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Three-dimensional Conformal Radiation Planning Study for Limited-stage Small-cell Lung Cancer

YUKINORI OKADA[1], TATSUHIKO ZAMA[1], TOMOHIRO ITONAGA[1], RYUJI MIKAMI[1], MITSURU OKUBO[1], SHINJI SUGAHARA[1], SHIHO WADA[1], TSUBASA KAWAMOTO[1], MASANORI ISHIDA[1], MOTOKI NAKAI[1], KOICHIRO ABE[1], MANA YOSHIMURA[1], TAKASHI KODAMA[2], MASAHIKO KUROOKA[2] and KAZUHIRO SAITO[1]

[1]Department of Radiology, Tokyo Medical University, Tokyo, Japan;
[2]Department of Radiation Therapy, Tokyo Medical University Hospital, Tokyo, Japan

Abstract

Background/Aim: To carry out a preliminary study to evaluate the dose distribution variation between the analytical anisotropic algorithm (AAA) and the Boltzmann transport equation, and between point and volume prescriptions in three-dimensional conformal radiation for limited-stage small-cell lung cancer.

Patients and Methods: We retrospectively selected patients with limited-stage small-cell lung cancer who received radiotherapy alone or chemoradiotherapy. Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were evaluated. Dose evaluation was performed for PTV, with AAA as point prescription, AAA as 50% prescription of PTV, Boltzmann transport equation as point prescription, and Boltzmann transport equation as 50% prescription of PTV.

Results: A total of 22 patients (15 males, 7 females; mean age=63.4 years) were included. The mean radiation doses for AAA/point AAA/D50, Boltzmann transport/point, and Boltzmann transport/D50 methods were 99.97±1.5%, 102.1±1.2%, 100.8±1.2%, and 101.3±1.3% to the GTV; 98.4±2.1%, 100.4±0.5%, 99.6±1.9%, 100.1±1.0% to the CTV; and 96.7±2.5%, 97.4±4.6%, 97.6±2.3%, 98.3±0.8% to the PTV, respectively. For AAA/point, AAA/D50, Boltzmann transport/point, and Boltzmann transport/D50 prescription methods, the correlation between the GTV (102.5±107.8 ml) and mean dose to the GTV was 0.23 (p=0.4), −0.476 (p=0.04), 0.00 (p=0.97), −0.79 (p<0.01); between CTV (342.7±242.6 ml) and mean dose to the CTV were 0.52 (p<0.01), −0.68 (p<0.01), 0.35 (p=015), −0.50 (p=0.03); between PTV (514.7±306.0 ml) and mean dose to the PTV were 0.59 (p<0.01) 0.75 (p<0.01),0.82 (p<0.01) and 0.78 (p<0.01), respectively.

Conclusion: The AAA point-prescription approach can systematically underestimate target dose in 3D conformal radiotherapy for limited-stage small-cell lung cancer and shows less robust dose–volume behavior across GTV, CTV, and PTV compared with volume-based prescription and Boltzmann transport calculations. Therefore, AAA with point prescription should be avoided for dose calculation in this setting.

Keywords: Limited-stage small-cell cancer, radiation, chemotherapy, Boltzmann transport, analytical anisotropic algorithm, three-dimensional conformal radiation.

Yukinori Okada, MD, Department of Radiology, Tokyo Medical University, 671 Nishishinjuku, Tokyo 1600023, Japan. Tel: +81 333426111, e-mail: okadayu@tokyo-med.ac.jp

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Introduction

Small-cell lung cancer is a high-grade neuroendocrine carcinoma, and its prognosis is poor (1). In extensive-stage small-cell lung cancer, chemotherapy plus immune checkpoint inhibitors is the standard first-line therapy. In a phase III study, anticancer agents plus the immune checkpoint inhibitor atezolizumab led to a median survival of 12.3 months whilst therapy with anticancer agent alone only achieved a median survival of 10.3 months (2). In limited-stage small-cell lung cancer, chemotherapy plus radiotherapy is the standard first-line therapy

In 1999, the utility of accelerated hyper-fractionated irradiation (1.5 Gy twice daily for a total of 45 Gy/30 times for 3 weeks) with cisplatin and etoposide was reported (3). In that study, accelerated hyper-fractionated irradiation improved overall survival outcomes compared with conventional fractionated irradiation (1.8 Gy once daily for a total of 45 Gy/30 fractions over 5 weeks) (3). However, important results of a clinical trial for limited-stage small-cell lung cancer were reported between 2023 and 2024. In platinum and etoposide-based chemotherapy, the median survival of 108 patients treated with intensity-modulated radiotherapy, 1.8 Gy twice daily for a total of 54 Gy/30 fractions, was 60.7 months, and that of 116 patients treated with 1.5 Gy twice daily for a total of 45 Gy/30 fractions was 39.5 months (4). Moreover, the utility of immune checkpoint inhibitor was then reported. The median survival was 55.9 months for 264 patients treated with chemoradiotherapy and then immune checkpoint inhibitor (durvalumab) compared with 33.4 months for 266 patients treated only with chemoradiotherapy (5). Radiation doses of 45 Gy/30 fractions/15 days and 60 Gy/30 fractions/15 days were used in 30% and 70% of those patients, and the group that received 45 Gy/30 fractions/15 days did not show statistically significantly altered median survival (5). From these results, (i) 54 Gy/30 fractions over 15 days of intensity-modulated radiotherapy with chemotherapy, and (ii) 60 Gy/30 fractions with chemotherapy plus immune checkpoint inhibitors after chemoradiotherapy were considered standard therapy for limited-stage small-cell lung cancer. Accelerated hyper-fractionated irradiation with 45 Gy/30 fractions over 15 days can be reduced and the radiation dose escalated for limited-stage small-cell lung cancer, if necessary.

In clinical practice, radiation therapy continues to evolve through advancements in irradiation techniques and dose-calculation methods. Three-dimensional (3D) conformal radiation therapy is widely used, while intensity-modulated radiation therapy is used in selected cases. Moreover, progress in dose-calculation models includes the development of a third-generation analytical anisotropic algorithm (AAA) (6), which allows the correction of inhomogeneous regions. Currently, the fourth-generation linear Boltzmann transport equation (7) is being used, which accurately models the behavior of particles (transport and interactions) in matter (8) and shows the actual density of materials with high accuracy. Point prescription, where the dose is administered at a single point within the target volume, has been used in 3D radiation therapy. However, it is necessary to consider statistical errors in the planned target volume (PTV) owing to the complexity of multi leaf collimator motion. Volumetric prescriptions are used to determine PTVs. Volume prescriptions can also be used for 3D radiation therapy. The 2024 edition of the Radiation Therapy Guidelines for Non-Small-cell Lung Cancer states that heterogeneity correction using point prescriptions may result in a lower target dose and that there is a method that uses 95% or 50% of the target lesion as the indicated dose (9). Furthermore, performing heterogeneous correction in dose-distribution calculations using an algorithm equivalent to superposition or higher (which is closer to the actual values) is recommended (9). However, whether the dose distribution differs between the AAA method and the Boltzmann transport equation, and between point and volume prescription in 3D conformal radiation is unclear. This study aimed to investigate whether the dose distribution differs between the AAA method and the Boltzmann transport equation, and between point and volume prescriptions in 3D conformal radiation for limited-stage small-cell lung cancer.

Patients and Methods

Study design. This study was a single-center, retrospective, dummy planning study and was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Review Committee of Tokyo Medical University Hospital (T2024-0100). An opt-out form was posted on the website of the Tokyo Medical University Hospital. Furthermore, only patients who provided permission to use their data in a patient questionnaire at the time of consultation at the Radiotherapy Department were included in this study.

Patient selection. We retrospectively selected patients with limited-stage small-cell lung cancer who received radiotherapy alone or chemoradiotherapy at the Tokyo Medical University Hospital from July 2019 to March 2025. The study population comprised individuals aged between 20 and 100 years. Exclusion criteria were as follows: patients with active multiple cancer at the time of small-cell lung cancer diagnosis, those with high probability of multiple cancer based on clinical course and imaging diagnosis, patients who were being treated for active cancer at the time of diagnosis of limited-stage small-cell lung cancer, those included in other clinical trials or studies, and those who declined consent for the use of their data. However, patients with a history of other cancer were not excluded if they were under observation without active treatment and showed no recurrent metastasis on positron-emission computed tomography (PET-CT), computed tomography (CT), or magnetic resonance imaging. Additionally, patients who were not enrolled in a clinical trial when radiotherapy was planned but were subsequently included for different purposes in other departments were also not excluded.

Dummy planning. A dummy plan based on images from a 16-row CT scanner (Aquilion: Canon Medical Systems Co, Otawara, Tochigi, Japan) was devised. CT was performed using 2-mm slice thickness. The targets for radiotherapy planning were written into CT images at the time of radiotherapy planning by Y.O., a Radiation Oncologist and Nuclear Medicine specialist.

The targets were the gross tumor volume (GTV), clinical target volume (CTV), and PTV. The GTV was defined as the area where the tumor was clearly present on the radiotherapy planning CT and included primary tumors and metastases. The CTV was defined as the GTV with a 1-cm margin. The PTV was defined as the CTV with a 0.5-cm margin.

Patients were treated with chemotherapy by including only PET/CT-positive lymph nodes and excluding the subclinical lymph nodes in the radiation field, as the lymph node recurrence rate was reportedly only 3% (10). For patients who received induction chemotherapy prior to radiotherapy, targets were written using CT images acquired after chemotherapy and before initiation of radiotherapy. In some patients who had received chemotherapy before radiotherapy, the fusion of PET-CT images at the initial visit with CT radiotherapy planning by MIM Maestro (Euro Meditech Co. Ltd, Tokyo, Japan/MIM Software Co. Ltd, Cleveland, OH, USA) was not performed. The target was not entered based on the tumor status on CT images before radiotherapy was initiated. PET-CT images were obtained from the electronic medical records (NEC, Tokyo, Japan).

Following target writing, the dummy plan was created using Eclipse (Varian Medical Systems Co., Ltd., Palo Alto, CA, USA) with a true-beam linear accelerator (Varian Medical Systems Co., Ltd.). A radiation therapy plan was designed using two anteroposterior and two lateral collimators, and 10 MV energy were used. The width of the multileaf collimator was 5 mm, and the leaf margin was set to 0 mm on the PTV. We assumed 30 Gy/20 fractions over 10 days for the 3D radiation (11) because it was possible to change the plan to 45 Gy/30 times/15 days. The dose ratios were assumed to be constant at 30% each for the two anteroposterior beams, and 20% each for the two oblique-entry beams. In this study, for patients with contralateral supraclavicular lymph node metastases, a dummy plan was not designed because planning radiotherapy was considered difficult with two anteroposterior and two oblique entry arms.

Dose prescription was performed for PTV, with AAA as point prescription, AAA as 50% prescription of PTV, Boltzmann transport equation as point prescription, and Boltzmann transport equation as 50% prescription of PTV. The prescription points were set at sites considered appropriate within the PTV and were common for comparison.

Dummy plan evaluation. The dummy plan was evaluated using the mean doses of the GTV, CTV, and PTV for each patient. The mean and variance of mean doses for all patients were determined. Furthermore, the correlation between the mean doses of GTV, CTV, and PTV and the volumes of the GTV, CTV, and PTV was examined. The analyses were conducted for the following: AAA with point prescription, AAA with 50% prescription of PTV, Boltzmann transport equation with point prescription, and Boltzmann transport equation with 50% prescription of PTV.

Statistical analysis. Eazy ZR, the statistical software developed by the Jichi Medical University Saitama Medical Center (12) was used for analyses. Data are reported as mean±standard deviation. Spearman's rank correlation coefficient was used to calculate the correlation coefficient; values of $p<0.05$ were considered statistically significant.

Previous studies. Although this study included all the patients of the previous study by Okada *et al.* (13), we considered this a new and separate study because the design of the previous study was different from the analysis of PET images using MIM Maestro, and the present study involved radiation therapy planning by dummy plan using Eclipse.

Results

Patient selection. A total of 22 patients (15 males and seven females) with a mean age of 63.4±8.8 years were selected for this study. All patients received chemotherapy. Three patients were excluded: two who were included in a clinical study on radiation pneumonia in our department, and one who refused consent to the use of his data.

Examination of dose distribution. Dummy plans were used in 19 cases, excluding the following three cases: a 65-year-old man and a 60-year-old man who had contralateral supraclavicular lymph node metastases which were considered difficult to irradiate with 3D radiation therapy, and a 57-year-old man who had a primary tumor located in the peripheral lung. Combining the tumor and lymph node metastases in a single irradiation field was expected to result in an increased lung dose.

GTV. The mean GTV in radiotherapy planning CT was 102.5±107.8 ml. In the AAA PTV point prescription, the maximum, mean, and minimum doses to the GTV were 104.1±2.9%, 100.0±1.5%, and 95.1±2.5%, respectively. For the AAA PTVD50 prescription, the maximum, mean, and minimum doses to the GTV were 106.4±1.4%,102.1±1.2%, and 95.5±2.2%, respectively. For the Boltzmann transport equation PTV point prescription, the maximum, mean, and minimum doses to the GTV were 107.1±2.4%, 100.8±1.2%, and 94.3±2.6%, respectively. For the PTVD50 formulation of the Boltzmann transport equation, the maximum, mean, and minimum doses to the GTV were 107.5±2.0, 101.3±1.3%, and 94.9±2.5%, respectively.

The mean dose to the GTV and GTV for the PTVD50 formulation of AAA were significantly inversely correlated ($r=-0.48$, $p=0.04$), as they were for the PTVD50 formulation of the Boltzmann transport equation ($r=-0.79$, $p<0.01$), and the minimum dose to the GTV and GTV. The correlations between the GTV and the maximum, average, and minimum GTV doses for each normalization method are shown in Table I.

CTV. The mean CTV in radiotherapy planning CT was 342.7±242.6 ml. For the AAA PTV point prescription, the maximum, mean, and minimum doses to the CTV were 99.8±24.1%,98.4±2.1%, and 72.6±6.4%, respectively. For the AAA PTVD50 prescription, the maximum, mean, and minimum doses to the CTV were 107.2±1.7%,

Table I. *Correlations between gross tumor volume (GTV) and maximum, average, and minimum GTV doses for each normalization method.*

Method of normalization	Maximum dose at GTV and GTV	Mean dose at GTV and GTV	Minimum dose at GTV and GTV
AAA and point prescription at PTV	r=0.25	r=0.23	r=0.07
	p=0.31	*p*=0.34	*p*=0.77
AAA and D50 prescription at PTV	r=−0.27	r=−0.48	r=−0.41
	p=0.26	***p*=0.04**	*p*=0.08
Boltzmann transport and point prescription at PTV	r=0.00	r=0.00	r=−0.39
	p>0.99	*p*=0.97	*p*=0.10
Boltzmann transport and D50 prescription at PTV	r=−0.382	r=−0.79	r=−0.66
	p=0.107	***p*<0.01**	***p*<0.01**

AAA: Analytical anisotropic algorithm; D50: dose covering 50% of the volume; PTV: planning tumor volume. Statistically significant *p*-values are shown in bold.

100.4±0.5%, and 74.8±27.1%, respectively. For the PTV point prescription of the Boltzmann transport equation, the maximum, mean, and minimum doses to the CTV were 108.1±2.6%, 99.6±1.9%, and 69.2±25.1%, respectively. For the PTVD50 prescription with the Boltzmann transport equation, the maximum, mean, and minimum doses to the CTV were 108.6±1.8%, 100.1±1.0%, and 68.7±25.3%, respectively.

Significant correlations were found between the mean dose to the CTV and CTV for the AAA PTV point prescription (r=0.52, p<0.01), the AAA PTVD50 prescription (r=−0.68, p<0.01), and the mean dose to the CTV and CTV for the PTVD50 prescription (r=−0.50, p=0.03) in the Boltzmann transport equation. The results are summarized in Table II.

PTV. The mean PTV in radiotherapy planning CT was 514.7±306.0 ml. For the AAA PTV prescription, the maximum, mean, and minimum doses to the PTV were 105.5±2.7%, 96.7±2.5%, and 47.0±24.9%, respectively. For the AAA PTVD50 prescription, the maximum, mean, and minimum doses to the PTV are as follows: 107.3±2.4%, 97.4±4.6%, and 43.3±25.0%, respectively. For the Boltzmann transport equation PTV point prescription, the maximum, mean, and minimum doses to the PTV were 108.6±2.8%, 97.6±2.3%, and 48.1±25.7%, respectively. For the PTVD50 prescription of the Boltzmann transport equation, the maximum, mean, and minimum doses to the PTV were 109.4±1.4%, 98.3±0.8% and 48.3±23.3%, respectively.

The mean dose to the PTV and PTV for the AAA PTV point prescription were significantly positively correlated (r=0.59, p<0.01), as they were for the AAA PTVD50 prescription (r=0.75, p<0.01), the Boltzmann transport equation PTV point prescription (r=0.821, p<0.01), and the PTVD50 prescription (r=0.78, p<0.01) in the Boltzmann transport equation. The results are shown in Table III.

Discussion

The study findings identified the dose distribution values for 3D conformal radiation planning in limited-stage small-cell lung cancer. In the Boltzmann transport equation for 50% of the PTV, which is used in intensity-modulated radiation therapy and is assumed to accurately reflect the dose distribution in the body, some differences in values between the dose-calculation algorithm and the dose prescription were observed. In GTV evaluation using the Boltzmann transport equation for 50% of the PTV, the average and minimum doses decreased as the GTV increased. However, there was no statistically significant correlation between the GTV and mean dose for the AAA point prescription and the Boltzmann transport equation point prescription. In CTV evaluation, for the AAA point prescription, the CTV and mean dose were statistically

Table II. *Correlations between clinical target volume (CTV) and maximum, average, and minimum CTV doses for each normalization method.*

Method of normalization	Maximum dose at CTV and CTV	Mean dose at CTV and CTV	Minimum dose at CTV and CTV
AAA and point prescription at PTV	r=0.41	r=0.52	r=0.12
	***p*=0.08**	***p*<0.01**	*p*=0.38
AAA and D50 prescription at PTV	r=−0.33	r=−0.68	r=−0.02
	p=0.13	***p*<0.01**	*p*=0.33
Boltzmann transport and point prescription at PTV	r=0.32	r=0.35	r=−0.15
	p=0.17	*p*=0.15	*p*=0.53
Boltzmann transport and D50 prescription at PTV	r=−0.106	r=−0.50	r=−0.06
	p=0.69	***p*=0.03**	*p*=0.82

AAA: Analytical anisotropic algorithm; D50: dose covering 50% of the volume; PTV: planning tumor volume. Statistically significant *p*-values are shown in bold.

Table III. *Correlations between planning tumor volume (PTV) and maximum, average, and minimum PTV doses for each normalization method.*

Method of normalization	Maximum dose at PTV and PTV	Mean dose at PTV and PTV	Minimum dose at PTV and PTV
AAA and point prescription at PTV	r=0.45	r=0.59	r=0.46
	p=0.06	***p*<0.01**	***p*=0.048**
AAA and D50 prescription at PTV	r=−0.38	r=0.75	r=0.48
	p=0.13	***p*<0.01**	***p*=0.047**
Boltzmann transport and point prescription at PTV	r=−0.39	r=0.82	r=0.49
	p=0.12	***p*<0.01**	***p*=0.03**
Boltzmann transport and D50 prescription at PTV	r=0.02	r=0.78	r=0.38
	p=0.95	***p*<0.01**	*p*=0.10

AAA: Analytical anisotropic algorithm; D50: dose covering 50% of the volume. Statistically significant *p*-values are shown in bold.

significantly positively correlated, whereas the AAA prescription for 50% PTV and the D50 prescription for PTV in the Boltzmann transport equation showed statistically significant negative correlation between the CTV and mean dose. In PTV evaluation, although there was statistically significant positive correlation between PTV and the mean dose for the AAA point prescription, AAA prescription for 50% of PTV, Boltzmann transport equation point prescription, and Boltzmann transport equation prescription for 50% of PTV, the correlation coefficient was the lowest in the AAA point prescription. Based on these results, we believe that the AAA point prescription has the following issues: (i) it fails to calculate the actual dose decrease as the GTV volume increases (overestimating the GTV dose); (ii) the dose increases with an increase in CTV (overestimating the CTV dose), despite the existence of a negative correlation between the increase in CTV and the average dose; (iii) there is insufficient dose increase corresponding to an increase in PTV volume. Therefore, the dose distribution in the AAA point prescription is not appropriate for 3D conformal radiation planning in limited-stage small-cell lung cancer.

Intensity-modulated radiotherapy provides highly accurate results and simultaneous integrated boost (SIB) makes it possible to vary the dose distribution by site. In a study of 35 patients who received SIB, the median survival was 37.7 months, and the 1-year and 2-year overall survival rates were 94.1% and 68.5%, respectively (14). In a study of 52 patients, with SIB-irradiated PTV at 54 Gy/30 fractions over 15 days, a median survival of 24 months was reported (15). Although information regarding the dose-calculation algorithms is insufficient

in these reports, the use of volume prescriptions in intensity-modulated radiotherapy and the possibility of dose constraints for the GTV, CTV, and PTV may have influenced treatment outcomes. Performance status and GTV were reported to be prognostic factors in 119 patients with limited-stage small-cell lung cancer treated with accelerated fractionated irradiation at 45 Gy/30 fractions over 15 days (16). In 105 patients with limited-stage small-cell lung cancer, tumor volume at the time of CT radiotherapy planning was a prognostic factor for the local control rate and overall survival (17). Based on these reports, we believe that GTV control in limited-stage small-cell lung cancer is important and may not be suitable for use in point prescription to the PTV in AAA and Boltzmann transport equation for 3D irradiation.

There are some limitations to this study that should be considered. The number of patients was limited, and the analysis was performed retrospectively. The results were not compared with actual clinical outcomes. Moreover, there are some planning study reports comparing intensity-modulated radiotherapy and 3D-CRT in gastric lymphoma (18) and non-small-cell lung cancer (19); in this study, we did not compare the dose distribution between 3D-CRT and intensity-modulated radiotherapy. Further studies with larger patient populations are required.

Conclusion

The algorithm of AAA point prescription underestimates the dose and has a wide range of variance. The use of the AAA point prescription as an algorithm for dose calculation in 3D irradiation should be avoided in patients with limited-stage small-cell lung cancer.

Conflicts of Interest

Yukinori Okada is a member of the Expert Imaging and Interventional Support Society; however, this is an unpaid role; he previously received lecture fees that were unrelated to the content of this study. All authors have no conflicts of interest for this study.

Authors' Contributions

Y.O: Conception (research idea), dummy planning, and analysis. T.Z., T.I, R.M, M.O, S.S, S.W. T.K: radiation oncological-related support. M.I, M.N, K.A, M, Y, K.S: medical imaging-related support. T.K., M.K: research medical physics-related support.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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