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Risk of radiation pneumonitis in patients with emphysema after stereotactic body radiotherapy for non-small cell lung cancer assessed by quantitative CT

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Abstract. Quantitative CT assessment of patients with pulmonary emphysema is used to measure pulmonary function. The present study evaluated whether the quantitative CT value can accurately estimate the risk of radiation pneumonitis (RP) after stereotactic body radiotherapy (SBRT) for non-small cell lung cancer (NSCLC) in patients with and without emphysema. A total of 80 patients with stage I NSCLC receiving SBRT at a dose of 50 or 60 Gy in five fractions at our hospital between November 2003 and October 2015 were included in the analysis. A total of 33 (41%) patients were diagnosed with emphysema on CT examination. Dosimetric parameters, quantitative CT percentage value of low attenuation area (LAA%) in the whole lung, and average whole lung CT density values were used to examine the risk of RP. Among the 80 patients, 26 (33%) and 3 (4%) experienced Grade 1 and Grade 2 RP, respectively, during the median observation period of 18.8 (1.8-106.8) months. The RP rate for patients with a LAA% (<-910 HU) of ≤25% was significantly higher than that of subjects with LAA% (<-910 HU) >25% (P=0.037). The RP rate in subjects with an average HU value of >-790 HU was significantly higher compared with that of patients with ≤-790 HU (P=0.036). Age (hazard ratio [HR]=2.46; P=0.03) and average HU (HR=3.39; P=0.02) were significantly associated with RP, whereas mean lung dose was not identified to be significant in multivariate analysis. The quantitative CT value was associated with RP after SBRT.

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Key words: stereotactic body radiotherapy, lung cancer, emphysema, radiation pneumonitis, quantitative CT value, non-small cell lung cancer

Introduction

Chronic obstructive pulmonary disease (COPD) is a risk factor for lung cancer (1). Patients with non-small cell lung cancer (NSCLC) with coexisting COPD tend to have poor survival (2,3). They also are at high risk of mortality after surgical resection (4). Compared with surgery, stereotactic body radiotherapy (SBRT) has a lower mortality risk and results in higher survival in patients with severe COPD (5). SBRT is now the treatment of choice for non-operable early-stage NSCLC; however, radiation pneumonitis (RP) may occur as an adverse event (6).

Dosimetric parameters, including mean lung dose and percentage of lung volume irradiated with ≥20 Gy, can estimate the risk of RP (7-9). However, whether patients with pulmonary emphysema are at a higher risk for RP is unclear.

Quantitative CT assessment of patients with emphysema is now used to measure pulmonary function (10-14) since Hayhurst *et al* (15) reported a correlation between emphysema and lung CT values in low attenuation areas. By quantitative assessment, we previously showed that patients with low average Hounsfield units (HU) of the whole lung had a low rate of RP after conventional low dose radiotherapy (75 Gy administered in 30 fractions) (16). However, the major criticism of our report was the use of a conventional low dose of SBRT rather than a high dose.

In this study, to investigate whether quantitative CT measurement and/or lung irradiated dose were associated with RP, we used a high dose of SBRT and observed the rates of RP in patients with and without emphysema.

Patients and methods

Patients. This retrospective study was approved by the institutional review board of the National Center for Global Health and Medicine Ethics Committee. Informed consent was waived by the Ethics Committee due to the retrospective nature of the study. According to the approval, informed consent from the patients was not required. Inclusion criteria were histologically/cytologically confirmed NSCLC or the tumor size enlarged more than 25% on sequential CT examination, clinical stage I (T1/2N0M0) staged by CT examination, age ≥20 years, Eastern Cooperative Oncology Group performance status 0-2 and no history of radiation therapy. Exclusion criteria were interstitial pneumonitis or huge bullae on CT examination, centrally located tumor, history of chemotherapy, sever psychologically disease and active infectious disease. Between November 2003 and October 2015, patients with stage I NSCLC receiving SBRT at a dose of 50 or 60 Gy over five fractions at our hospital were studied. Eighty consecutive patients were identified. The median age was 75.5 years (range, 29-95 years), 54 and 26 patients were male and female, respectively, and there were 49 and 31 T1 and T2 tumors, respectively (Table I). There were no patients with interstitial pneumonitis. Patients with interstitial pneumonitis did not undergo SBRT because of a risk of pneumonitis in our treatment policy. Centrally located tumor was treated by a different dose fraction. None underwent chemotherapy or molecular targeting therapy during the observation period. Two experienced radiologists diagnosed 33 patients with emphysema based on CT examination before radiotherapy. RP was determined according to common terminology criteria for adverse events (CTCAE v. 4.0). All patients underwent physical examination, blood tests, and chest X-rays at least every 4 months up to 3 years, and then every 6 months. CT examinations were performed at least every 6 months up to 3 years and then every year or if tumor enlargement was suspected upon chest X-ray.

Table I. Patient characteristics.

Variable	Value (n=80)
Median age, years (range)	75.5 (29-95)
Sex, n (%)	
Male	54 (67.5)
Female	26 (32.5)
T factor	
T1	49 (61.3)
T2	31 (38.8)
Tumor location in lung, n (%)	
Right lung	49 (61.3)
Left lung	31 (38.8)
Tumor location in lobe, n (%)	
Upper lobe	31 (38.8)
Middle or lingual lobe	11 (13.8)
Lower lobe	38 (47.5)
Histological type, n (%)	
Adenocarcinoma	43 (53.8)
Squamous cell carcinoma	16 (20)
NSCLC	4 (5)
LCNEC	1 (1)
Unproven	16 (20)

NSCLC, non-small cell lung cancer; LCNEC, large cell neuroendocrine cancer.

Radiotherapy technique and dose evaluation. A planning CT was acquired with patients in the supine position on a vacuum cushion with their arms raised. To assess intra-fraction tumor movement, four-dimensional (4-D) CT images were obtained using commercial software (Real-Time Position Management System [RPM] system®, Varian Medical System, Inc.). The respiratory cycle was controlled by a self-monitoring device for respiratory movement (Abches®, APEX Medical, Inc.) Ten equally spaced respiratory time bins from CT images were reconstructed from 4-D CT. An inspiratory phase CT image was also obtained using a self-monitoring device. Typically, three bins were used to create the gross tumor volume (GTV) in each bin. Internal target volume (ITV) was created from each GTV and contoured on an inspiratory phase CT image. Planning target volume (PTV) was generated by adding 5 mm to the ITV. Respiratory-gated irradiation or breath-hold technique was used according to patients' respiratory cycles and tumor movement. CT images were obtained within at least 10 days before the initiation of radiotherapy. Dose calculation was performed by a planning system (Eclipse ver. 10®, Varian Medical Systems). A dose of 50 or 60 Gy given in five fractions was prescribed to the isocenter. Five to 10 (median, seven) ports to optimize the directions for non-coplanar static beams or dynamic arcs using 6 MV energy were planned. Mean lung dose and the percentage of normal lung volume receiving ≥20 Gy (V20) and >5 Gy (V5) were evaluated in the inspiratory phase of CT images. On-board cone beam CT was performed to reduce inter-fraction error before every irradiation session.

CT assessment of emphysema. Parameters of the 64-detector CT (Aquilion TSX-101HA, Toshiba Medical System, Inc.) were as follows: Auto exposure control mA (tube current range, 40-200 mA); tube voltage, 120 KV; and gantry rotation time, 0.5 sec. CT data were reconstructed in an axial CT image with 1.6-mm section thickness. CT values varied with the CT scanner, and thus all patients underwent CT using the same machine. The details of quantitative assessment by CT have been reported elsewhere (16). CT images of the inspiratory phase were obtained from a planning CT, and quantitative assessment of the percentage of lung CT voxels below the threshold of -910 HU were analyzed (Synapse Vincent® software, Fujifilm Co.). The percentage of low attenuation areas (LAA%) in both whole lungs and the average density value of both lungs were obtained.

Statistical analysis. Quantitative CT value and dosimetric parameters were analyzed by Wilcoxon's rank-sum test. The time to RP development was calculated from the first day of SBRT. The time to RP was estimated by Kaplan-Meier analysis and compared with log-rank tests. Cox's proportional hazard model was used to analyze risk factors for RP. The CT values assessed for emphysema were evaluated by a receiver operating characteristic (ROC) curve. Most cases of radiation pneumonitis occurred within 1 year, and hence ROC analysis is an acceptable approach to clarify radiation pneumonitis. A two-sided probability value ($P<0.05$) was considered statistically significant. Statistical analysis was performed with commercial software (STATA v. 13®, StataCorp).

Table II. Quantitative CT value for non-emphysema and emphysema.

Quantitative CT value	Total (n=80)	Non-emphysema (n=47)	Emphysema (n=33)	P-value
Percentage of low attenuation area less than -910 HU, %	29.5±2.1	6.7±1.3	36.2±2.8	<0.001
Average HU of whole lung, HU	-772.4±59.3	-737.2±6.4	-822.5±6.7	<0.001

Data are presented as the mean ± SD. HU, Hounsfield unit.

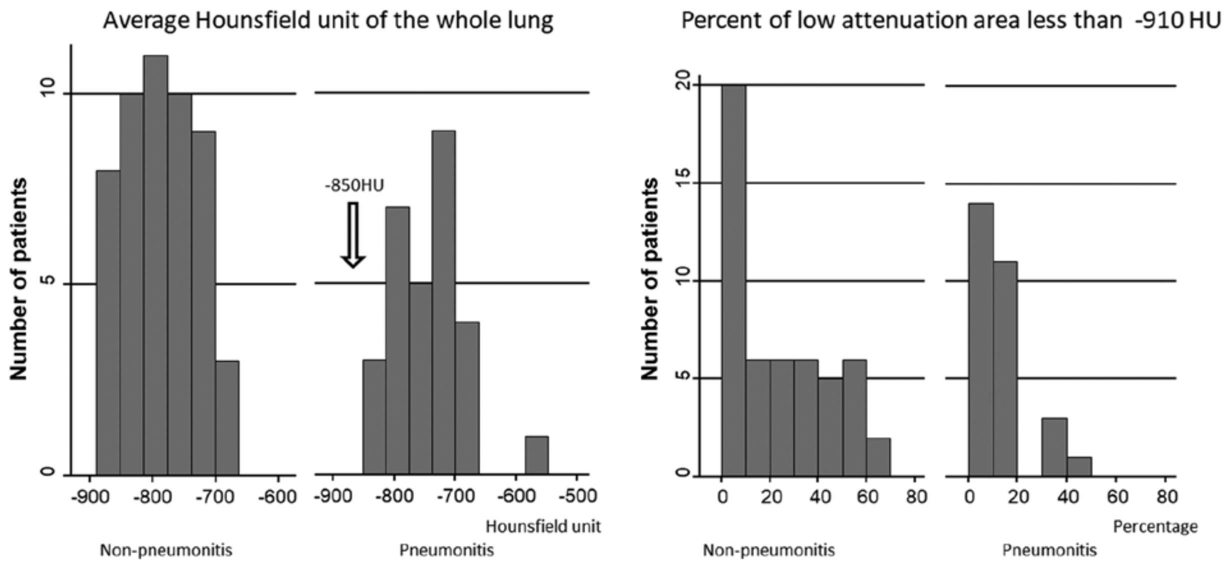

Figure 1. Histogram showing the number of patients with an average density (HU) in both lungs and a LAA% of -910 HU or less. Radiation pneumonitis did not occur in patients with an average density <-850 HU (arrow). HU, Hounsfield unit; LAA%, percentage of low attenuation area.

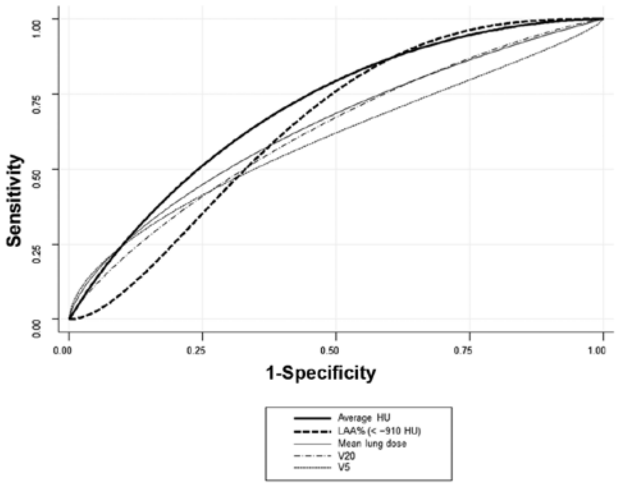

Figure 2. Receiver operating characteristic curve analysis of radiation pneumonitis. The area under the curve values of average HU, mean lung dose, LAA% of -910 HU, V20 and V5 were 0.692, 0.643, 0.641, 0.619 and 0.591, respectively. HU, Hounsfield unit; LAA%, percentage of low attenuation area.

Results

RP rate. During the median observation period of 18.8 (1.8-106.8) months, 26 (33%) and three (4%) patients experienced Grade 1 and Grade 2 RP, respectively. Three patients with Grade 2 RP were successfully treated with steroids. No patients suffered from ≥Grade 3 RP. The median time to development of RP was 14 months. Actuarial RP rates at 6, 12 and 18 months were 16.9% [95% confidence interval (CI), 9.7-28.5%)], 49.0% (95% CI, 35.1-65.0%), and 74.1% (95% CI, 51.6-92.0%), respectively.

The quantitative CT value of emphysema. LAA% (<-910 HU) in patients with emphysema was significantly higher than that in patients with non-emphysema (P<0.001, Table II). The average HU of the whole lung in patients with emphysema was significantly lower than that in patients without emphysema (P<0.001). Fig. 1 shows the number of patients with an average HU of the whole lung and LAA% of -910 HU and less. No patients who had an average HU of ≤-850 HU experienced RP (Fig. 1).

In ROC analysis of patients with and without emphysema, the AUC of LAA% (<-910 HU) and average HU were 0.948 and 0.942, respectively. Fig. 2 shows a ROC curve comparing patients with and without RP. The AUC of average HU, mean lung dose, LAA% (<-910 HU), V20, and V5 were 0.692, 0.643, 0.641, 0.619, and 0.591, respectively.

RP and the quantitative CT value. Table III shows the difference in the quantitative CT value and dosimetric parameters between RP and non-RP. A LAA% (<-910 HU) in patients

Table III. Quantitative CT value and dosimetric parameters for non-pneumonitis and pneumonitis.

Quantitative CT value and dosimetric parameters	Non-pneumonitis (n=51)	Pneumonitis (n=29)	P-value
Percent of low attenuation area <-910 HU, %	22.9±2.1	11.8±1.2	0.037
Average HU of whole lung, HU	-787.5±7.9	-745.8±10.2	0.004
V20, %	5.4±0.4	7.0±0.7	0.078
V5, %	17.8±0.8	20.4±1.4	0.178
Mean lung dose, Gy	3.8±0.2	4.6±0.3	0.034

V20 and V5 denotes the percentage of the whole lung volume irradiated with a dose of ≥20 and ≥5 Gy, respectively. HU, Hounsfield unit.

Table IV. Risk factors for radiation pneumonitis analyzed using a Cox proportional hazard model.

Factor	Hazard ratio	95% CI	P-value
Age (<75 years vs. >75 years)	2.46	1.07-5.67	0.03
Sex (male vs. female)	0.43	0.17-1.07	0.07
T factor (T1 vs. T2)	2.04	0.90-4.62	0.09
Mean lung dose (<4 Gy vs. >4 Gy)	1.75	0.80-3.85	0.16
Average CT value (<-790 cs. >-790 HU)	3.39	1.24-9.24	0.02

HU, Hounsfield unit; CI, confidence interval.

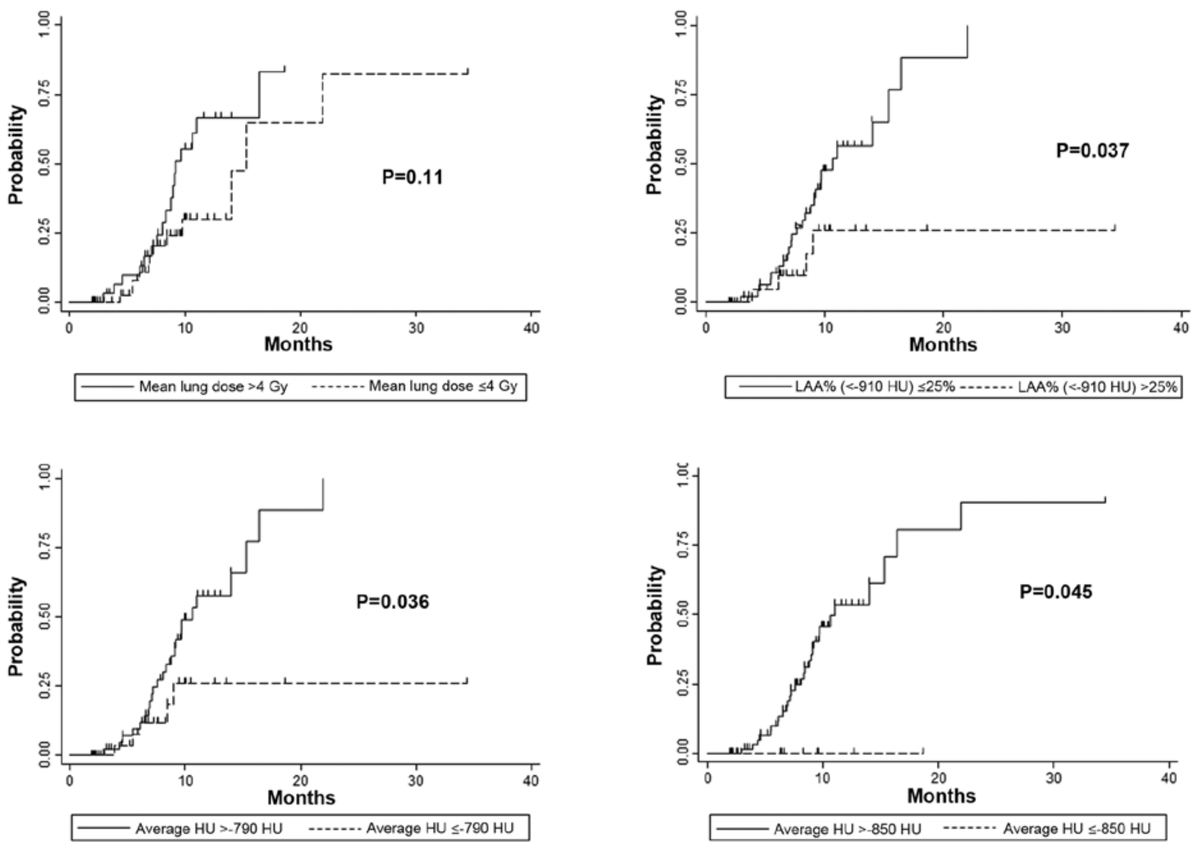

Figure 3. Kaplan-Meier analysis of patients with and without RP. The actuarial RP rate in patients with a mean lung dose of ≤4 Gy was not significantly different from the rate in patients receiving >4 Gy (P=0.11). The RP rate in patients with a LAA% <-910 HU of ≤25% was significantly higher compared with that of patients with a LAA% <-910 HU of >25% (P=0.037). The RP rate in patients with average HU in the whole lung of >-790 HU was significantly higher compared with that in patients with an average HU in the whole lung of ≤-790 HU (P=0.036). The RP rate in patients with an average HU of the whole lung of >-850 HU was significantly higher compared with that in patients with an average HU of the whole lung of ≤-850 HU (P=0.045). No patient with an average HU of ≤-850 HU developed RP. HU, Hounsfield unit; LAA%, percentage of low attenuation area; RP, radiation pneumonitis.

without RP was significantly higher than that in patients with RP (P=0.037). The average density of the whole lung in patients without RP was significantly lower than that in patients with RP (P=0.004). V20 (P=0.078) and V5 (P=0.178) were not significantly different between subjects with and without RP. The mean lung dose in patients with RP was higher than that in patients without RP (P=0.034). Fig. 3 shows RP rates analyzed by the Kaplan-Meier method. The RP rate with a mean lung dose of <4 Gy was not significantly different compared with doses ≥4 Gy (P=0.11). The RP rate in LAA% (<-910 HU) of ≤25% was significantly higher compared with that of subjects with an LAA% (<-910 HU) >25% (P=0.037). The RP rate in subjects with an average HU >-790 HU was significantly higher compared with those with ≤-790 HU (P=0.036). The RP rate at an average HU of >-850 HU was significantly higher compared with those with an average HU of ≤-850 HU (P=0.045).

Table IV shows age [hazard ratio (HR)=2.46, P=0.03] and average HU (HR=3.39, P=0.02) were significant risk factors for RP by multivariate analysis. Sex, T factor, and mean lung dose were not significant.

Discussion

Radiation oncologists are concerned about RP after SBRT, especially in the case of emphysema. This study showed that patients with emphysema can be safely treated with SBRT. In our cohort, no patient suffered ≥Grade 3 RP and none had emphysema. Takeda *et al* (17) reported that patients with severe COPD could be treated with SBRT; however, they did not specifically distinguish between emphysema and COPD. Some authors also reported that patients with stage I NSCLC who had emphysema had a low rate of RP after SBRT (18,19). Based on these results, we believe that emphysema is not a contraindication for SBRT.

In our previous study, the actuarial rates of RP at 6 and 12 months were 52 and 75%, respectively, when a conventional dose of 75 Gy was administered in 30 fractions (16). In this study, the rate of RP at 12 and 18 months was 49 and 74%, respectively. The rate of RP was similar in both studies, but RP events in SBRT were late compared with the conventional dose. Recently, a prospective randomized trial of an SBRT dose of 66 Gy given in three fractions compared with a conventional dose of 70 Gy given in 35 fractions (20) showed that the rate of RP was not significantly different between the two dose schedules, suggesting that RP may not be prevented by hyperfractionation.

The effectiveness of the quantitative CT method relating LAA% and anatomical emphysema has been proven. Gevenois *et al* (21,22) described a cutoff value of -950 HU corresponding closely with pathological emphysema. They noted a cutoff value of >-950 HU overestimated emphysema whereas <-950 HU underestimated emphysema. Müller *et al* (23) reported a <-910 HU threshold of LAA was the best predictor for discrimination between normal lung and emphysema. Therefore, we chose -910 HU as the cut-off value for LAA. Reports on the correlation between pulmonary function tests and LAA% have reported cut-off thresholds of LAA from -960 to -860 HU (10,11,13,14).

This study showed that quantitative CT is a good predictor for RP risk. Another study suggested that quantitative CT values correlated with RP after radiotherapy (24). Yamamoto *et al* (24) showed a quantitative CT value of LAA% was associated with Grade 1 RP, but not with Grade 2 and 3 because they were affected by other factors such as V20. These results were similar to ours, where no patient had Grade 3 or higher RP in our study, and thus we did not observe LAA% or average HU to be associated with Grade 3 RP. The previous study showed that V20 was associated with radiation pneumonitis; however, we did not include interstitial disease in our study and used the average HU of the whole lung, which we believe to be the reason for the different results.

This study showed that the average HU of the whole lung was associated with RP, with a higher AUC for average HU compared with that of LAA%. The patients with an average HU of <-850 HU (implying severe emphysema) did not develop RP. Patients with severe emphysema had a low risk of RP, which is in accordance with our previous studies (16,25). We speculate that average whole lung HU is a convenient measurement in quantitative CT assessment to estimate the risk RP.

This study had some limitations. This research was a retrospective single institution study and included relatively small numbers. Smoking history and histological grade information were not available. However, in this study we showed that the average HU value of the whole lung was associated with RP after SBRT. A prospective multi-institution study is required to validate the association between the quantitative CT value and RP after SBRT.

In conclusion, pulmonary emphysema patients, especially those with severe emphysema, can safely undergo SBRT. The quantitative CT value was associated with RP after SBRT.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

The present study was designed by HN and RM. Data of CT values were analyzed by TT, YT and FU. Statistical analyses was performed by HN and WW. The manuscript was written by HN with contributions from FU, YU, WW and RM. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present retrospective study was approved by the Institutional Review Board of the National Center for Global Health and Medicine Ethics Committee (approval no. NCGM-G-002164-00). The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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