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FULL PAPER

Is severe emphysema, as defined by quantitative CT measurement, a negative risk factor of radiation fibrosis?

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Objective: To investigate whether patients with emphysema, as evaluated by quantitative CT image measurement, are at risk of developing radiation pneumonitis (RP) after radiotherapy (RT) for non-small cell lung cancer (NSCLC).

Methods: Between March 2011 and June 2015, 68 consecutive patients with Stage I NSCLC treated with a RT dose of 75 Gy given in 30 fractions were enrolled. The median age was 79 years and there were 45 males and 23 females. The number of patients with T_1 and T_2 were 49 and 19, respectively. The severity of emphysema was evaluated by the percentages of the low attenuation area (LAA) of ≤ -860 or -950 Hounsfield unit (HU) and average HU in the whole lung.

Results: The mean difference percentages of LAA of ≤ -860 ($p = 0.0004$) or -950 HU ($p = 0.005$) and average HU ($p = 0.001$) in patients with RP were significantly lower than those in patients without RP. The area under curve (AUC) of average HU was significantly higher than AUC of LAA of ≤ -860 ($p < 0.0001$) or -950 HU ($p < 0.0001$). The RP rate after RT was significantly lower when the average HU values were ≤ -850 HU ($p = 0.0003$).

Conclusion: Patients with emphysema evaluated by average HU (≤ -850 HU) in the whole lung were found to be at low risk of RP after RT.

Advances in Knowledge: Quantitative measurement of average HU from CT images was predicted of RP after RT.

INTRODUCTION

Stereotactic body radiotherapy (RT) is the standard care for patients with medically inoperable stage I non-small cell lung cancer (NSCLC), and has been shown to improve survival compared to observation alone.¹ The elderly population is increasing rapidly in Japan, and thus the incidence of medically inoperable lung cancer is also expected to increase.² Chronic obstructive pulmonary disease (COPD), which is one of the reasons for inoperability of NSCLC, is one of the risk factors for radiation pneumonitis (RP).^{3,4} RP develops in most patients who receive RT for the lung,⁵⁻⁷ and severe RP develops in a small number of cases.⁸

However, it is unclear whether NSCLC patients with pulmonary emphysema (PE) can be treated safely by RT. We previously reported that patients with severe PE classified by Goddard's criteria had a low risk of RP.⁹ However, in Goddard's criteria, PE severity is classified based on the appearance of CT images,¹⁰ and thus the reproducibility of the classification is limited by interobserver variability.

To overcome the limitations of Goddard's criteria, a method for evaluating PE based on the percentage of low attenuation area (LAA) on CT images of lung has been introduced.^{11,12} However, the correlation between the predictions of RP based on this new method of evaluating PE and the actual incidence of RP after RT has not been studied. To address this relation, we examined whether the classification of PE based on the evaluation of LAA on CT images can predict the likelihood of RP following RT.

METHODS AND MATERIALS

Patients

The ethical committee of Tokyo Medical University, Tokyo, approved this study. Between March 2011 and June 2015, 68 consecutive patients with Stage I NSCLC treated by RT a dose of 75 Gy given in 30 fractions at Tokyo Medical University were enrolled. The patients' characteristics are shown in Table 1. The median age was 79 (range, 49–90) years. There were 45 male and 23 female patients, and the numbers of patients with T_1 and T_2 were 49 and

Table 1. Patients' characteristics

	All (<i>n</i> = 68)	Non-pneumonitis (<i>n</i> = 16)	Pneumonitis (<i>n</i> = 52)	<i>p</i> value
Age (years)	78.1 ± 8.0	77.5 ± 6.2	78.2 ± 8.5	0.47
<i>T</i> ₁ : <i>T</i> ₂	49 : 19	13 : 3	36 : 16	0.53
Male : female	45 : 23	10 : 6	35 : 17	0.77
Surgery + : -	37 : 31	9 : 7	28 : 24	1.00
Upper and middle/lingual : lower	30 : 38	7 : 9	23 : 29	1.00

19, respectively. 31 patients (46%) had previously undergone thoracic surgery. There was no significant difference in any of the patients' characteristics between patients with and without RP. 27 patients were histologically proven NSCLC and remaining 41 patients were diagnosed by fludeoxyglucose-positron emission tomography positive tumor and/or 25% enlarged tumor over a 2 months period on CT image.

PE evaluation and RT method

55 of the patients (80.8%) were participants in a Phase II study at our institute; that study evaluated the local control rate achieved by a dose of 75 Gy given in 30 fractions for patients with stage I NSCLC. The RT procedures were described elsewhere.^{9,13} Briefly, the planning target volume was determined by adding 0.5 cm for respiratory uncertainties to the clinical target volume in the craniocaudal direction and 0.5 cm in all other directions. Five non-coplanar ports with or without intensity-modulated filters (decimal Co. Ltd., FL) were typically used. In the three-dimensional conformal RT planning, a 100% dose was prescribed to the iso-center of the tumor. The 95% dose line was set to cover the PTV in intensity-modulated RT planning. None underwent chemotherapy.

Volumetric chest CT images were acquired at the end of expiration and inspiration phases for the treatment planning. No contrast material was administered. CT images acquired during expiration phases were used to quantify PE. Parameters of the 16 multislice CT (Aquilion LB, Toshiba Medical Systems, Tokyo, Japan) were as follows: tube current: 250 mA; tube voltage: 120 KV; gantry rotation time: 0.5 s; CT pitch factor: 15. Row CT data were reconstructed into an axial CT image with 2 mm slice thickness. The analysis of CT images was performed using software (Synapse Vincent, Fujifilm Co., Tokyo, Japan). LAA was calculated as a percentage of lung pixels with an attenuation of ≤−950 Hounsfield unit (HU) or −860 HU in the whole lung of CT images. In addition to LAA, the average lung attenuation value of the whole lung was recorded. When atelectasis or pleural

effusion was observed, these areas on CT images were excluded from the measurement.

All patients received physical examinations, blood tests and a chest X-ray every month, and a thoracic CT examination every 3 months for 1 year after completion of RT. Thereafter, they underwent chest X-ray analysis every 3 months and CT examinations every 6 months when chest X-ray analysis did not disclose abnormal shadows. The grade of pulmonary toxicity was determined according to the common terminology criteria for adverse events v. 4.0. by two chest radiologists from different groups in our department. The RP was classified into five grades as follows. Grade 1 RP is asymptomatic, revealed by clinical or diagnostic observation only; intervention is not indicated. Grade 2 is symptomatic, and medical intervention is indicated; the grade shows limited instrumental activities of daily living. Grade 3 is severe symptoms, limiting self-care activities of daily living and oxygen is indicated. Grade 4 is life-threatening respiratory compromise, and urgent intervention is indicated. Grade 5 is death.

Statistical analysis

Categorical variables were evaluated using the chi-squared test and Fisher's exact test. Continuous variables were evaluated using the Wilcoxon rank-sum test. The time to RP was calculated from the first day of RT. The time to RP was estimated using Kaplan-Meier method and compared by Log-rank test. Cox proportional hazards model was employed to analyze independent variables. The evaluated parameters of CT image were assessed through the non-parametric area under the receiver operating characteristic curve (ROC). The cut-off value was defined as the one point closest to the (0, 1) point. The comparison of the area under the curves (AUC) was performed by methods of DeLong. Statistical analyses were performed using the statistical software of STATA v. 13 (StataCorp, College Station, TX). A probability value of <0.05 with the two-sided test was considered statistically significant.

Table 2. The difference of low attenuation area on CT images between patients with non-pneumonitis and pneumonitis

Percentage of area under low attenuation area (mean ± SD)	All	Non-pneumonitis	Pneumonitis	<i>p</i> value
−860 HU (%)	45.3 ± 22.3	62.3 ± 15.4	40.0 ± 21.5	0.0004
−950 HU (%)	9.1 ± 12.4	16.0 ± 16.2	6.9 ± 10.3	0.005
Average HU (HU)	−845.6 ± 36.3	−869.8 ± 16.0	−838.2 ± 37.6	0.001

HU, Hounsfield unit, SD, standard deviation.

Table 3. Risk for radiation pneumonitis by univariate analysis

			Fisher's exact test <i>p</i> value	Log-rank test <i>p</i> value
Percentage of LAA –860 HU	≤50%	>50%		
Pneumonitis –	3	13		
Pneumonitis +	35	17	0.001	0.002
Percentage of LAA –950 HU	≤10%	>10%		
Pneumonitis –	9	7		
Pneumonitis +	48	4	0.002	0.03
Average HU	≤–850 HU	>–850 HU		
Pneumonitis –	14	2		
Pneumonitis +	21	31	0.001	0.0003

HU, Hounsfield unit; LAA, low attenuation area.

RESULTS

The median observation period was 18 (range, 3.8–56.2) months. 52 (76.5%) patients had RP on CT image. One patient had been administered a steroid and another patient had undergone oxygen therapy. The remaining of 50 had asymptomatic. So 50 patients, 1 patient and 1 patient had Grade 1, 2 and 3 RP, respectively. None had Grade 4 and more. Because of the low number of high Grade RP, the analysis was performed with 52 patients with RP and 16 patients without RP. The median time of RP was 6 months. The actuarial rate of RP at 6 and 12 months was 52.3% [95% confidence interval (CI) 41.0–64.7%] and 74.7% (95% CI 63.2–84.9%), respectively.

Table 2 showed the mean difference percentages of LAA of ≤–860 or –950 HU, and average HU in the whole lung. The mean different percentages of LAA of ≤–860 HU ($p = 0.0004$) or –950 HU ($p = 0.005$), and average HU ($p = 0.001$) in patients with RP were significantly lower than those in patients without RP. The cut-off of LAA of ≤–860 or –950 HU, and average HU in all

patients were determined as 50%, 10% and 850 HU, respectively; these values were taken from respective mean values.

In univariate analysis, when percentages of LAA of less ≤–860 HU were >50%, the incidence ($p = 0.001$) and rate ($p = 0.002$) of RP were significantly lower than those when the LAA percentage was ≤50% (Table 3). When percentages of LAA of ≤–950 HU were >10%, the incidence ($p = 0.002$) and rate ($p = 0.03$) of RP were statistically significantly lower than those when the LAA percentage was ≤10%. The RP incidence ($p = 0.001$) and rate ($p = 0.0003$) were significantly lower when the average HU values were ≤–850 HU.

In multivariate analysis, the cut-off values of 50% in the percentage of LAA of ≤–860 HU and average HU value ≤–850 HU were significant risk factors for RP. The location of the tumor, gender and the dose of the T factor were not significant (Table 4).

Figure 2 showed the ROC curves of LAA of ≤–860 or –950 HU, and average HU. The cut-off value of average HU was determined as –850 HU by ROC. AUC of average HU was significantly higher than that of LAA of ≤–860 ($p < 0.0001$) or –950 HU ($p < 0.0001$).

DISCUSSION

Although stereotactic body RT is the standard care for stage I NSCLC, there has been no randomized trial to compare directly large dose hypofraction to conventional fraction. The trans-tasman radiation oncology group conducts randomized trial comparing hypofraction with conventional fraction for stage I NSCLC.¹⁴ This study showed that based on CT images, 75% of patients had Grade 1 RP and only 3% of patients had Grade 2 or 3 RP. In our current results, conventional fraction achieved less RP compared to other hypofractionated stereotactic studies.^{5–7}

Pulmonary emphysema is characterized by anatomical alterations enlargement of the air spaces distal from the terminal bronchiole. The LAA value, which is an index of the enlargement of air spaces, can be concretely calculated from the CT value and is now available for clinical use.^{11,12} The presence or absence of emphysema can then be determined based on the thus-calculated LAA values. Most

Figure 1. Kaplan-Meier's curve of radiation pneumonitis after initiation of RT for patients with non-small cell lung cancer. The actuarial radiation pneumonitis rate is significantly lower when the average HU values were ≤–850 HU compared to >–850 HU ($p = 0.0003$). HU, Hounsfield unit.

Table 4. Prognostic factor associated with radiation pneumonitis

	HR	95% CI	p value	HR	95% CI	p value		HR	95% CI	p value
Average HU							Percentage of area under -950 HU			
≤ -850 HU : > -850 HU	0.40	0.22–0.73	0.003			0.08	$\leq 10\%$: $> 10\%$	0.38	0.13–1.10	0.008
Location							Location			
Upper : middle or lingual and lower lobe	0.80	0.43–1.47	0.47			0.52	Upper : middle or lingual and lower lobe	0.93	0.50–1.72	0.81
Gender							Gender			
Male: female	0.79	0.44–1.44	0.45	0.81	0.44–1.47	0.48	Male: female	0.66	0.36–1.21	0.18
Dose							Dose			
≤ 78 Gy : > 78 Gy	0.80	0.43–1.49	0.49	0.72	0.39–1.33	0.3	≤ 78 Gy : > 78 Gy	0.94	0.48–1.83	0.85
T factor							T factor			
1 : 2	0.89	0.46–1.73	0.73	0.95	0.50–1.81	0.87	1 : 2	0.89	0.46–1.71	0.72

CI, confidence interval; HU, Hounsfield unit; HR, hazard ratio.

Figure 2. ROC curve of LAA of ≤ -860 or ≤ -950 HU, and average HU estimated by binomial distribution. AUC of LAA of ≤ -860 or ≤ -950 HU, and average HU are 0.207, 0.267 and 0.771, respectively. The cut-off value is determined as -850 HU, which is closest distance from the maximum vertical (0,1) point. AUC of average HU is significantly higher than those of ≤ -860 ($p < 0.0001$) or ≤ -950 HU ($p < 0.0001$). AUC, Area under curve; HU, Hounsfield unit; LAA, low attenuation area; ROC, Receiver operating characteristic.

quantitative CT studies have defined emphysema according to a threshold value ranging between -856 HU and -950 HU. Wang et al defined emphysema as an LAA value above -950 HU,¹⁵ while Busacker et al used a threshold of -850 HU.¹⁶ Some researchers stated that LAA values above -856 HU strongly correlated with physiological measurements of airway obstruction.^{11,17} Thus, we set thresholds of -860 HU and -950 HU to find the optimal cut-off values. To the best of our knowledge, there was no report concerning the association between average HU in the whole lung and RP after RT. In the present study, our ROC analysis showed that average HU was better predicted of RP than was an LAA of ≤ -860 HU or an LAA of ≤ -950 HU.

Rancati et al performed multivariate analysis in patients with NSCLC who underwent RT and reported that the existence of COPD was a risk factor for RP but not dosimetric parameters.⁴ They denoted that patient with COPD was contra-indicated for RT because of the risk of RP. Kimura et al investigated the risk of RP in patients with PE, but the results of their two reports were contradictory.^{6,18} When patients with NSCLC underwent stereotactic body RT, most patients with PE did not suffer from RP.⁶ In contrast, when patients with NSCLC and small cell lung cancer received involved field RT, PE was a risk factor for RP.¹⁸ In the latter study, 80% of patients underwent chemotherapy, and thus they considered that chemotherapy might increase the risk of RP. Our present findings indicated that patient with PE was not contra-indicated for RT.

RT induces cytokine cascades in parenchymal lung.¹⁹ The total amount of cytokine production in PE appears lower than that in chronic bronchitis, because the lungs of patient with emphysema have less parenchymal tissue than those of individuals without PE. Our study showed patient with PE had a low rate of RP.

This research had limitation. First, the study is limited by its retrospective design. In addition, few of the enrolled patients experienced clinically relevant RP. However, approximately three-quarters of the patients had Grade 1 RP, which was predicted by the quantitative measurement of the average HU.

CONCLUSION

The quantitative measurement of average HU in the whole lung from CT images is a useful tool to predict RP after RT. Further studies using quantitative CT images are needed to confirm whether PE patients can be treated safely by a standard hypofractionated dose of stereotactic.

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