

Marginal prescription equivalent to the isocenter prescription in lung stereotactic body radiotherapy: preliminary study for Japan Clinical Oncology Group trial (JCOG1408)

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ABSTRACT

A new randomized Phase III trial, the Japan Clinical Oncology Group (JCOG) 1408, which compares two dose fractionations (JCOG 0403 and JCOG 0702) for medically inoperable Stage IA NSCLC or small lung lesions clinically diagnosed as primary lung cancer, involves the introduction of a prescribed dose to the D_{95%} of the planning target volume (PTV) using a superposition/convolution algorithm. Therefore, we must determine the prescribed dose in the D_{95%} prescribing method to begin JCOG1408. JCOG 0702 uses density correction and the D_{95%} prescribing method. However, JCOG 0403 uses no density correction and isocenter-prescribing method. The purpose of this study was to evaluate the prescribed dose to the D_{95%} of the PTV equivalent to a dose of 48 Gy to the isocenter (JCOG 0403) using a superposition algorithm. The peripheral isodose line, which has the highest conformity index, and the D_{95%} of the PTV were analyzed by considering the weighting factor, i.e. the inverse of the difference between the doses obtained using the superposition and Clarkson algorithms. The average dose at the isodose line of the highest conformity index and the D_{95%} of the PTV were 41.5 ± 0.3 and 42.0 ± 0.3 Gy, respectively. The D_{95%} of the PTV had a small correlation with the target volume ($r^2 = 0.0022$) and with the distance between the scatterer and tumor volumes ($r^2 = 0.19$). Thus, the prescribed dose of 48 Gy using the Clarkson algorithm (JCOG0403) was found to be equivalent to the prescribed dose of 42 Gy to the D_{95%} of the PTV using the superposition algorithm.

KEYWORDS: D_{95%}, SBRT, Clarkson algorithm, superposition algorithm

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is considered as an ‘ablative’ dose for early-stage lung cancer [1] because it uses hypofractionations and results in the delivery of a high biological

effective dose. SBRT is an effective treatment option for Stage I non-small cell lung cancer (NSCLC) if the cancer is inoperable or the patient refuses surgery. The Japan Clinical Oncology Group (JCOG) 0403 recently reported that the proportion of overall

survival for 3 years in patients with inoperable and operable Stage IA NSCLC were 59.9 and 76.5%, respectively [2–5]. They concluded that SBRT used by JCOG 0403 for both inoperable and operable Stage I NSCLC is effective, with low number of incidences of severe toxicity. Additionally, this treatment can be considered a standard treatment for inoperable Stage I NSCLC, and is promising as an alternative to surgery for operable Stage I NSCLC.

For radiotherapy planning, the dose calculated with and without heterogeneity corrections deviate dramatically, especially in the thoracic region. A JCOG 0403 trial adopted an isocenter prescribing method using a Clarkson-type algorithm (isocenter Clarkson prescription). This dose-calculation algorithm, which is based on a simple 1D equivalent path for a primary component with a heterogeneity correction and the lateral transport of a scattering component, was not modeled with homogeneity. On the other hand, the superposition/convolution method, a collapsed cone convolution superposition/convolution algorithm, which is available in Pinnacle³ (Philips Radiation Oncology Systems, Fitchburg, WI), is a more accurate algorithm for heterogeneity correction [6]. The PTV peripheral dose could be lower owing to the effect of 2D scatterer compensation, which can be determined using a superposition algorithm but not a Clarkson-type algorithm. Additionally, the PTV dose can vary significantly, with a point-dose prescription depending on the tumor position and the tumor volume [7]. In radiation therapy oncology groups (RTOGs) 0236 and 0813, and the radiosurgery or surgery for an operable early stage non-small cell lung cancer (ROSEL) study, which provided accreditation and dosimetry guidelines for SBRT, a dose that covered 95% ($D_{95\%}$) of the PTV ($D_{95\%}$ prescription) was introduced that was conformally covered by the prescribed isodose surface [8, 9]. Using this prescribing method, the peripheral dose of the PTV is expected to vary insignificantly. Based on other Japanese clinical studies, the JCOG study (JCOG0702) reported the recommended dose of SBRT for peripheral T2N0M0 NSCLC with a PTV <100 cm³ was 55 Gy at $D_{95\%}$ of the PTV in four fractions [10]. Although the prescription has been shifted from point doses to volume doses, i.e. the $D_{95\%}$ of the PTV in clinical trials, most institutions in Japan still use the isocenter prescribing method.

Subsequently, in a new randomized Phase III trial, JCOG 1408, which compares two dose fractionations (JCOG 0403 and JCOG 0702) for medically inoperable Stage IA NSCLC or small lung lesions clinically diagnosed as primary lung cancer, the prescribed dose to the $D_{95\%}$ of the PTV using a superposition/convolution algorithm. Therefore, we must determine the prescription dose in the $D_{95\%}$ -prescribing method to begin JCOG1408. The purpose of this study is to evaluate the prescribed dose to the $D_{95\%}$ of the PTV by evaluating the $D_{95\%}$ of the PTV equivalent to a dose of 48 Gy to the isocenter (JCOG 0403).

MATERIALS AND METHODS

Patient background

We retrospectively analyzed treatment plans of 40 patients with lung cancer who underwent SBRT at Hiroshima University Hospital. The characteristics of the patients and their tumors are presented in Table 1. These 40 patients were not enrolled into the

Table 1. Patient characteristics

Age (years)	Median (Range)	81 (58–90)
Gender	male	32 (77%)
	Female	9 (23%)
Tumor location	Right lobe	24 (60%)
	Left lobe	16 (40%)
Tumor diameter (mm)	>0 to ≤10 mm	12 (30%)
	>10 to ≤20 mm	18 (45%)
	>20 to ≤30 mm	10 (25%)

JCOG 0403, but these cases were eligible for JCOG 0403. The use of clinical materials in this study was approved by the Institutional Review Board of Hiroshima University.

Treatment planning

All the patients were immobilized using a Vack-Lok positioning bag (CIVCO, Kalona, IA). Breath holding was coordinated in the expiratory phase using Abches (APEX Medical, Tokyo, Japan) —a device that allows patients to control their chest and abdominal respiratory motion [11]. The tumor position reproducibility during several expiratory breath-hold intervals was verified to be within 5 mm using X-ray fluoroscopy. Computer tomography (CT) scans were performed during expiratory breath holding by using a CT scanner (Lightspeed RT16, GE Healthcare, Little Chalfont, UK). The slice thickness and the slice interval were 1.25 mm. The clinical target volume (CTV) margin was usually 0–5 mm around the gross tumor volume (GTV). A PTV margin of 5–8 mm around the CTV, including the respiratory motion reproducibility and the set-up error, was usually added. The isocenter was defined in the centroid of the GTV. Eight beams with coplanar and noncoplanar angles were used for all the patients. If possible, the beam directions did not cross critical organs at risk (OARs), such as the normal lung and spinal cord. Treatment plans with a dose of 48 Gy in four fractions were prescribed to the isocenter, and the dose was calculated using the Clarkson algorithm on Pinnacle³ (Phillips Medical Systems, Fitchburg, WI, USA).

Treatment plan evaluation

The plan, which was prescribed to the isocenter using the Clarkson algorithm, was recalculated using the superposition/convolution method with the scatterer compensation in heterogeneous tissues and the same monitor units. First, we evaluated the correlation of the $D_{95\%}$ of the PTV with the tumor diameter and the correlation of $D_{95\%}$ with the distance between the PTV and a scatterer, such as the chest wall, mediastinum, or heart, to confirm whether the $D_{95\%}$ of the PTV depends on the tumor size and the distance between the PTV and the scatterer. Next, we evaluated the dose of the highest conformity index (D_{Cmax}) and the $D_{95\%}$ of the PTV to determine the prescribed dose using the $D_{95\%}$ -prescribing method.

Correlation of $D_{95\%}$ of PTV with distance between the PTV and a scatterer

The correlation factor (r^2) of the $D_{95\%}$ of the PTV with the distance between the target and a scatterer was calculated. Various scatterers, such as the heart, chest wall, and diaphragm, were used. The positive and negative distances are shown in Fig. 1. The negative distance represents the largest overlapping distance between the PTV and the chest wall.

Correlation of the $D_{95\%}$ of the PTV with tumor diameter

The correlation factor (r^2) of $D_{95\%}$ of the PTV with the maximal tumor diameter was evaluated. The maximal tumor diameter was considered as the tumor diameter. The median tumor diameter was 16 mm (range of 8–30 mm).

Evaluation of $CI_{D_{max}}$ and $D_{95\%}$ of the PTV

The $D_{95\%}$ of the PTV is the dose covering 95% of the PTV. Various indices have been proposed for characterizing the degree of the dose conformity of the treatment volume to the PTV. We define a $CI_{(D)}$ that is modified from the $CI_{Paddick}$ suggested by Paddick [12, 13], defined as

$$CI_{(D)} = \frac{TV_{V(D)}}{V(D)} \times \frac{TV_{V(D)}^2}{TV} = \frac{TV_{V(D)}^2}{V(D) \times TV} \quad (1)$$

where $V(D)$ is the reference isodose volume of D , and $TV_{V(D)}$ is the target volume covered by $V(D)$. This formula shows whether the arbitrary dose completely covers the target. In the ideal case, $TV_{V(D)} = TV = V_{(D)}$. $CI_{D_{max}}$ is $V_{(D)}$, at which $CI_{(D)}$ is maximized, as shown in Fig. 2. We introduced $CI_{D_{max}}$ to evaluate the reference isodose that yields the highest dose conformity to the PTV.

The average doses— $D_{CI_{max}}$ and $D_{95\%}$ —were evaluated by considering the weighting factor (WF), which is defined as the inverse of the difference between the doses calculated using the superposition/convolution and Clarkson algorithms at the isocenter. We calculated the weighted average dose (D_{wav}) considering the WF, as follows:

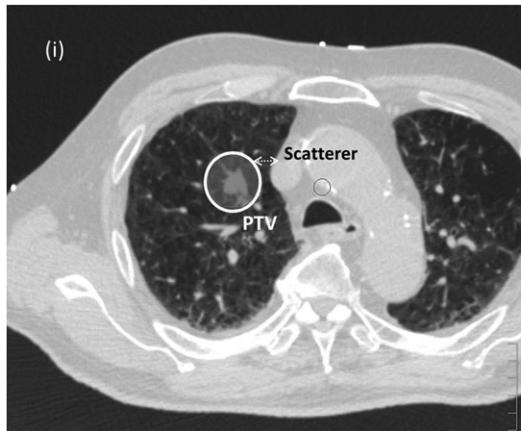


Fig. 1. Schematics of the relationship between the PTV and the scatterer. (i) The positive distance: the distance between the PTV and the scatterer is >0 mm. (ii) The negative distance: the distance between the PTV and the scatterer is <0 mm.

$$D_{wav} = \frac{\sum \frac{D_{sp} - D_{Cl}}{(D_{sp}/D_{Cl})^2}}{\sum (D_{sp}/D_{Cl})^2} \quad (2)$$

where D_{sp} is the dose calculated using the superposition/convolution algorithm, and D_{Cl} is the dose calculated using the Clarkson algorithm. D_{wav} has uncertainty σ_{wav} , which is defined as

$$\sigma_{wav} = \frac{1}{\sqrt{\sum \frac{1}{(D_{sp}/D_{Cl})^2}}} \quad (3)$$

This calculation is similar to the Chi-square method, in which the error is defined as the difference between D_{sp} and D_{Cl} .

RESULTS

Correlation of $D_{95\%}$ of the PTV with distance between the PTV and a scatterer

The characteristics of the distances between the PTV and scatterers, such as the chest and heart, are shown in Table 2. For the majority of the patients (85%), the PTV was close to the scatterer (≤ 0 cm). As shown in Fig. 3, the r^2 of $D_{95\%}$ is small with a significant distance

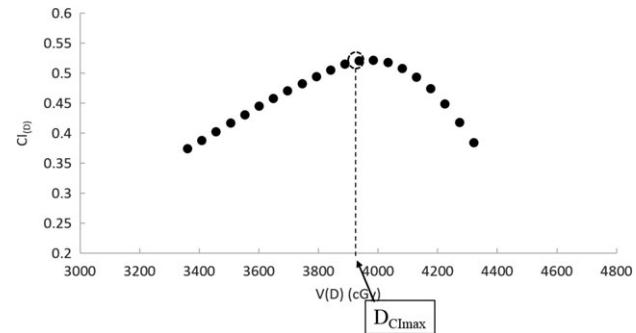


Fig. 2. $CI_{(D)}$ as a function of AI. AI is the volume of the arbitrary isodose line, which is the dose volume after the calculation. Maximal $CI_{(D)}$ is defined as $D_{CI_{max}}$.

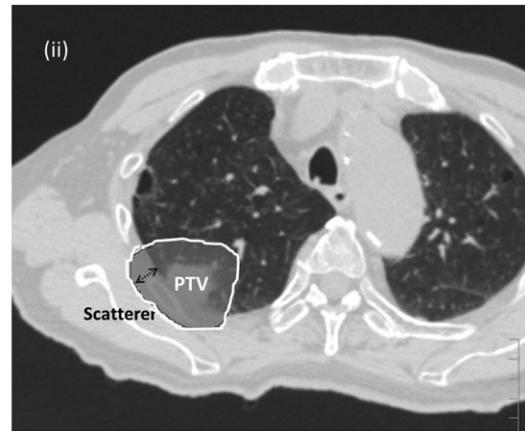
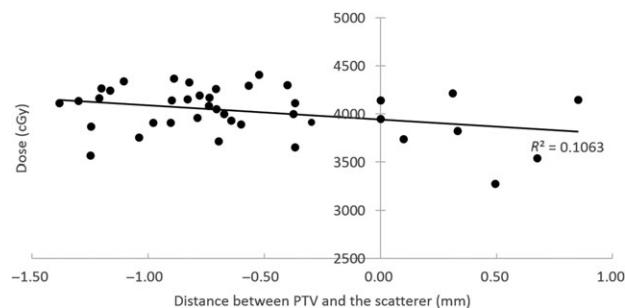


Table 2. The correlation between PTV and the scatterer

The shortest distance between the PTV margin and the scatterer (mm)	Average \pm SD (mm)	-5.9 ± 5.6
	Median (mm)	-7.1
	Range (mm)	-13.8 to 8.5
The PTV overlap with the scatterer	Patients (%)	34 (85%)

**Fig. 3. Correlation of D_{95%} of the PTV with the tumor diameter and with the distance between the PTV and the scatterer.**

between the PTV and the scatterer. All cases show a weak correlation ($r^2 = 0.1063$).

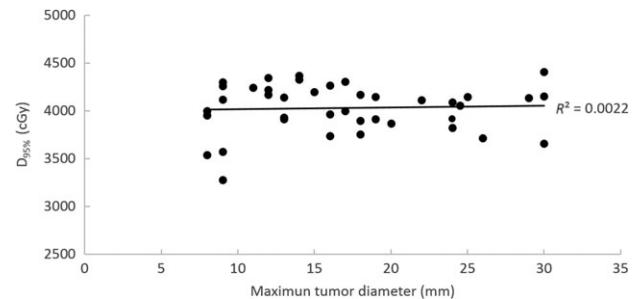
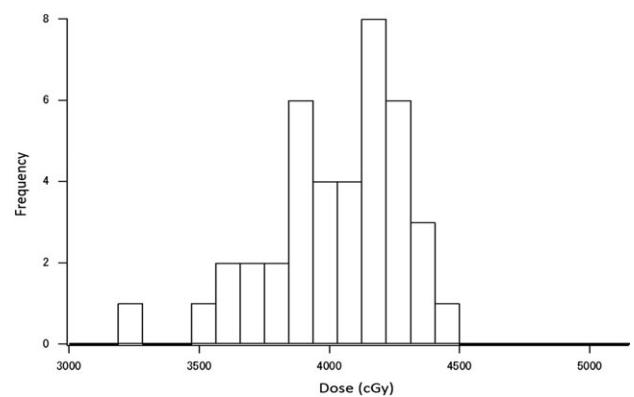
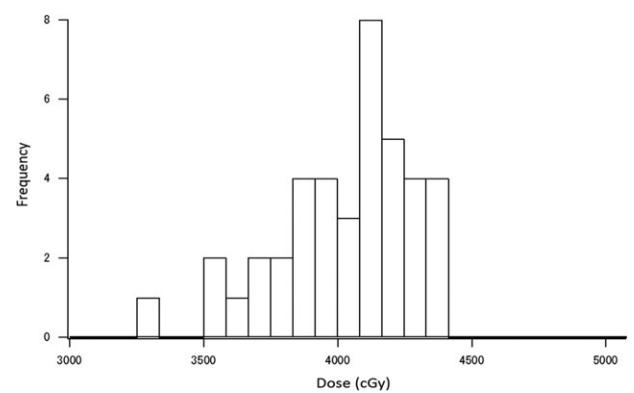
Correlation of D_{95%} of the PTV with tumor diameter

The characteristics of the patients, maximal tumor diameters, and tumor locations are shown in Table 2. The variation of the maximal tumor diameters was large (8–30 mm). The tumor maximal diameter for approximately half of the patients (45%) ranged from 10 to 20 mm. As shown in Fig. 4, the r^2 of the D_{95%} of the PTV with the tumor diameter is small. All cases show a weak correlation ($r^2 = 0.0022$).

Evaluation of D_{Clmax} and D_{95%} of the PTV

Figure 5 shows the histogram of D_{Clmax}. The minimal and maximal D_{Clmax} values are 30.7 and 44.1 Gy, respectively. Figure 6 shows the histogram of D_{95%} of the PTV. The minimal and maximal D_{Clmax} values were 32.9 and 44.1 Gy, respectively. The difference between the isocenter doses calculated using the superposition/convolution and Clarkson algorithms was 0.25 Gy (range of 0.09–0.56 Gy). This corresponds to an average prescribed dose difference of ~5%. The weighting averages for D_{Clmax} and D_{95%} of the PTV were 41.5 ± 0.3 Gy (range of 30.7–44.1 Gy) and 42.0 ± 0.3 Gy (range of 32.8–44.1 Gy), respectively.

The dose of the PTV with the highest conformity was 42.0 Gy, and the D_{95%} of the PTV was sufficient if the prescribed dose was 41.5 Gy. Therefore, the equivalent prescribed dose in the D_{95%}-prescribing method was determined to be 42 Gy by retrospectively

**Fig. 4. Correlation of D_{95%} of the PTV with the tumor diameter.****Fig. 5. D_{Clmax} which was recalculated using the superposition/Clarkson method after the calculation using the Clarkson method. D_{wav} is 42.0 Gy, and σ_{wav} is 0.03 Gy.****Fig. 6. D_{95%} of the PTV, which were recalculated using the superposition/Clarkson method after the calculation using the Clarkson method. D_{wav} is 41.5 Gy, and σ_{wav} is 0.03 Gy.**

reviewing the plan, yielding the equivalent prescription of 48 Gy in the isocenter-prescribing method.

DISCUSSION

Various prescription methods, doses, and heterogeneity corrections in dose calculations are used for lung SBRT at different institutions.

The dose calculation algorithm was changed to perform a heterogeneity correction with the development of computation technology [14–17]. In a clinical trial (RTOG 0236), no tissue density heterogeneity correction was allowed, and the prescribed dose for the D_{95%} of the PTV was 60 Gy in three fractions. However, a later analysis properly considering the density heterogeneity showed that the RTOG 0236 trial overpredicted the actual PTV dose and that the delivered dose was closer to 54 Gy in three fractions. Hence, we must consider the difference between the dose calculation algorithms. Several other studies have investigated the impact of heterogeneity corrections on the dose calculation with similar findings [14–16]. These studies revealed that heterogeneity corrections strongly influence the dose delivered to the PTV and the OARs. Ueki *et al.* [14] compared two dose calculation algorithms: the Batho power law (BPL) and the anisotropic analytical algorithm (AAA). PTV doses calculated using the BPL are lower than those calculated using the AAA, which is superior to the BPL owing to its heterogeneity correction. Zhuang *et al.* [16] reported that pencil beam calculations yield overestimation, and that a Monte Carlo method with heterogeneity correction is preferable. In the present study, we recalculated the plan of JCOG 0403 using the superposition/convolution algorithm, which is superior to the Clarkson algorithm regarding heterogeneity correction. The maximal difference between the isocenter doses calculated using these algorithms was >10%. In the previous studies, the target dose tended to be lower if the superposition/convolution algorithm was used than if the Clarkson algorithm was used [18, 19]. The trend of these papers is similar to that of our research. Generally, this implies that although pencil beam-like algorithms achieved a good PTV coverage, they are not good practically. The reason for this is lateral electron scattering, which is neglected if the Clarkson algorithm is used. In the present study, the weighting average of the dose calculations was evaluated using the residual between the Clarkson and the superposition/convolution algorithms as the WF. The equivalent prescribed dose to the D_{95%} of the PTV in JCOG 1408 was determined to be 42 Gy by retrospectively reviewing the plan of the isocenter-prescribing method.

Studies have revealed the correlation between dose calculation algorithms with respect to the tumor location and size [15, 20, 21]. In these studies, the patients were roughly separated by the tumor size, and the difference in D_{95%} between the two algorithms was larger for small tumors. The results of studies that investigated various calculation algorithms cannot be compared without considering the variation in the target-volume characteristics. Lateral electron transport is affected by the size of the target volume and by the surrounding tissue, e.g. the chest wall. In this study, we evaluated the correlation of the D_{95%} of the PTV with the tumor diameter and with the distance between a tumor and a scatterer. However, the correlations of the D_{95%} are weaker. Therefore, the size of the target volume and the surrounding tissue did not affect the target dose in the present study.

The variations of the D_{Clmax} and the D_{95%} of the PTV are large in the isocenter-prescribing method. The minimal and maximal D_{95%} values of the PTV are 25.6% and 30.4%, respectively, in D_{Clmax}. Although the treatment is performed using the same prescribing method, the target dose is not necessarily the same.

However, a new prescribing method using a dosimetrically equivalent marginal prescription can decrease this variation. It will be possible to reduce the dose difference among patients and to evaluate impartial treatment outcome.

The tumor density is not considered in our calculation, which is a limitation of this study. Voort *et al.* [20] discussed the effect of the medium density on lateral electron transport. Further studies need to assess the correlation of the tumor dose with the tumor density from a report [22] wherein various densities of the tumor and cancer-cell types are presented. Moreover, we did not clinically validate the dose prescription of D_{95%}. For this, we wish to wait for the treatment outcome of JCOG 1408.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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