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Comparison of Dose Distribution Between VMAT-SBRT and Scanning Carbon-ion Radiotherapy for Early-stage NSCLC

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Abstract. *Background/Aim: The purpose of this study was to compare the dose distribution between scanning carbon-ion radiotherapy (sCIRT) and volumetric-modulated arc therapy with stereotactic body radiation therapy (VMAT-SBRT) for stage I non-small cell lung cancer (NSCLC). Patients and Methods: Fifteen patients with early-stage NSCLC who underwent sCIRT at Kanagawa Cancer Center between 2018-2020 were enrolled. Dose-volume histogram parameters of the planned target volume and normal organs for sCIRT and VMAT-SBRT were evaluated. Results: The homogeneity index of the target volume of sCIRT was significantly lower than that of VMAT-SBRT. The dose of sCIRT was significantly lower than that of VMAT-SBRT at low volumes in the lung, heart, spinal cord, and esophagus. Conclusion: The dose distribution of sCIRT for early-stage NSCLC was better than that of VMAT-SBRT.*

Lung cancer has been the leading cause of cancer-related deaths worldwide (1). Although it is more common in men, the number of lung cancer cases and deaths in women has been increasing in recent years. Radiation therapy is the standard treatment for inoperable early-stage non-small cell lung cancer (NSCLC). Even in operable cases, patients may refuse surgery due to old age, risk of anesthesia, concern about postoperative pulmonary function decline, complications, or fear of surgery. Stereotactic body radiotherapy (SBRT) is the definitive treatment of choice for these patients. The Japanese society for radiation oncology (JASTRO) Guidelines 2020 for Radiotherapy Treatment Planning recommends high-dose local irradiation with improved dose concentrations, such as SBRT and carbon-ion beam therapy (CIRT) (2).

Carbon-ion beams, a type of heavy ion beam, have characteristics different from those of high-energy X-rays used in conventional radiotherapy. It has physical and biological advantages over conventional X-rays, and the Bragg peak and sharp penumbra showed a good dose distribution (3). The biological effect is three times higher than X-rays (4, 5).

Ebara *et al*. compared the dose distribution between broad-beam CIRT (bCIRT) and multiple static-beam SBRT for stage I NSCLC. bCIRT for stage I NSCLC showed a superior dose distribution compared to conventional multiple static SBRT (6). Miyasaka *et al*. reported that the results of bCIRT for stage I NSCLC were better than those of SBRT, with fewer adverse events (7).

At the ion beam Radiation Oncology Center in Kanagawa (i-ROCK) at Kanagawa Cancer Center, scanning CIRT (sCIRT) was started in 2015 (8). All cases were treated using the spot-scanning method. The spot-scanning method produces more flexible dose distributions by moving a narrow beam at a high speed compared with bCIRT (9). The Kanagawa Cancer Center has reported good results with sCIRT for prostate cancer (10).

Volumetric-modulated arc therapy (VMAT) is a type of intensity-modulated radiation therapy (IMRT). This irradiation method uses dynamic multi-leaf collimator motion, variable dose rate, and gantry speed adjustment to allow intensity-modulated radiation delivery during gantry rotation (11). VMAT-SBRT is an SBRT that uses VMAT technology to focus the dose on the tumor (12).

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Key Words: Dosimetric comparison, carbon ion radiotherapy, stage I non-small cell lung cancer.

VMAT-SBRT is superior to conventional multiple static SBRT in terms of shortening the treatment time and dose concentration (13). Therefore, it is easier to meet the dose constraints of risk organs (13). To date, no quantitative comparison between sCIRT and VMAT-SBRT for early-stage NSCLC has been performed. The purpose of this study was to compare the dose distribution of sCIRT and VMAT-SBRT for stage I NSCLC.

Patients and Methods

There were 15 patients enrolled in this study with stage I NSCLC who underwent sCIRT at the i-Rock from 2018-2020 (Table I). Staging was based on the Union for International Cancer Control TMN classification of Malignant Tumors, 8th edition. This study was approved by the hospital's institutional review board (approval number: 2021-14).

Table I. *Patient characteristics*.

Age (median)	55-88 y.o. (77.0)
Gender	
Male	12
Female	3
T stage	
1b	7
1c	6
2a	1
2b	1
Tumor location	
RUL/RML/RLL	10/1/1
LUL/LLL	2/1

RUL: Right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: light lower lobe; y.o: year old.

Treatment planning. In this virtual planning study, we used planning computed tomography (CT) images for actual sCIRT. In all patient cases, 4D-CT volume data was taken with respiration waveform under free-breathing by 16 multi-detector-row CT scanner (Aquilion LB, Canon Medical Systems Co., Ltd., Tochigi, Japan), and sequential CT image sets are reconstructed along with respiration phage at 10% intervals. The slice thickness was set to 2 mm during reconstruction.

The gross total volume (GTV) was defined as the volume in which the tumor was clearly determined to exist on diagnostic images, such as CT and positron emission tomography (PET). The GTV was drawn on CT images of each respiration phase using MIM Maestro (ver. 6.9.6, MIM Software, Cleveland, OH, USA), and the maximum motion range of GTV center was measured. Since our clinical criteria are to keep the respiratory motion within 5mm to form the uniform dose distribution by the respiratory synchronous irradiation with carbon-ion fast scanning beam (14), we selected CT image set of GTV motion within 5mm from the end of the expiration phase. The clinical target volume (CTV) was defined as the GTV with a 3 mm margin in all directions within the lung parenchyma. GTVs and CTVs were prepared as internal GTVs and internal CTVs (IGTVs and ICTVs, respectively) by adding up the GTVs and CTVs at the phase where the movement of GTVs was within 5 mm. The planning target volume (PTV) was set as the ICTV+5 mm. However, depending on the positional relationship with organs at risk (OAR) such as the skin and central nervous system, the PTV was set so that it did not exceed the tolerable dose for normal organs. The lungs, heart, spinal cord, esophagus, and skin were delineated as OAR. The skin dose was evaluated by creating a 2-mm thick inner ring structure from the auto-drawn body surface contour (15).

The calculation conditions of sCIRT were as follows: wire type, carbon; ridge filter, 3-mm aluminum; spot placement intervals, 2 mm in the plane direction and 2.5 mm in the depth direction. To maintain the smoothness of the irradiation field, the number of re-scanning cycles per slice was set at six, and the treatment plan was formulated on the premise that each irradiation would be performed in four different directions, based on two-port irradiation (horizontal and vertical). The prescribed dose was 60 Gy relative biological effectiveness (RBE) over 4 fractions. Under these conditions, the dose distribution was optimized to cover the PTV at 95% of the prescribed dose, with the highest priority given to meeting the permissible dose to normal organs. The same structure was used for both VMAT-SBRT and sCIRT. The maximum dose for the spinal cord was 25 Gy or Gy RBE, and the percentage of the lungs receiving 20 and 15 Gy (V20 and V15, respectively) was <20% and <25%, respectively.

sCIRT was planned using Monaco for Carbon (Ver. 5.20, Elekta AB, Stockholm, Sweden). VMAT-SBRT was planned using Eclipse (Ver. 11, Varian Medical Systems, Palo Alto, CA, USA). The beam geometry was optimized for VMAT at 2 arcs using a 6-MV photon beam.

All treatment plans were transferred to MIM Maestro for comparison. PTV was calculated using the minimum doses to 98%, 95%, and 5% of the volume (D98, D95, and D5, respectively), mean dose (Dmean), and the homogeneity index (HI), where HI was calculated as (D2-D98)/D50 (16).

Normal lung volume was defined as the bilateral lung volume minus the GTV (lung-GTV). V5-V60 and Dmean for the lung (MLD), maximum dose (Dmax), and Mean dose (D mean) were recorded for the heart, spinal cord, and esophagus, and Dmax was recorded for the skin.

Statistical analysis. DVH parameters for each treatment method were compared using the Wilcoxon matched-pairs test. Statistical analysis was performed with SPSS (ver.26.0.0, IBM, Armonk, NY, USA). Statistical significance was established at $p<0.05$.

Results

PTV. A typical dose distribution diagram and dose-volume histogram (DVH) are shown in Figure 1. Table II shows the PTV parameters. D98 was significantly higher in the sCIRT group, and D5 was significantly higher in the VMAT-SBRT group. There was no significant difference in D95 or Dmean. The HI was significantly lower in sCIRT than in VMAT-SBRT.

OAR. Table III shows the OAR parameters. Figure 2 shows the relative volume of a normal lung receiving a dose above the threshold. V5, V10, and V60 were significantly lower in the sCIRT group than in the VMAT-SBRT group. In contrast,

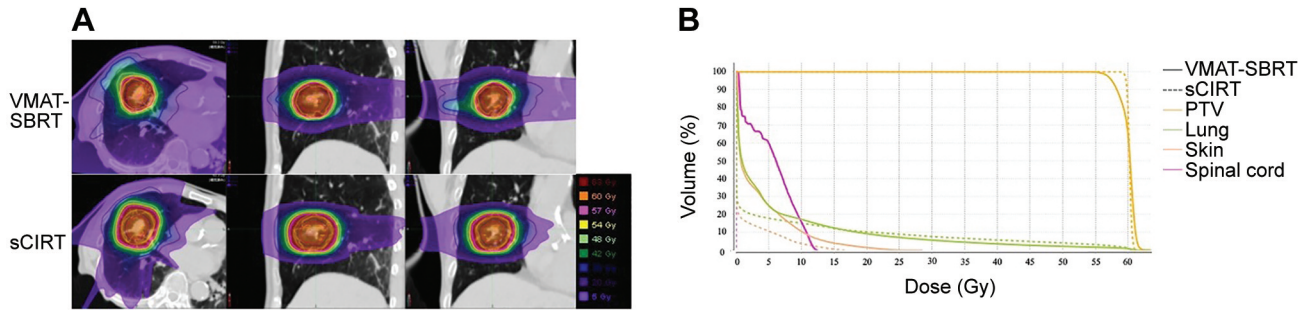

Figure 1. *Comparison of representative dose distributions. Comparison between volumetric-modulated arc therapy with scanning stereotactic body radiation therapy (VMAT-SBRT) and scanning carbon-ion radiotherapy (sCIRT) for stage IB non-small cell lung cancer (NSCLC). A total dose of 60 Gy/Gy RBE was administered to the planning target volume (PTV). (A) Color-corded dose distribution is shown with percent isodose lines for VMAT-SBRT (upper) and sCIRT (lower). (B) Dose-volume histogram (DVH) of VMAT-SBRT (dash lines) and sCIRT (solid lines).*

Table II. *Dosimetric comparison of PTV between sCIRT and VMAT-SBRT.*

	VMAT-SBRT	sCIRT	
PTV	Mean±SD		*p*-value
D98 (Gy, GyRBE)	57.53±0.97	58.71±0.59	0.01
D95 (Gy, GyRBE)	58.25±0.74	59.04±0.50	0.06
D5 (Gy, GyRBE)	61.21±0.50	60.55±0.13	0.01
Dmean (Gy, GyRBE)	60.09±0.39	59.92±0.21	0.20
HI	0.07±0.02	0.03±0.01	0.00

sCIRT: Scanning carbon ion radiotherapy; VMAT-SBRT: volumetric modulated arc therapy-stereotactic body radiotherapy; D: dose; SD: standard deviation; GyRBE: gray relative biological effectiveness; HI: homogeneity index.

Table III. *Dosimetric comparison of OAR between sCIRT and VMAT-SBRT.*

	VMAT-SBRT	sCIRT	
OAR	Mean±SD		*p*-value
Esophagus			
Dmax (Gy, GyRBE)	13.6±5.8	6.0±7.1	0.007
Dmean (Gy, GyRBE)	6.0±3.5	0.9±1.3	0.01
Spinal Cord			
Dmax (Gy, GyRBE)	12.7±5.5	3.6±5.8	0.001
Dmean (Gy, GyRBE)	6.1±3.0	0.7±1.3	0.001
Heart			
Dmax (Gy, GyRBE)	10.4±16.5	9.0±15.7	0.02
Dmean (Gy, GyRBE)	1.7±3.2	0.3±0.9	0.001
Skin			
Dmax (Gy, GyRBE)	2.2±9.1	18.5±8.8	0.01

OAR: Organ at risk; sCIRT: scanning carbon ion radiotherapy; VMAT-SBRT: Volumetric modulated arc therapy-Stereotactic body radiotherapy; Dmean: mean dose; Dmax: maximum dose; SD: standard deviation; Gy: gray; RBE: relative biological effectiveness.

V30, V40, and V50 were significantly lower in VMAT-SBRT. The MLD was 4.42±1.86 Gy RBE for sCIRT and 4.96±2.14 Gy for VMAT-SBRT (p=0.016).

The maximum and mean doses to the heart, spinal cord, and esophagus were significantly lower in sCIRT. The maximum dose to the skin was significantly lower in VMAT-SBRT.

Discussion

In this study, we compared the dose distributions of sCIRT and VMAT-SBRT for stage I NSCLC. To the best of our knowledge, this is the first report to compare the distribution of SBRT using VMAT and sCIRT. The HI of PTV was significantly better than that of VMAT-SBRT for sCIRT, indicating a uniform dose distribution. sCIRT showed a reduction in lung V5 and V10, MLD, and skin, spinal cord, esophagus, and heart doses compared to VMAT-SBRT. sCIRT was able to deliver a more uniform dose to the target volume and reduce the dose to OAR compared to VMAT-SBRT. In the present study, sCIRT resulted in 10%, 25%, 12%, and 20% lung dose reductions in MLD, V5, V10, and V60 compared to VMAT-SBRT. Radiation pneumonitis (RP) is significantly correlated with the extension of relatively low doses, such as V20 and MLD (17).

Because X-rays use a low-dose concentration, SBRT and IMRT require irradiation of the tumor from multiple directions to compensate for this (12, 18). Therefore, caution should be exercised in patients with underlying diseases, such as interstitial pneumonia or reduced lung function, who are more likely to experience side effects. Side effects from radiotherapy for lung cancer require the greatest attention, because the radiosensitivity of normal lung tissue is high and the resulting RP is sometimes lethal (19). In contrast, V30, V40, and V50 were significantly lower with VMAT-SBRT in this study. In a study by Barriger *et al*., MLD and V20 were

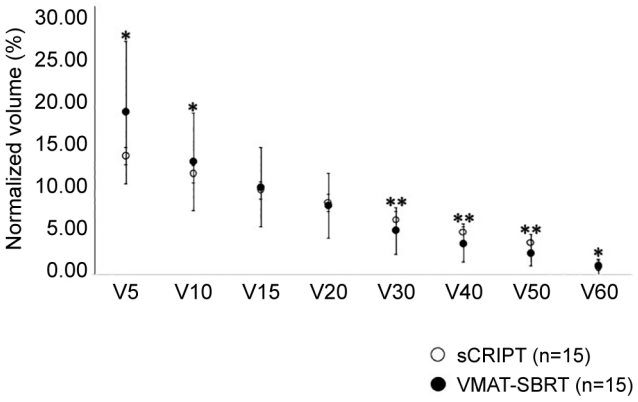

Figure 2. *The relative volumes of the normal lung receiving more than the threshold dose. The differences between scanning carbon-ion radiotherapy (sCIRT) and volumetric-modulated arc therapy with scanning stereotactic body radiation therapy (VMAT-SBRT) increased when the received dose decreased. Data are presented as the mean±SD. *p<0.05, **p<0.01.*

found to be significant risk factors for RP (20). On the other hand, Matsuo *et al*. concluded that only V20 and V25 are indicators of RP and that MLD, V5, V10, V15, V30, and V40 are not associated with RP (21). Lu *et al*. stated that the lung dose parameters of V5, V10, V20, and MLD are indicators of RP in SBRT of the lung (12).

Low-dose parameters such as V5, V10, and V20 are considered more useful as indicators of RP than high-dose parameters. The UK consensus on dose constraints for normal tissue during SBRT recommends V20 <10% as a uniform dose constraint for normal lungs, regardless of the 3-, 5-, or 8-fraction schedules (22). It is important to minimize the spread of low and medium doses to the normal lung and to concentrate the dose on the cancer lesion for successful treatment. In this respect, CIRT is highly useful because of its superior dose concentration.

The difference in each parameter in this study was less than that reported by Ebara *et al*., who compared multiple static beam SBRT with bCIRT, which may be due to the advancement of SBRT technology. bCIRT reduced the MLD of the normal lung by approximately 50%, and V5, V10, and V20 by about 20%, 10%, and 5%, respectively, compared with SBRT for stage I lung cancer (6).

In the present study, the dose reductions to the spinal cord, esophagus, and heart were statistically significant, but the absolute differences were small. The clinical significance of these findings is unknown. The maximum and mean doses to the heart were significantly lower in sCIRT.

For most radiation-induced cardiac diseases, a clear quantitative dose and/or volume dependence has not yet been demonstrated. However, patients with early-stage NSCLC are expected to have better long-term survival than late-stage patients; therefore, cardiac dosing should be performed with caution.

Proton radiation has been shown to reduce the spinal cord dose (23). The dose was similarly reduced in the sCIRT group.

In the heart and spinal cord, sCIRT reduced the dose to a greater extent than VMAT-SBRT. This suggests that carbon radiation can provide a safer treatment, especially for central nervous system tumors.

In this study, the maximum skin dose was shown to be higher with sCIRT than with VMAT-SBRT. An area irradiated with 40 Gy RBE has been noted as a risk factor for acute-phase dermatitis from bCIRT (15). For late toxicity, 60 Gy RBE is a risk factor (24). In our study, the maximum dose of carbon radiation was sufficiently lower than that reported previously (15). The risk of serious adverse skin events was expected to be low. This study had several limitations, including a small sample size, and the fact that the appropriate irradiation range for sCIRT is still unknown.

Conclusion

The dose distribution of sCIRT for stage I NSCLC was better than that for VMAT-SBRT. Dose reduction to OAR is expected to be useful in decreasing toxicity.

Conflicts of Interest

Dr. Hiroyuki Katoh, Dr. Daisaku Yoshida, and Dr. Shinichi Minohara received research funding from Toshiba Energy Systems and Solutions Corporation.

Authors' Contributions

DY collected and analyzed data and drafted the manuscript. TK and HK analyzed the data and contributed to the final draft of the manuscript. KK, WA and KT collected and analyzed the data of VMAT-SBRT. YT and YK collected and analyzed the data of sCIRT. ET aided in writing the manuscript and contributed to the final draft of the manuscript. All Authors read and approved the final manuscript.

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