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Research paper

Assessment of treatment response after lung stereotactic body radiotherapy using diffusion weighted magnetic resonance imaging and positron emission tomography: A pilot study

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ABSTRACT

Background and purpose: There is no early predictor of treatment response after lung stereotactic body radiotherapy (SBRT). We conducted this pilot study to evaluate whether serial diffusion weighted magnetic resonance imaging (DW-MRI) or positron emission tomography (PET) could predict response after SBRT.

Material and methods: Early stage non-small cell lung cancer patients who received SBRT were eligible. DW-MRI and PET were undertaken pretreatment and every 3 months after SBRT in the first year. Patients with < 1 year of follow-up were excluded from the analysis. The apparent diffusion coefficient (ADC) value and maximum standardized uptake value (SUV_{max}) of tumors were measured and compared between groups with or without local recurrence (LR).

Results: Fifteen patients were enrolled and the data of 14 patients were analyzed. The median ADC value was significantly lower in patients with LR (n = 3) than in those without LR (n = 11) at 3 and 6 months (1.11 vs. 1.54 and 0.98 vs. 1.69 [$\times 10^{-3}$ mm^2/s]; p = 0.039 and 0.012, respectively) while there was no significant difference pretreatment and at 9 and 12 months after treatment. No significant difference was observed in the SUV_{max} at any time point.

Conclusions: DW-MRI could be an early predictor of treatment response after lung SBRT.

1. Introduction

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, has now been established as a standard treatment for medically inoperable patients [1]. SBRT achieves excellent local control with limited toxicity and could be a treatment option comparable to surgery, even for medically operable patients [2]. The most predominant pattern of failure is distant metastasis, and the local recurrence (LR) rate is reported to be 10–15% [3,4]. The early and accurate diagnosis of isolated LR is important especially for candidates for salvage surgery, because salvage surgery has been shown to be feasible and is related to good prognosis [5,6].

However, diagnosis of LR is very difficult because of the radiographic changes around the irradiated tumor caused by radiation induced lung injury. LR is usually diagnosed using computed tomography (CT) findings, based on the presence of morphologic features or serial change, or using CT in combination with ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG/PET) [7]. Currently, the usefulness of routine serial PET-CT after SBRT has not been determined.

Diffusion weighted magnetic resonance imaging (DW-MRI) is a functional imaging modality that reflects the diffusion motion of water molecules. Change in the apparent diffusion coefficient (ADC) value of tumors, calculated from DW-MRI scans, has been shown to be predictive of treatment response in various cancers [8,9]. Technological advancement of fast imaging techniques has made it possible to obtain DW-MRI with a high b-factor, even in the thoracic region. In addition, previous studies have reported the usefulness of ADC values in predicting treatment response for lung cancer [10,11]. However, there has been no previous study that has examined whether the ADC value is a predictor of LR after lung SBRT.

We conducted the current study to elucidate the role of serial DW-MRI and PET-CT in assessing treatment response after lung SBRT.

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2. Materials and methods

2.1. Patients and study protocol

This study was approved by our institutional review board. Patient eligibility criteria were as follows: (1) pathologically confirmed non-small cell lung cancer; (2) clinical T1a-T2aN0M0 (Union for International Cancer Control staging criteria, 7th edition), staged using PET-CT and brain MRI; (3) Eastern Cooperative Oncology Group performance status 0–2; (4) treatment with SBRT because of inoperability or patient refusal of surgery; and (5) informed consent was obtained.

Follow-up visits were scheduled at 1, 2, 3, 6, 9 and 12 months in the first year and every 3–6 months thereafter. FDG-PET and chest MRI were obtained pretreatment and every 3 months in the first year, that is, at 3, 6, 9 and 12 months. A plain chest CT scan was performed every 3–6 months thereafter. If there was suspicion of disease progression, PET-CT was also undertaken at the discretion of the treating physician. LR was diagnosed when tumor size increased for > 6 months, or abnormal FDG uptake was judged to be viable tumor and not inflammatory change by the diagnostic radiologist. Pathologic confirmation was not mandatory.

2.2. MRI and FDG/PET protocol

Details of the image acquisition protocol and image interpretation have been described previously [12]. All MRIs were obtained using a 1.5T MR unit (Avanto, Siemens, Erlangen, Germany) with a phased-array coil. Initially, axial HASTE images were obtained as an anatomical guide. Subsequently, both T2-weighted and DW-MRI with prospective acquisition correlation (PACE) utilizing sensitivity encoding (SENSE; with a SENSE factor of 2) and echo planar imaging (EPI; with an EPI factor of 96) were obtained. Parameters used in DW-MRIs were as follows: TR/TE, 2746.3–12030.4/72–79 ms; FOV, 320 mm; slice thickness, 4.0 mm; matrix, 96 × 128 mm; and band width, 1860 Hz/pixel and five excitations. All DW-MRIs were acquired with MPG pulses in three directions (the x, y and z axes) with b-values of 0, 500 and 1000 s/mm^2. ADC maps were generated from DW-MRI scans. One author (S.U. with > 10 years of experience in chest imaging) placed three different regions of interest (ROIs) on tumors and measured the mean signal intensity; the ADC value of the tumors was defined as the average of these. All ROIs were made as large as possible and placed in the center of the tumor to avoid artifacts from the tumor/air interface or from blood flow. When establishing ROIs, T2-weighted MRIs were used as a reference to avoid necrotic regions. The respiratory gating method was used for the MRI scan.

As for FDG-PET, 18 F-FDG (~3.7 MBq/kg) was administered to patients after a fasting period of ≥4 h. At 1 h later, images were obtained using a PET/CT scanner (Discovery ST Elite, GE Healthcare Waukesha, WI, USA). First, low-dose CT images were acquired with a 16-detector row scanner during shallow breathing (20–100 mA, using the auto-mA setting with a noise index of 30, 120 kV, 0.6 s tube rotation, slice thickness 3.75 mm, matrix 512 × 512 and a pitch of 1.75). Next, a whole-body PET scan was performed in 3D-acquisition mode with an acquisition time of 2–3 min per bed position. The PET images were attenuation-corrected using the CT data and were reconstructed with a 3D ordered-subsets expectation maximization algorithm. A single observer (S.U.) measured the maximum standardized uptake values (SUV_{max}) of the tumors.

2.3. SBRT procedure

The details of the SBRT procedure at our institution have been published previously [13]. Briefly, gross tumor volume (GTV) was determined on CT images. The internal target volume (ITV) was created to cover the GTV in all the respiratory phases. Respiratory motion was assessed, using four-dimensional CT and X-ray fluoroscopy. A 5 mm margin was added to the ITV to constitute the planning target volume. Irradiation was performed with 6 MV photons. The dose was prescribed to the isocenter. Dose prescription was determined depending on the tumor size and location. The total radiation dose was 48 Gy delivered in 4 fractions for T1a-1b tumors, 56 Gy in 4 fractions for T2a tumors, and 60 Gy in 8 fractions for centrally located tumors within 2 cm of the trachea or proximal bronchial tree, great vessels and other mediastinal structures. Patients were treated on weekdays.

2.4. Statistical analysis

Patients with > 1 year of follow-up were included in the analysis. We divided the patients into two groups based on LR to examine whether there was a difference in the ADC value or SUV_{max}. We compared patients' characteristics between groups, using the Fisher's exact test for categorical data and the Mann-Whitney *U* test for continuous data. We also compared the ADC value or SUV_{max} between groups using the Mann-Whitney *U* test. The P-value was obtained from two-sided tests and considered statistically significant when it was < 0.05.

All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

3. Results

Fifteen patients were enrolled in this study between January and December 2010. One patient died of lung cancer at 7 months after SBRT without evidence of local progression and was excluded from the analysis. The remaining 14 patients were included in this analysis. Patient characteristics are listed in Table 1. The median tumor diameter, pretreatment ADC value and SUV_{max} of all patients were 30 (range 14–42) mm, 1.04 × 10^{-3} mm^2/s (range 0.83–1.29 × 10^{-3} mm^2/s) and 9.10 (range 1.5–30.0), respectively. There was no statistically significant difference between groups in characteristics, as shown in Table 1.

The median follow-up time was 35.5 (range 13.7–68.4) months. At the time of this analysis, three patients were alive and free of lung cancer, one patient was alive with lung cancer, five patients had died of lung cancer and five patients had died from other diseases. Out of 14 tumors treated with SBRT, there were only three LRs. LRs occurred at 9.8, 17.3 and 27.7 months after SBRT. The LR diagnosis of all of these three patients was based on PET-CT findings which showed focal intense FDG uptake. Sputum cytology of one patient was suspicious of malignancy, but histologic confirmation by bronchoscopy or CT-guided biopsy was not performed. No salvage therapy was given to these three patients due to medical comorbidities or poor general conditions. All of these patients died of lung cancer at 13.7, 17.9 and 39.7 months after SBRT. The median follow-up time of patients without local recurrence was 41.4 (range 16.9–68.4) months, and the number of patients and each follow-up period were as follows: 4 for 1–2 years, 1 for 2–3 years, 1 for 3–4 years, 2 for 4–5 years and 3 for > 5 years.

Pretreatment PET and MRI scans were obtained from every patient and also at 3 months after SBRT; however, there were three, two and three patients at 6, 9 and 12 months, respectively who did not undergo chest MRI because of other comorbidities or scan refusal. There were two, one and two patients at 6, 9 and 12 months, respectively who did not receive PET-CT.

We divided patients into two groups, namely a group without LR (n = 11) and a group with LR (n = 3). The ADC values for tumors with or without LR are listed in Table 2.There was no significant difference in pre-treatment ADC values, but the serial change of ADC value after SBRT appeared to differ between the two groups. The ADC value