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Original paper

Evaluation of functionally weighted dose-volume parameters for thoracic stereotactic ablative radiotherapy (SABR) using CT ventilation

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ABSTRACT

For the purpose of reducing radiation pneumontisis (RP), four-dimensional CT (4DCT)-based ventilation can be used to reduce functionally weighted lung dose. This study aimed to evaluate the functionally weighted dose-volume parameters and to investigate an optimal weighting method to realize effective planning optimization in thoracic stereotactic ablative radiotherapy (SABR).

Forty patients treated with SABR were analyzed. Ventilation images were obtained from 4DCT using deformable registration and Hounsfield unit-based calculation. Functionally-weighted mean lung dose (fMLD) and functional lung fraction receiving at least x Gy (fVx) were calculated by two weighting methods: thresholding and linear weighting. Various ventilation thresholds (5th-95th, every 5th percentile) were tested. The predictive accuracy for CTCAE grade ≧ 2 pneumonitis was evaluated by area under the curve (AUC) of receiver operating characteristic analysis.

AUC values varied from 0.459 to 0.570 in accordance with threshold and dose-volume metrics. A combination of 25th percentile threshold and fV_{30} showed the best result (AUC: 0.570). AUC values with fMLD, fV_{10}, fV_{20}, and fV_{40} were 0.541, 0.487, 0.548 and 0.563 using a 25th percentile threshold. Although conventional MLD, V_{10}, V_{20}, V_{30} and V_{40} showed lower AUC values (0.516, 0.477, 0.534, 0.552 and 0.527), the differences were not statistically significant.

fV_{30} with 25th percentile threshold was the best predictor of RP. Our results suggested that the appropriate weighting should be used for better treatment outcomes in thoracic SABR.

1. Introduction

CT ventilation is a state-of-the-art imaging modality using four-dimensional computed tomography (4DCT) and deformable image registration [1]. Its clinical validation studies have been done by comparing other ventilation modalities, such as nuclear medicine [2–6], Xenon-CT [7], hyperpolarized ^{3}He-MRI [8], and pulmonary function test [3,9]. These studies showed reasonable correlations between CT ventilation and other modalities. Because 4DCT has already been used in clinical routine and high resolution ventilation maps can easily be calculated only by image processing, this technique is more suitable for high-precision radiotherapy than the other ventilation modalities. These advantages have strongly motivated currently undergoing clinical trials (NCT02843568, NCT02308709, NCT02528942). These trials have been aimed for preservation of post-treatment lung function [10,11] and reduction of radiation pneumonitis (RP) [12–15] by avoiding irradiation to highly functioning lung region [16].

However, different optimization methods were used in each research group. There are two major types of reported optimization strategy to consider inhomogeneity of lung function. The first utilizes the threshold to divide functioning and non-functioning area. Yamamoto et al. [12] used 33th and 66th percentile to divide the total lung into three equal volumes: high, moderate, and low-functional lung. They set optimization constraints in each region. Kadoya et al. [15] used 90th percentile for thresholding the functional lung for planning optimization. The second one is linear weighting. Yamamoto et al. [17] and Kida et al. [18] converted ventilation values into percentile and set weight values linearly to the percentile ventilation. Functionally

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weighted dose distribution was calculated by the product of weight value and physical dose and used for input to an inverse optimization process. The latter strategy has also been used to correlate functionally weighted dose-volume parameters with incidence of pneumonitis [19].

The optimal weighting strategy which should be used for clinical implementation has been studied by Faught et al. [20] They studied 70 patients treated with conventionally fractionated radiotherapy (CFRT) and concluded that the thresholding-based approach with 84th percentile was the most correlated to grade 3 and higher RP. However, there are no studies which report the correlation between RP and functional dose-volume metrics in thoracic stereotactic ablative radiotherapy (SABR). SABR is characterized as highly conformal dose distribution and hypo-fractionation. These characteristics are known to affect the dose–response of RP[21].

To the best of our knowledge, this is the first study which attempts to quantify clinical significance of CT ventilation in a SABR cohort. We performed receiver operating characteristics (ROC) analysis and evaluated a predictive accuracy of RP by area under the curve (AUC). We also investigated the dependency of AUC values with different weighting approach; thresholding and linear-weighting.

2. Materials and methods

2.1. Patients and images

This study was a retrospective single-institution analysis approved by our institutional review board. Between February 2013 and August 2016, all patients who underwent a pre-treatment 4DCT scan and subsequent thoracic SABR were included. Patients with the following conditions were excluded: (1) History of thoracic radiotherapy, (2) Concurrent chemotherapy, and (3) Follow-up period less than 90 days. In total, 40 patients were analyzed. Patients' characteristics are summarized in Table 1. Incidence of pneumonitis was evaluated by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. 4DCT images were acquired as part of clinical therapy to determine internal margin using GE Light Speed RT16 (GE Healthcare, Wisconsin, USA) and Real-time Position Management System (Varian Medical Systems, California, USA). X ray tube current and voltage were 120 mA and 120 kV, respectively. The matrix size in the axial plane was 512 × 512. The axial field of view was determined to include patients' body. Slice thickness was 2.5 mm. 4DCT images were reconstructed in ten respiratory phases using Advantage 4D workstation (GE Healthcare, Wisconsin, USA)

2.2. Calculation of functionally weighted dose-volume parameters

For a correction of different fractionation schemes, physical dose distributions were firstly converted into biologically equivalent dose in 2 Gy/fraction (EQD_2) using linear-quadratic (LQ) model-based calculation with $\alpha/\beta = 3$ [22].

Table 1
Patients' characteristics and incidence of radiation pneumonitis (RP).

Age (y)	58–89 (median 77)
Gender	
Male	32
Female	8
RP	
Grade 0	18
Grade 1	13
Grade 2	9
Dose prescription (Gy)	
Total dose	40–72 (median 40)
Dose per fraction	3–10 (median 10)

Deformable image registration was applied between maximum-inhale CT image $HU_{in}(x)$ and the maximum-exhale image $HU_{ex}(x)$. We then calculated the deformation vector u(x) and deformed inhale image $HU_{deformed}(x + u(x))$ in each voxel x. The registration process was performed by the elastix [23]: open source registration toolkit. We used a previously reported parameter setting (parameter 2 in [24]) because the mean registration error for lung tissue was reasonably small (< 1.3 mm). All registration results were visually inspected to assure registration accuracy. A Gaussian filter smoothing with a variance $\sigma^2 = 1.5\,mm^2$ was subsequently applied to reduce the influence of CT noise [5]. Ventilation value was calculated by Hounsfield unit-based metric (V_{HU}) [1] as:

$$V_{HU}(x) = 1000\frac{HU_{deformed}(x+u(x)) - HU_{ex}(x)}{HU_{ex}(x)\{HU_{deformed}(x+u(x)) + 1000\}} + 1 \tag{1}$$

To follow other previous studies [12,15,18,19], every ventilation value was converted into percentile. The lowest and the highest ventilation value corresponded to 0th percentile and 100th percentile, respectively. We tested linear weighting method and thresholding method. In linear weighting method, the weight function W(x,v) in each voxel (x) was calculated by percentile ventilation (v) as:

$$W(x,v) = \frac{v}{50} \tag{2}$$

Above equation means that the highest functioning lung is twice as sensitive to radiation pneumonitis. We obtained weighted dose distribution in each voxel by the product of weight function and dose. Functionally-weighted mean lung dose (fMLD) and functional lung fraction receiving at least 10, 20, 30 and 40 Gy (fV_{10}, fV_{20}, fV_{30} and fV_{40}) were calculated by the weighted dose distribution.

In thresholding method, 19 different percentile thresholds (from 5th to 95th, every 5th percentile) were tested. Functional dose-volume metrics (fMLD, fV_{10}, fV_{20}, fV_{30} and fV_{40}) were calculated only within voxels which have higher ventilation values than those thresholds.

2.3. ROC analysis and statistical analysis

The predictive accuracy of grade 2 or greater pneumonitis (CTCAE version 4.0) following radiotherapy was assessed by AUC value of ROC analysis. AUC value is a quantitative value which can assess predictive accuracy of particular indices. AUC value has been used in many studies [19,25,26] because the different prediction from different dose-volume parameters can be easily understood. ROC analysis was performed by in-house MATLAB (The MathWorks Inc., Massachusetts, USA) software. This analysis enabled us to quantify how well different kinds of dose-volume parameters can predict the incidence of radiation pneumonitis. Additionally, the correlation between dose-volume parameters and pneumonitis was also evaluated by univariate analysis. Equality of variance and normality had been confirmed by F-test and Shapiro-Wilk test. Student's *t* test was then applied to assess statistical significance with a significance level of 0.05. Statistical analysis was performed by JMP® Pro ver. 12.2.0 (SAS Institute Inc., North Carolina, USA).

3. Results

Median follow-up period was 14.8 months (range: 3.5–36.9 months). Grade 0, 1, and 2 pneumonitis were observed in 18, 13, and 9 patients, respectively. Fig. 1 shows the summary of AUC values with different methods; thresholding method, linear weighting method and conventional dose-volume parameters. Higher AUC value indicates higher predictive accuracy of the dose-volume parameter. A combination of fV_{30} and 25th percentile threshold showed the highest predictive accuracy (AUC: 0.570). Twenty-fifth percentile threshold also resulted in good AUC value with fMLD (0.541), fV_{20} (0.548) and fV_{40} (0.563), while lower AUC value with fV_{10} (0.487). These AUC values were higher than those with conventional dose-volume