	4R, 10L, SLN
9	3A, 4R, 4L, 7	4R, 7
10	2R, 4, 6, 7, 10R	2R, 4, 6, 7, 10R
11	4R, 5, 10L	10L
12	–	–
13	2R, 4R, 7, SLN	2R, 4R, 7, SLN
14	2R, 4R, 7, 10R	4R, 7, 10R
15	2R, 4R, 4L, 7, 10R, SLN	2R, 4R, 7, 10R, SLN
16	4R, 4L, 7, 10R	4R, 7, 10R
17	2R, 4R, 4L, 7	–
18	4R, 4L, 5, 7, 10L, SLN	7, 10L
19	4R, 4L, 5L, 10L	4L, 10L
20	4R, 7, 10R	4R, 10R
21	3P, 4R, 7	–
22	2R, 4R, 7, 10R	2R, 4R, 7, 10R
23	–	–
24	4R, 7	–

CT = computed tomography, MR = magnetic resonance, SLN = supraclavicular lymph nodes.

3.4. DVH comparison

The DVH comparison showed organ at risk (OAR) based on CT/MR got less exposure compared with plan from CT. The total lung mean dose, total lung V20, mean esophagus dose, and maximal esophagus dose from CT/MR plan were all significantly lower than that of CT plan (all $P<0.05$ or 0.01, respectively) (Table 3). As for healthy lung V5, V20, spine and heart dose, no significant differences were found between the CT/MR plan and CT plan.

3.5. Objective response and local recurrence rates

No patient was lost during the follow-up. Eight patients died by the end of the follow-up; the median follow-up time was 18 months for the surviving patients and 15.5 months (range,

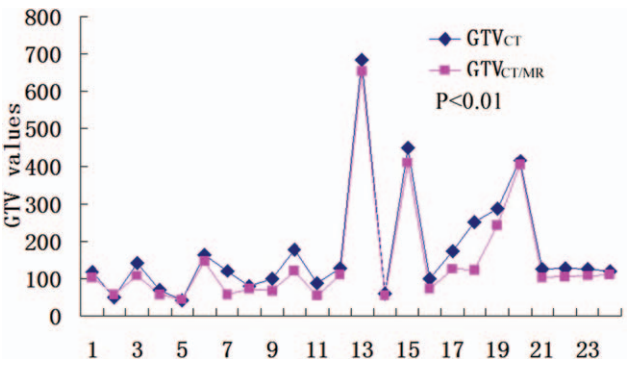

Figure 1. The GTV differences between CT and CT/MR. CT = computed tomography, GTV = gross tumor volume, MR = magnetic resonance.

Table 3

Dosimetric factors of the esophagus and the lung in all patients with both MR and CT (mean ± SEM).

Parameter	MRI/CT	CT	*P*
Lung			
Total lung V20 (%)	20.06 ± 5.19	23.29 ± 6.60	0.05
Total lung mean dose (Gy)	11.65 ± 2.31	13.79 ± 2.56	0.01
Esophagus			
Maximal esophagus dose (Gy)	13.79 ± 2.56	49.57 ± 9.78	0.01
Mean esophagus dose (Gy)	24.90 ± 7.89	28.46 ± 7.39	0.01

CT = computed tomography, MR = magnetic resonance, SEM = standard error of mean.

10–24 months) for the whole group. There was a complete response in 9 (37.5%) patients, a partial response in 11 (45.8%) patients, making an ORR of 83.3%. The l-year OS was 87.5%. The survival curves were depicted in Fig. 2. As shown in Fig. 3, the progression-free survival rate for 1 year was 75% and the median time of treatment failure is 12 months.

Figure 4 listed the failure patterns of the patients. In total, 12 patients were failure, among which 6 patients recurred in the radiation field including primary tumor and nodal areas, 5 patients failed in distant areas, and only 1 patient failed in the margin of radiation field. Among the 5 cases failed in distant areas, 2 patients failed in new nodal areas, and 3 patients failed in brain or liver.

Radiotherapy plans according to CT/MR did not increase the local recurrence rate in the areas out of the radiation field compared with the plans based on CT alone. The highest local recurrence region was in the involved lymph node and primary lesion on CT and MR images. In 1 patient, the local recurrence region was found in the uninvolved lymph node on CT and MR images. In 2 patients, the recurrence place was found in CT but not in MR, but in 1 patient, the recurrence place was found in MR but not in CT.

4. Discussion

Involved field radiotherapy which can reduce the radiation-induced toxicity has been regarded as the standard treatment method for NSCLC. In this method, how to determine the range of tumor and lymph node status has become particularly important. At present, CT is the main tool for target volume delineation of lung cancer radiotherapy, but it cannot correctly distinguish the primary tumor and normal tissue and cannot judge the nature of regional lymph nodes.[10] Therefore, a more effective imaging method for radiotherapy is desirable.

Previous studies have showed that PET/CT has advantages over CT in differentiating malignant from benign lymph nodes of lung cancer.[11,12] Selective mediastinal irradiation on the basis of the PET/CT scan did not result in a high incidence of isolated nodal failures.[13] Therefore, PET/CT has been regarded as a positioning method in lung cancer radiotherapy. But compared with MR, the sensitivity and specificity of PET/CT for individual metastatic lymph node status were lower.[5,7,14–16] MR has a potentially important value for radiotherapy planning.[7,17,18] In

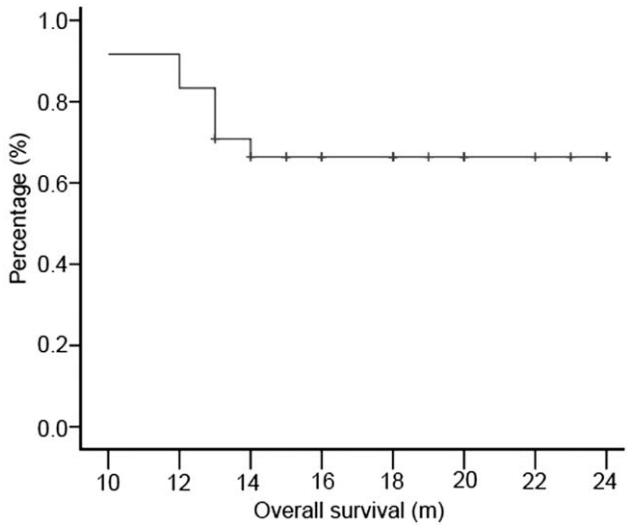

Figure 2. Overall survival of the patients.

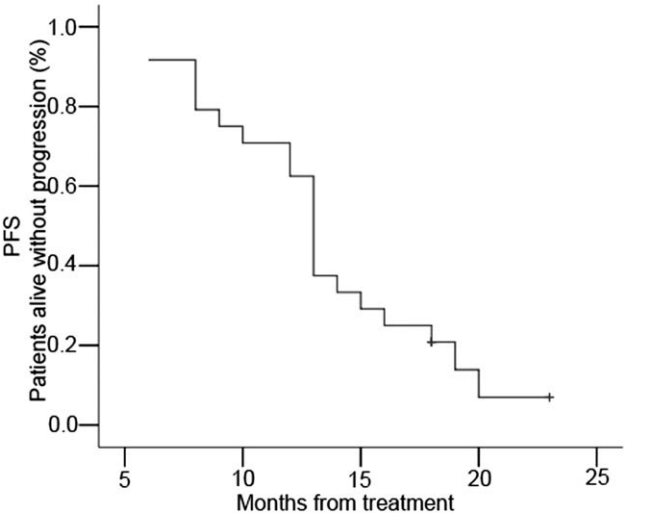

Figure 3. The progression-free survival of the patients.

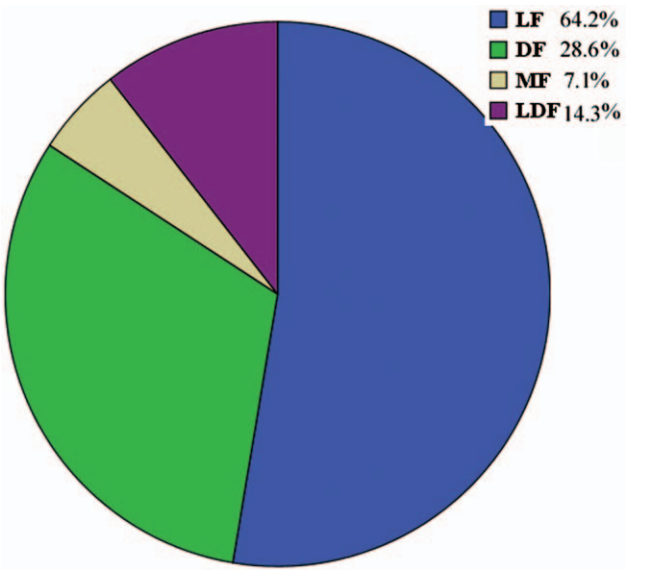

Figure 4. The patterns of failures are shown for 12 patients. DF = distant failure, LDF = local and distant failure, LF = local failure in field, MF = margin failure.

this study, we found that the median volume of $GTV_{CT/MR}$ and GTV_{CT} were 105.42 cm^3 and 124.45 cm^3, respective, and the mean value of $GTV_{CT/MR}$ was significantly smaller than that of GTV_{CT}. The clinical target field was modified in 37.5% patients, among which 7 patients were due to under staging and 2 patients were because of over staging. The information gathered from MR image could have a different effect on target delineation for primary tumors and nodal regions. To date, the addition of MR data in the delineation of the primary tumor, compared with CT data alone, has shown limited value. However, in our study, we found that MR data can safely avoid the CT abnormalities and decrease the target volume.[14–16]

Patients with central lung tumors are often accompanied by atelectasis, it is very important to distinguish the boundaries between incompletely expanded lung tissue and tumor tissue, which is necessary for targeted radiotherapy.[1,19] CT is the most widely available and commonly used method for patients with lung cancer, but it was difficult to distinguish atelectasis of the lung from the tumor using CT alone.[20] PET/CT can provide differentiation of tumor and atelectasis via increased FDG uptake, but this method is very expensive. MR is widely used and remains a promising diagnostic means for tumor imaging because it provides excellent soft tissue contrast and high spatial resolution.[21,22]

MR image not only reflects the anatomical structure of the human body, but also can provide physiological, pathological, and biochemical information, which is considered to be the molecular level of imaging. Therefore, it provides valuable information and has potential for clinical differentiation of central lung carcinoma from atelectasis.[23,24] In our study, compared with GTV_{CT}, $GTV_{CT/MR}$ decreased in 22 cases and increased in 2 patients. In all, GTV volumes changed more than 20% in 9 patients (37.5%). In the 17 patients with atelectasis, the mean $GTV_{CT/MR}$ decreased from −8.36 to 127.58 cm^3 compared with that of $GTV_{CT.}$ At the end of the follow-up, only 1 local recurrence (4.2%) was found at the margin of the target of $GTV_{CT/MR}$, which is comparable to the results observed in other studies.[25–27] The OAR from CT/MR got less exposure compared with from CT alone; therefore, this method may decrease radiation side effects.

The mediastinal lymph node status plays a pivotal role in modern treatment planning. CT is a useful tool for assessment of lymph node involvement. PET/CT has been demonstrated to be highly sensitive even in lymph nodes smaller than 1 cm,[28] but the main disadvantage of PET/CT is the large amount of false-positive results in patients with concurrent inflammatory lymphadenitis.[29,30] Moreover, PET/CT is not as widely available as MR. MR has been considered to be superior to CT in mediastinal staging, and recently, the diagnostic power of integrated MR/CT has been shown to be greater than either CT or MR alone.[31]

Many studies have been carried out to determine the accuracy of MR for the status of mediastinal lymph node. Many researchers have proved that the sensitivity, accuracy, and negative predictive value for mediastinal lymph node by MR were significantly higher than those by PET/CT or CT alone.[31,32] In some studies, diffusion coefficient values of metastatic lymph nodes were significantly lower compared with benign lymph nodes.[31,32] Therefore, we used MR to sketch clinical target in this study. MR imaging have changed the status of metastatic lymph node in 16 patients, including 14 patients rule out and 2 patients bring into metastasis. According to the result of follow-up, only 1 patient with local recurrence proved positive in regional lymph nodes by MR; therefore, this method might not increase the local recurrence rate.

5. Conclusion

MR images combined with CT may help increase significantly the sensitivity for detecting nodal metastasis and defining the lung atelectasis and may have an accuracy that was impossible using CT images alone. Therefore, it may improve target volume delineation and the results obtained from this study encourage further exploration of MR as an adjunct for radiotherapy planning in NSCLC. However, the number of cases in this study is small, and it is difficult to fully explain the result of this study. Further studies are warranted to confirm these findings. Different radiotherapy plans and treatment responds based on DWI images with different *b* values should be compared in the future study.

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