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Accelerated hypofractionated radiotherapy with 3 Gy per fraction for central/ultra-central lung tumors: toxicity to mediastinal organs

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Abstract

Background: Accelerated hypofractionated radiotherapy with 3 Gy per fraction is routinely performed for central lung tumors in Japan. However, the tolerable doses to mediastinal organs at risk during this procedure are unclear. This study aimed to clarify the rate of toxicities and tolerable doses to mediastinal organs.

Methods: Patients treated with accelerated hypofractionated radiotherapy using a total dose of 60–75 Gy, with 3 Gy per fraction, for central lung tumors (July 2009–April 2021) were retrospectively reviewed. We extracted patients who received ≥30 Gy irradiation to each mediastinal organ and analyzed dosimetric factors, including doses to 0.03, 0.5, 1, 4 and 10 mL of each organ, in relation to grade 3–5 toxicities, except for radiation pneumonitis.

Results: In total, 251 organs in 91 (ultra-central, 24) lesions were analyzed, with a median follow-up duration of 26 months (range, 4–94). The prescribed doses were 75/72/69/66/63/60 Gy for 52/14/16/3/2/4 lesions, respectively. Grade 3 bronchopulmonary hemorrhage was confirmed in two (2.2%) patients, whose tumors were located ultra-centrally. The two patients with toxicity received up to 74.5 and 71.6 Gy to the bronchus. Among patients who received 70 Gy or more to the bronchus, the incidence rate was 7% (2/28 patients).

Conclusion: The rate of severe toxicities was low (2.2%). Although we did not identify the dose tolerance of the organs, because of the low incidence rate, we did note that doses of >70 Gy to the bronchus were likely to cause bronchopulmonary hemorrhage.

Key words: Accelerated hypofractionated radiotherapy, lung neoplasms, mediastinal organs, ultra-central lung tumor

Introduction

Stereotactic body radiotherapy (SBRT) for peripheral lung tumors has achieved excellent tumor control with low toxicity (1–4); hence, it is an established treatment for patients with inoperable early-stage non-small cell lung cancer (NSCLC) or for those declining surgery (5). Additionally, based on several randomized phase II trials, SBRT is widely performed for oligometastatic lung tumors, suggesting a survival benefit (6,7).

However, high-dose per fraction SBRT is difficult to administer for centrally located tumors because of its toxicity to serial organs (8). A phase II trial of SBRT with doses of 60–66 Gy in three fractions showed grade 3–5 toxicities in 6 out of 22 patients (27%) with central tumors (9). Therefore, attempts have been made to decrease the risk of toxicity while maintaining the delivered dose to the tumor, by using an increased number of lower dose fractions (an accelerated hypofractionated radiotherapy [AHRT]) (10–12). In Japan, AHRT, a total of 75 Gy at 3 Gy per fraction, is widely used for central and ultra-central lung tumors (10). We previously reported that the AHRT regimen provided comparable local control (LC) and survival compared with SBRT (10).

However, the tolerable doses to mediastinal organs at risk (OARs) are unclear in the AHRT regimen. The aim of this study was to investigate the incidence of adverse effects (AEs) and tolerable doses to mediastinal OARs in a patient cohort treated with AHRT with 3 Gy per fraction.

Materials and methods

Patients and data acquisition

We retrospectively reviewed the outcomes of patients treated with AHRT for central and ultra-central early-stage NSCLC and lung metastases at a single institution between July 2009 and April 2021. Four lesions (4.4%) were treated before November 2009; the remaining 87 lesions (95.6%) were treated after September 2012 (when our institution installed high-precision radiotherapy equipment). Patients were included if they met the following criteria: (i) pathologically or clinically diagnosed stage I NSCLC (Union for International Cancer Control staging criteria, 7th edition (13)) or ≤3 lung metastases (diameter: ≤5 cm); (ii) centrally located target tumor; (iii) AHRT with a total dose ≥60 Gy using 3 Gy per fraction was performed and (iv) patients were followed up for at least 12 months or until death. No contraindications for AHRT, based on the location of the lung tumor, were documented.

Centrality was defined either as tumors located within 2 cm of the proximal bronchial tree (PBT: the carina, right and left main bronchi, right and left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus and right and left lower lobe bronchi); or those whose planning target volume (PTV) came in contact with the mediastinal or pericardial pleura, according to the RTOG0813 trial (14). An ultra-central lung tumor was defined as one abutting the trachea or PBT (15).

This study was approved by our institutional ethical review board (approval number: 1151), and informed consent was obtained in the form of an opt-out option displayed on the website.

Stereotactic body radiotherapy

The prescribed dose was 75 Gy in 25 fractions over 5 weeks. However, some patients underwent modified AHRT with a reduced 1–5 fraction size (total dose, 60–72 Gy) for safety, at the discretion of radiation oncologists in charge.

The treatment methods of the few patients (4/91 lesions) treated before November 2009 were previously described in detail (10). The majority of patients (87/91 lesions) were treated after September 2012 using the following methods. Patients were immobilized using VacLok cushions (CIVCO Medical Solutions, Coralville, IA, USA). Gated computed tomography (CT) scans were acquired at the end of exhalation. Four-dimensional (4D)-CT was performed to assess the respiratory tumor motion. The gross tumor volume (GTV) was delineated on gated CT with reference to diagnostic enhanced CT and positron emission tomography/CT. An internal target volume (ITV) was created as the union of the GTVs from all 10 phases of 4D-CT, and a PTV was created with a 5-mm margin around the ITV. Dose distributions were calculated with heterogeneity correction using the Monte Carlo algorithm in iPlan RT Dose (Brainlab AG, Feldkirchen, Germany) or collapsed cone algorithm in RayStation (RaySearch Laboratories AB, Stockholm, Sweden). Image guidance was performed using kilovoltage cone-beam CT before each treatment. All treatments were performed using 4–6 MV linear accelerators with multi-leaf collimators. Intensity-modulated radiotherapy (IMRT) technique was used for some patients. The AHRT required 50% of the PTV to receive 100% of the prescribed dose. In addition, the dose received by 2% of the PTV was limited to 115% of the prescribed dose to achieve a homogenous dose distribution. The dose constraints used in the study are summarized in the Table 1.

Delineation and dose quantification of OARs

We re-delineated the mediastinal organs (the aorta, superior vena cava, pulmonary artery, pulmonary vein, trachea/bronchi and esophagus) in all patients. The pulmonary artery was contoured to include the pulmonary trunk, bilateral pulmonary arteries, bilateral superior lobar arteries, middle lobar artery, lingular artery and bilateral inferior lobar arteries. The pulmonary vein was contoured to include the bilateral superior and inferior pulmonary veins. The bronchus consisted of the bilateral mainstem bronchi, upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus and the bilateral inferior lobe bronchi. No planning OAR volume margin associated with respiratory and heartbeat motion was added to any organs.

In this study, we investigated each OAR irradiated with 30 Gy or more during AHRT. OARs were evaluated using dose-volume histograms (DVHs). The doses irradiated to 0.03 mL ($D_{0.03\,mL}$), 0.5 mL ($D_{0.5\,mL}$), 1 mL ($D_{1\,mL}$), 4 mL ($D_{4\,mL}$) and 10 mL ($D_{10\,mL}$) in each organ were analyzed as potential predictors based on previous studies (16). This study used near-maximum dose ($D_{0.03\,mL}$) with less uncertainty than with maximum dose (17).

Evaluation and statistical analysis

The primary endpoint was the incidence of grade 3 or higher AEs and tolerable doses to mediastinal OARs. AEs were graded according to the Common Terminology Criteria for Adverse Events (version 5) (18). Toxicities were determined as one of 'definite/probable/possible/negative/none' radiotherapy-related AEs, and 'definite/probable/possible' were defined as the events. Study observation was terminated when definitive or palliative re-irradiation at the same site was administered.

The secondary endpoints were the overall survival (OS) and LC. OS was calculated in months from the start date of AHRT to the most recent follow-up, or death from any cause. LC was defined as the interval between the start date of AHRT and local tumor recurrence.

Table 1. Dose constraints in accelerated hypofractionated radiotherapy

Organs	Volume (ml)	Dose (Gy)	Avoidance endpoint
Aorta	10	70	Aneurysm
Superior vena cava	10	70	Stenosis/fistula
Pulmonary artery	1	75	Aneurysm
	10	70	
Pulmonary vein	10	70	Stenosis/fistula
Trachea/bronchi	1	75	Stenosis/fistula
	10	70	
Esophagus	5	55	Stenosis/fistula

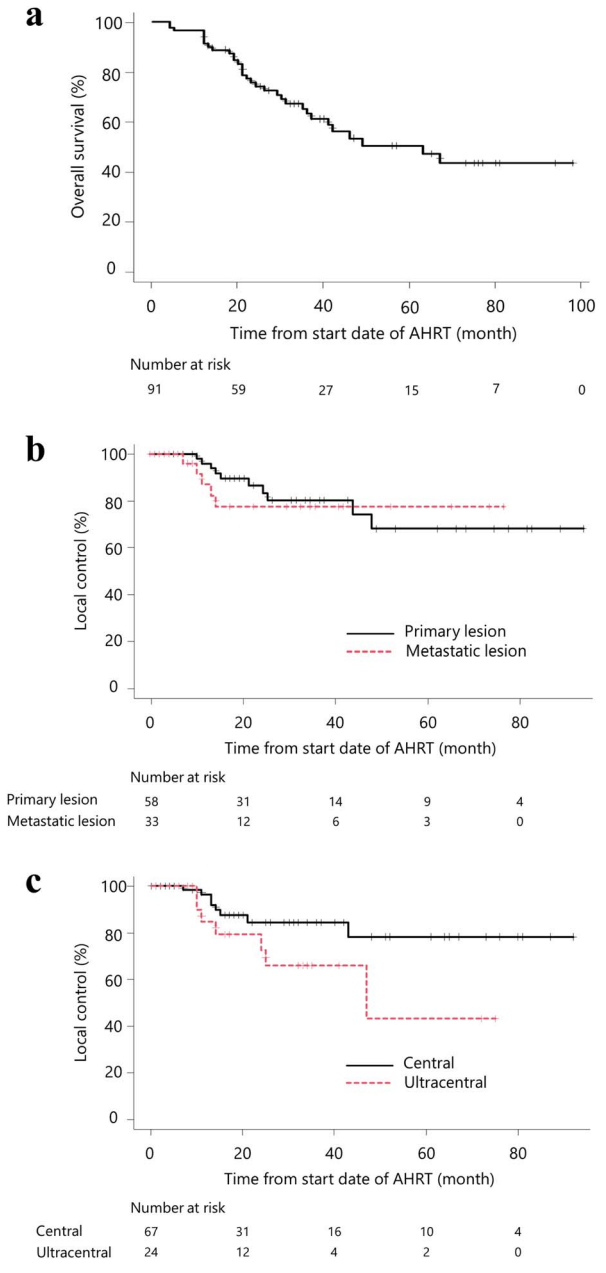

Figure 1. Kaplan–Meier curves of (a) overall survival, local control in patients with (b) primary lung cancer and lung metastases and (c) central and ultra-central lung tumors.

Follow-up CT was scheduled every 3 months for 2 years after AHRT and every 6 months thereafter. Local tumor recurrence was defined as progressive CT soft-tissue abnormalities that corresponded to avid areas on positron emission tomography/CT or post-treatment biopsy showing carcinoma.

Kaplan–Meier curves were constructed to estimate OS and LC. These statistical analyses were performed using the EZR version 1.54 (19).

Results

A total of 91 lesions (24 ultra-central lesions) in 88 patients were included in this study. Patient and treatment characteristics are shown in Table 2 and divided according to central and ultra-central lung tumors. Patients most commonly underwent AHRT of 75 Gy (57%), followed by 69 and 72 Gy (18 and 15%, respectively). The number of OARs irradiated with ≥30 Gy was 47, 18, 58, 37, 65 and 26, namely, these included the aorta, superior vena cava, pulmonary artery, pulmonary vein, trachea/bronchi and esophagus, respectively. The IMRT technique was used for 11 (12%) lesions.

Clinical outcomes

The median follow-up period was 26 months (range, 4–94 months). The 2-year OS and median survival times were 74% and 63 months, respectively (Fig. 1a). During the follow-up, there were 15 local tumor recurrences. The 2-year LC rate was 83% for primary lesions and 77% for metastatic lesions (Fig. 1a). The 2-year LC rate was 85% for central lesions and 73% for ultra-central lesions (Fig. 1c).

Table 3 summarizes the incidence of mediastinal organs' AEs induced by AHRT. Grade 2 or higher AEs were confirmed in two (2.2%) patients who experienced grade 3 bronchopulmonary hemorrhage 30 and 35 months after AHRT (detailed information is provided in the next section). Among patients with ultra-central lung tumors, the incidence rate was 8% (2/24 patients). No other AEs ≥ grade 3 were observed.

Detailed information of patients with severe AEs

The first patient was a 75-year-old man with lung metastases from liver cancer in the right superior lobe who underwent AHRT of 75 Gy in 25 fractions (Fig. 2a and b). The patient was referred for hemoptysis 35 months after the AHRT. Catheterization revealed that the source of bleeding was the right bronchial artery toward the irradiated lesion (Fig. 2c), and hemostasis was achieved using embolization. He did not experience re-bleeding or local tumor recurrence during the 37 months of follow-up. It was judged

Table 2. Patient and treatment characteristics divided according to central and ultra-central lung tumor

	Central tumor ($n = 67$)	Ultra-central tumor ($n = 24$)
Sex*		
Male/Female	45/22	17/7
Age (years)		
Median (range)	76 (40–91)	75 (54–88)
ECOG PS		
0/1/2/3/4	18/39/10/0/0	7/13/4/0/0
Tumor type		
Primary lung cancer	45	13
Lung metastases	22	11
Dose fraction schedules		
75 Gy in 25 fractions	45	7
72 Gy in 24 fractions	10	4
69 Gy in 23 fractions	7	9
66 Gy in 22 fractions	1	2
63 Gy in 21 fractions	1	1
60 Gy in 20 fractions	3	1
Irradiation technique		
3D-CRT/IMRT	61/6	19/5
OARs irradiated with ≥30 Gy		
Aorta	37	10
Superior vena cava	13	5
Pulmonary artery	36	22
Pulmonary vein	23	14
Trachea/bronchi	41	24
Esophagus	19	7

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IMRT, intensity-modulated radiotherapy; OARs, organs at risk; 3D-CRT, three-dimensional conformal radiotherapy

[a]Sex was counted by the number of patients. A patient received two radiotherapies for central and ultra-central lung tumors.

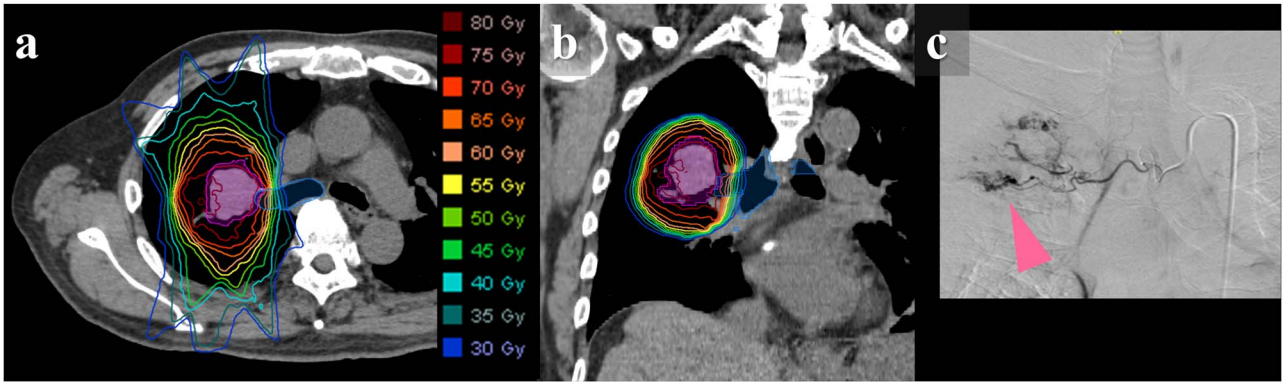

Figure 2. Imaging findings for a 75-year-old man with definite radiotherapy-related hemoptysis. (a) Axial and (b) coronal view of computed tomography (CT) images with the dose distribution of accelerated hypofractionated radiotherapy. (c) A radiograph at catheterization showing the source of bleeding in the right bronchial artery.

to be 'definite' AHRT-related toxicity from irradiation to the bronchus.

The second patient was an 88-year-old man with primary NSCLC in the left inferior lobe (cT2aN0M0), who received AHRT of 69 Gy in 23 fractions (Fig. 3a and b). Although local tumor recurrence was confirmed 10 months after AHRT, aggressive cancer treatment was not indicated due to his advanced age. This patient experienced a large amount of bloody sputum 30 months after AHRT and was treated with conservative treatments, including red blood cell transfusion. Since it was unclear whether the hemoptysis was due to a recurrent tumor or AHRT, it was judged as 'possible' treatment-related toxicity, and the source of bleeding was considered to be from the bronchus, pulmonary artery or pulmonary vein.

Dosimetric data

Figure 5 shows the DVH of each OAR. The two patients with toxic events were irradiated with 74.5 and 71.6 Gy which is the maximum dose to the bronchus (Fig. 4e and Table 4). Among patients irradiated

Table 3. Adverse effects in mediastinal organs

	Grade 2	Grade 3	Grade 4–5
Bronchopulmonary hemorrhage	1	2	0
Atelectasis	1	0	0
Esophagitis	1	0	0
Total	3 (3.3%)	2 (2.2%)	0

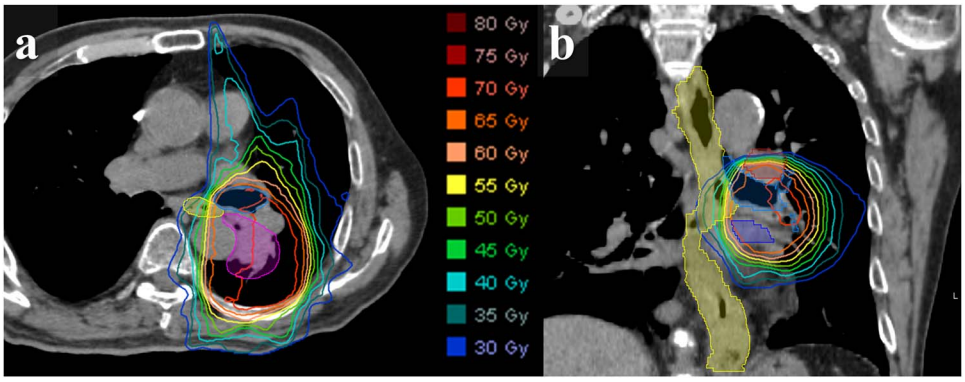

Figure 3. Imaging findings for an 88-year-old man with possible radiotherapy-related bloody sputum. (a) Axial and (b) coronal view of CT images with the dose distribution of accelerated hypofractionated radiotherapy.

with 70 Gy or more to the bronchus, the incidence rate of adverse events was 7% (2/28 patients). There were no grade 3 or more AEs involving the aorta, superior vena cava and esophagus despite high-dose irradiation (Fig. 4a, b and f).

Discussion

Our single-institution study retrospectively evaluated the clinical outcomes in patients with central lung tumors treated with AHRT (3 Gy per fraction). Only two (2.2%) patients had grade 3 AEs. Additionally, AHRT achieved good LC for both central and ultra-central lesions.

SBRT for peripherally located lung lesions achieves excellent tumor control with low toxicity; however, excessive toxicity, including hemoptysis, bronchial stricture formation and even treatment-related death, has been reported when treating centrally located disease (8). The American Society for Radiation Oncology guidelines recommend that SBRT of 3-fraction regimens, directed at central lung tumors should be avoided and that SBRT should be delivered in a larger number of fractions (5). The optimal dose fractionation schedule for central tumors remains unclear. A phase I/II trial performed by Roach et al. (20) showed the clinical outcomes of SBRT with 55 Gy in five fractions. A high occurrence rate of late AEs of 41% was confirmed, and safer dose fractionation was desired. In Japan, SBRT of 60 Gy in eight fractions is widely used based on a phase I study of the JROSG10–1 trial, which showed no dose-limiting toxicity in nine patients (21). However, that trial adopted strict dose constraints in mediastinal organs (i.e. dose to 1 mL in the superior vena cava and pulmonary vein <48 Gy, and 5 mL in the esophagus <40 Gy); hence, it is difficult to deliver a high enough dose to ultra-central lung tumors according to that protocol. In contrast, AHRT was feasible even for ultra-central lung tumors, based on the findings of this study.

The present, the AHRT regimen of 75 Gy in 25 fractions over 5 weeks has several advantages. By increasing the number of fractions, the risk of toxicity to serial organs was reduced. Nevertheless, the dose to the tumor was 97.5 Gy (biological equivalent dose of α/β of 10 Gy [BED10]), which is close to the threshold of good LC, at 100 Gy (BED10) (22). Additionally, a homogeneous dose distribution was adopted because the serial organs were moving with respiration. It is technically easy to perform this procedure, and reproducible results can be obtained. Retrospective data suggested that high heterogeneity within the target might not be necessary to achieve a high LC (23), and the present study also supported this notion.

A meta-analysis reported that hemorrhage was the most common severe AE in SBRT for ultra-central tumors (24). High doses, especially to the pulmonary arteries and bronchi, caused grade 3–5 toxicities in retrospective data (25). The present results, in which two patients experienced bronchopulmonary hemorrhage, were consistent with these reports. The above meta-analysis also indicated that excessive maximum dose irradiation was a risk factor for fatal hemoptysis (24). In the present study, both patients with toxicity had a maximum bronchial dose of more than 70 Gy. These data are useful as the dose constraints when performing AHRT with 3 Gy per fraction, and the IMRT technique can satisfy the dose constraints easily.

This study has some limitations. First, the number of severe AE events was small, with only 2 (2.2%) out of 91 lesions. As a result, DVH predictors for the development of mediastinal organ toxicities could not be identified. However, it has been suggested that a maximum dose of more than 70 Gy to the PBT may be dangerous. Second, the median follow-up period was relatively short (26 months). The rate of AEs obtained in our study may have been underestimated because both toxic events occurred after 30 months. However, the median follow-up duration in previously reported studies about SBRT for central lung tumors is 10–29 months,[8] which

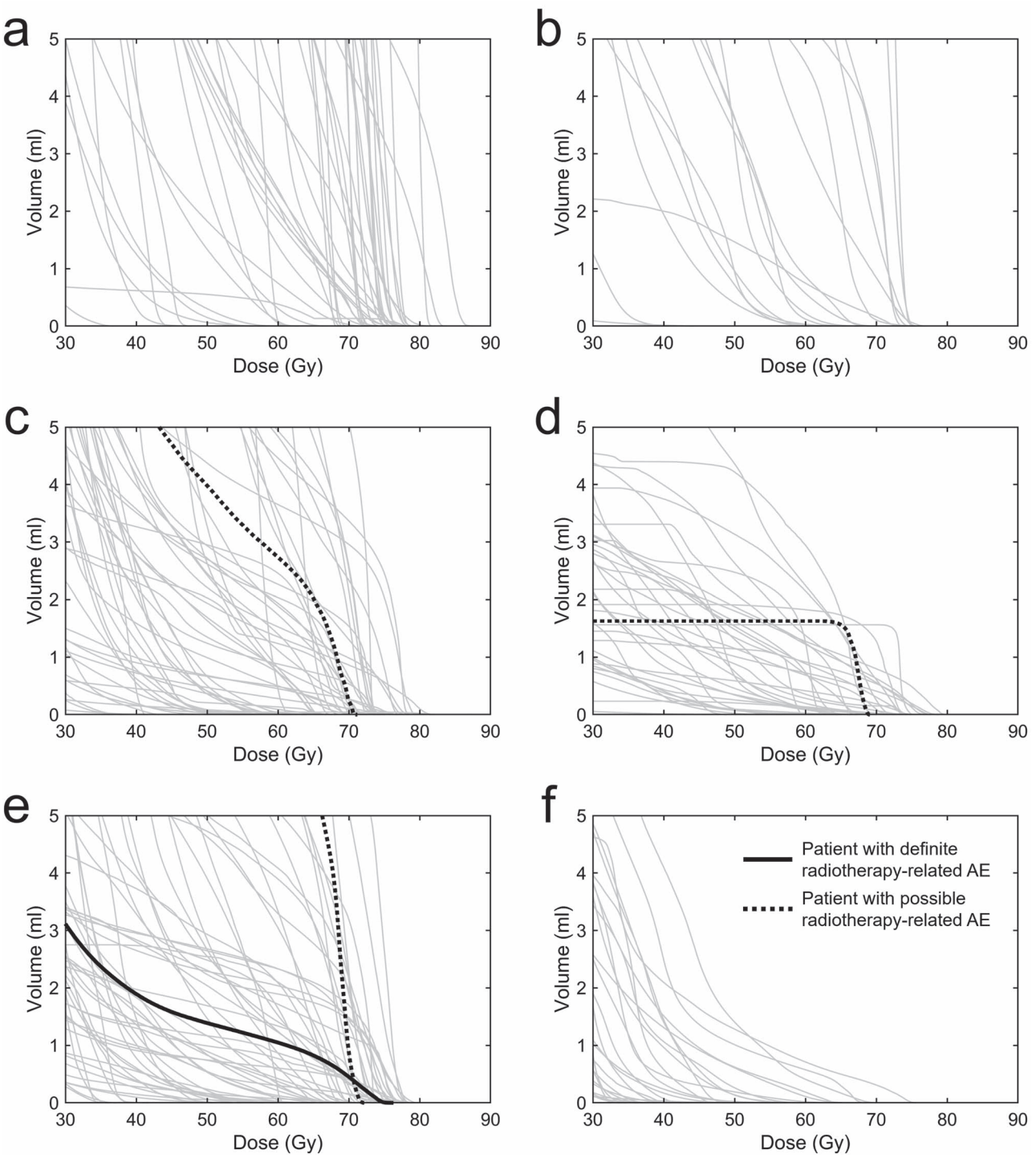

Figure 4. Dose–volume histograms of the organs at risk in the central region. (a) Aorta, (b) superior vena cava, (c) pulmonary artery, (d) pulmonary vein, (e) trachea/bronchus and (f) esophagus. The bold black lines represent two cases with bronchopulmonary hemorrhage.

is equivalent to ours. Therefore, AHRT used in the present study seems to be still safer compared with previous studies. Third, the irradiated dose was calculated without the internal margins of the OARs. OARs may have been exposed to doses higher than those calculated in some patients. Fourth, four regions (4.4%) were corrected for setup error with orthogonal X-ray films every 1–2 weeks. This includes uncertainty in the delivered dose, which introduces uncertainty in the analysis of dosimetric factors using small volume such as $D_{0.5\,mL}$. To prove the efficacy and safety of AHRT, large-scale clinical trials are required. The outcomes observed in the present study can be used as a foundation and benchmark for a future trial.

Table 4. Dosimetric characteristics of organs at risk

	D_{max} (Gy) Median (range)	$D_{0.5\ ml}$ (Gy) Median (range)	$D_{1\ ml}$ (Gy) Median (range)	$D_{4\ ml}$ (Gy) Median (range)	$D_{10\ ml}$ (Gy) Median (range)
Aorta ($n = 47$)	72.8 (35.0–86.4)	71.0 (28.9–85.0)	67.9 (25.9–84.4)	65 (4.7–79.3)	50.9 (2.0–73.9)
Superior vena cava ($n = 18$)	67.3 (37.3–75.8)	61.8 (18–74.1)	56.9 (9.9–73.8)	48.9 (1.3–72.9)	25.6 (3.0–69.6)
Pulmonary artery ($n = 58$)	69.3 (35.2–80.9)	62.0 (13.0–77.7)	57.5 (8.7–77.2)	35.1 (2.9–71.5)	23.1 (1.3–56.7)
Patient 2	70.6	69.5	68.3	49.9	36.8
Pulmonary vein ($n = 37$)	67.2 (35.1–79.1)	57.6 (7.4–74.9)	52.7 (3.7–73.3)	27 (9.4–52.2)	N/A
Patient 2	68.8	67.8	67.1	N/A	N/A
Trachea/Bronchi ($n = 65$)	69.4 (34.0–78.8)	62.6 (25.1–76.7)	56.8 (20.5–76.2)	27.5 (4.5–74.0)	17.7 (1.3–63.9)
Patient 1	74.5	69.5	61.3	26.4	17.5
Patient 2	71.6	70.5	69.9	67.8	29.7
Esophagus ($n = 26$)	45.6 (32.1–74.6)	35.3 (15.7–65.0)	32.1 (9.4–54.8)	23.7 (3.3–40.4)	4.6 (1–27.4)

Abbreviations: $D_{X\ ml}$, dose irradiated to X ml.
Patients 1 and 2 experienced definite and possible adverse effect induced by accelerated hypofractionated radiotherapy, respectively.

Conclusion

The present study demonstrated that AHRT using 3 Gy per fraction for central and ultra-central lung tumors achieved good LC with mild toxicities. Although the correlated DVH parameters and tolerable doses of risk organs could not be identified due to the small number of toxic events, this study indicated that AHRT of 75 Gy in 25 fractions was a useful approach for ultra-central lung tumors.

Abbreviations

AE, adverse effect; AHRT, accelerated hypofractionated radiotherapy; CT, computed tomography; DVH, dose-volume histogram; $D_{X\ ml}$, dose irradiated to X ml; GTV, gross tumor volume; ITV, internal target volume; LC, local control; NSCLC, non-small-cell lung cancer; OAR, organ at risk; OS, overall survival; PBT, proximal bronchial tree; PTV, planning target volume; SBRT, stereotactic body radiotherapy

Conflict of interest statement

Kei Ito was a member of the advisory board and has received honorariums from Varian Medical Systems K. K. The other authors declare no conflict of interest.

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References

1. Wen SW, Han L, Lv HL, et al. A propensity-matched analysis of outcomes of patients with clinical stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: a meta-analysis. *J Invest Surg* 2019;32:27–34.
2. Li C, Wang L, Wu Q, et al. A meta-analysis comparing stereotactic body radiotherapy vs conventional radiotherapy in inoperable stage I non-small cell lung cancer. *Medicine (Baltimore)* 2020;99:e21715.
3. Zhang B, Zhu F, Ma X, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. *Radiother Oncol* 2014;112:250–5.
4. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2014;90:603–11.
5. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017;7:295–301.
6. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051–8.
7. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;17:1672–82.
8. Chen H, Laba JM, Zayed S, Boldt RG, Palma DA, Louie AV. Safety and Effectiveness of Stereotactic Ablative Radiotherapy for Ultra-Central Lung Lesions: A Systematic Review. *J Thorac Oncol* 2019;14:1332–42.
9. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, Timmerman R. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677–82.
10. Karasawa K, Hayakawa S, Machitori Y, et al. Accelerated hypofractionated radiotherapy versus stereotactic body radiotherapy for the treatment of stage I nonsmall cell lung cancer-a single institution experience with long-term follow-up. *Technol Cancer Res Treat* 2018;17:153303381880631.
11. Yung T, Giuliani ME, Le LW, et al. Outcomes of accelerated hypofractionated radiotherapy in stage I non-small-cell lung cancer. *Curr Oncol* 2012;19:e264–9.
12. Lucas JT Jr, Kuremsky JG, Soike M, et al. Comparison of accelerated hypofractionation and stereotactic body radiotherapy for Stage 1 and node negative Stage 2 non-small cell lung cancer (NSCLC). *Lung Cancer* 2014;85:59–65.
13. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*, 7th edn. Malden: Wiley-Blackwell, 2011; 138146.
14. Bezjak A, Paulus R, Gaspar LE, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: nrg oncology/RTOG 0813 trial. *J Clin Oncol* 2019;37:1316–25.

15. Chaudhuri AA, Tang C, Binkley MS, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. *Lung Cancer* 2015;89:50–6.
16. Xue J, Kubicek G, Patel A, Goldsmith B, Asbell SO, LaCouture TA. Validity of current stereotactic body radiation therapy dose constraints for aorta and major vessels. *Semin Radiat Oncol* 2016;26:135–9.
17. Ma TM, Emami B, Grimm J, et al. Volume effects in radiosurgical spinal cord dose tolerance: how small is too small? *J Radiat Oncol* 2019;8:53–61.
18. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) version 5.0*. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (1 August 2022, date last accessed).
19. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.
20. Roach MC, Robinson CG, DeWees TA, et al. Stereotactic body radiation therapy for central early-stage NSCLC: results of a prospective phase I/II trial. *J Thorac Oncol* 2018;13:1727–32.
21. Kimura T, Nagata Y, Harada H, et al. Phase I study of stereotactic body radiation therapy for centrally located stage IA non-small cell lung cancer (JROSG10-1). *Int J Clin Oncol* 2017;22:849–56.
22. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623–31.
23. Stephans KL, Woody NM, Reddy CA, et al. Tumor control and toxicity for common stereotactic body radiation therapy dose-fractionation regimens in stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2018;100:462–9.
24. Rim CH, Kim Y, Kim CY, Yoon WS, Yang DS. Is stereotactic body radiotherapy for ultra-central lung tumor a feasible option? A systemic review and meta-analysis. *Int J Radiat Biol* 2019;95:329–37.
25. Nishimura S, Takeda A, Sanuki N, et al. Toxicities of organs at risk in the mediastinal and hilar regions following stereotactic body radiotherapy for centrally located lung tumors. *J Thorac Oncol* 2014;9:1370–6.