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III기 폐암 치료에서 체적조절호형방사선치료(VMAT)에 기초한 새로운 하이브리드 방사선 치료기술의 유용성에 대한 검증

Verification for the usability of a novel hybrid radiation therapy technique based on volumetric modulated arc therapy (VMAT) in stage III lung cancer treatment

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이 논문을 의학박사 학위 논문으로 제출함

2020년 8월

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Abstract

Purpose: It is occasionally difficult to deliver sufficient radiation dose by using existing 3-dimensional conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT), or volumetric modulated arc therapy (VMAT) techniques in stage III lung cancer patients. To address this problem, we developed a new hybrid VMAT (hVMAT) technique. This study aimed to demonstrate the usability of the new hVMAT technique in stage III lung cancer treatment.

Methods and Materials: 32 consecutive patients with stage III lung cancer who had been treated with hVMAT were included. The hVMAT plan was made by adding two static beams to the original VMAT plan. To evaluate the superiority of the hVMAT plan, we compared the three techniques (3DCRT vs. VMAT vs. hVMAT) using the conformity index (CI), conformation number (CN), homogeneity index (HI), and the dosimetric parameters of organs at risk (OARs).

Results: The mean V_{20} of the lung from the hVMAT plans (27.2%) was significantly lower than 3DCRT plans (40.5%) and VMAT plans (35.0%). Additionally, the hVMAT plans showed the best results for other lung dose parameters (V_5, V_{10}, mean lung dose) among the three plans, while maintaining an irradiated dose at an acceptable level for the spinal cord, esophagus, and heart. In addition, hVMAT also showed non-inferior results for CI, CN, and HI compared with the VMAT plans.

Conclusion: This novel hybrid technique can improve all dosimetric parameters of lung while maintaining the acceptable dose for other OARs. Therefore, the new hVMAT could be a useful planning technique for treating stage III lung cancer and it might be a solution for patients who cannot receive a sufficient dose with the existing 3DCRT or VMAT plans.

Keywords: stage III lung cancer, hybrid VMAT

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INTRODUCTION

Radiation therapy (RT) is an important treatment modality for lung cancer patients. Several studies have demonstrated improved local control and overall survival by radiation dose escalation [1-3]. Since the irradiated volume of lung is associated with the risk of radiation pneumonitis [4], it is especially important to keep the irradiated volume of lung below an acceptable level. However, it is sometimes difficult to achieve acceptable lung protection in locally advanced lung cancer patients. As a result, it is occasionally hard to escalate the dose above 60Gy in such patients.

Generally, intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) can provide a more conformal dose distribution and exhibit more satisfactory organ at risk (OAR) protection than 3-dimensional conformal radiation therapy (3DCRT). According to studies comparing volumetric modulated arc therapy (VMAT) with IMRT, VMAT plan showed more satisfactory results in the aspects of better OAR protection, lower monitor units (MUs) and shorter treatment time. Although VMAT offers

more conformal dose distribution through continuous beam arrangement, it also increases low dose volume of lung due to rotational beam delivery. Despite advanced radiation delivery techniques and improvements in dose conformity, it is sometimes difficult to achieve satisfactory lung dose limits by using 3DCRT, IMRT, or VMAT in stage III lung cancer patients. There were few studies which have attempted to reduce the irradiated lung volume using hybrid techniques in lung cancer patients [5-10]. In these previous studies, hybrid IMRT (hIMRT) or hybrid VMAT (hVMAT) plan was made by combining 3DCRT with IMRT or VMAT.

In our institution, we developed hVMAT technique for reducing low dose irradiated lung volume (V5, V20 etc.) in stage III lung cancer patients. We compare 3DCRT, VMAT and hVMAT plans before treatment of locally advanced lung cancer, and then select the best one. In this study, we compared the dosimetric parameters of hVMAT with 3DCRT and VMAT in stage III lung cancer patients who had been treated using hVMAT technique. The aim of this study is to demonstrate usability and necessity of hVMAT technique for stage III lung cancer treatment.

MATERIALS and METHODS

Patients selection

From January 2014 to October 2018, 32 consecutive stage III lung cancer patients were treated with hVMAT; all patients were treated with curative intent. We retrospectively reviewed the treatment plans that were made for each patient prior to their treatment. Planning computed tomography (CT) images were acquired using the Brilliance CT Big Bore (Philips Medical Systems, CL, USA). If the respiratory movement of the tumor was greater than 1 cm, then a respiratory gated four-dimensional CT (4D-CT) technique was used. And CT images of 3mm slice thickness were obtained from the chin to the first lumbar vertebra. Gross tumor volume (GTV), clinical target volume (CTV) and internal target volume (ITV) were contoured by a qualified radiation oncologist; thereafter, 1 cm margin were expanded from CTV to generate the planning target volume (PTV). Contouring of OARs was conducted in line with the Radiation Therapy Oncology Group (RTOG)

recommendation (RTOG 1106) [11]. Thus, normal lung was defined as whole lung minus GTV.

The goal of the dose prescription was delivering 66Gy in 30 to 33 fractions to PTV. We tried to meet the planning objective which was as follows: 100% prescription dose covers more than 95% of PTV and the maximum dose of PTV ($D_{2\%}$) is less than 107% of the prescription dose. The dose constraints for the OARs were the following: maximum point dose (D_{max}) of the spinal cord < 50Gy, lung volume receiving more than 20Gy (V_{20}) < 35%, mean lung dose (MLD) < 20Gy, V_{40} of the heart < 60%, mean heart dose < 20Gy, and D_{max} of the esophagus < 107%.

We made all treatment plans using the Eclipse treatment planning system (TPS) with the Anisotropic Analytic Algorithm (AAA, version 13.6, Varian Medical System, Palo Alto, CA, USA) for tissue heterogeneity correction. We used 6, 10 or 15 MV photon beams generated from the trueBEAM equipped with HD multi-leaf collimator (MLC) or iX with 120 leaf Millennium MLC (Varian Medical System, Palo Alto, CA, USA). All patients received treatment during the full respiration cycle without the use of the respiratory gating

technique. Pretreatment patient-specific quality assurance (QA) was performed using the combination of Matrixx and MULTICube phantom (IBA, Louvain-La-Neuve, Belgium).

Radiation therapy planning

3-dimensional conformal radiation therapy (3DCRT) plan

3DCRT plans were made using five static beams in 29 patients, and the plans of the remaining patients were made using four, six, and seven static beams. Beams eye view displays were used to select the appropriate gantry angles, collimator angles, and beam geometries. Beam weights were manually optimized to meet the planning criteria. The dose rate was set at 400 MU/min.

Volumetric modulated arc therapy (VMAT) plan

We chose rotational angle and number of arcs to minimize the irradiated lung volume especially contralateral lung volume. We used either half or full-rotating coplanar beams with two or three arcs according to the location and size of the PTV. The collimator angle of 30 ° or 330 ° was used to minimize MLC tongue-and-groove effects. Tissue heterogeneity

corrections were applied during dose calculations to all VMAT plans. Each plan was composed of 6MV or 10MV photon beams and the maximum dose rate was set to 600 MU/min.

Hybrid volumetric modulated arc therapy (hVMAT) plan

The hVMAT plan consisted of VMAT and CRT components. The VMAT component was exactly the same plan as the VMAT plan and the CRT component was consisted of two static beams with the arrangements in anterior-posterior opposing directions for decreasing irradiated lung volume. We sometimes modified the static beam to anterior-oblique or posterior-oblique direction to decrease heart or spinal cord dose. After completion of static beam arrangement, beam weights of the static fields were manually adjusted to deliver the optimal dose distribution, especially low dose volume of lung. As a result of this adjustment, the dose contribution of the CRT component became approximately 20% of total dose. All hVMAT plans were made using the same isocenter as each VMAT plan.

Dosimetric evaluation and plan comparison

The quantitative evaluation of each plan was performed based on the comparison of conformity index (CI), conformation number (CN), dose homogeneity index (HI) and dose-volume histogram (DVH).

The CI was defined as follows [12]:

$$Conformity\ index\ (CI) = \frac{TV_{RI}}{V_{RI}}$$

where TV_{RI} is the target volume covered by the reference isodose, and V_{RI} is the volume of the reference isodose. The CI ranges from 0 (no spatial concordance between the two volumes and no protection of healthy tissues in the isodose concerned) to 1 (perfect protection of healthy tissue). But this CI alone is not enough to evaluate PTV coverage. Thus, CN was additionally calculated to compensate for the defects in the CI. This CN simultaneously consider irradiation of the PTV and OARs.

The CN was calculated as follows [12]:

$$Conformation\ number\ (CN) = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}}$$

where TV_{RI} is the target volume covered by the reference isodose, TV is the target volume, and V_{RI} is the volume of the reference isodose. The CN ranges from 0 to 1, where 1 means the ideal dose distribution. A value close to 0 indicates either total absence of conformation, i.e., the target volume is not irradiated or a very large volume of irradiation compared to the target volume. We also compared HI to quantify the dose homogeneity in the target volume.

The HI was calculated as follows [13]:

$$\text{H}omogeneity\ \ index\ \ (HI) = \ \ \frac{D_{2\%} - \ D_{98\%}}{D_P}$$

where $D_{2\%}$ and $D_{98\%}$ are the minimum dose to 2% and 98% of the target volume and D_P is the prescribed dose. The ideal value is 0 and it increases as homogeneity decreases.

The absolute volume of the PTV does not sufficiently represent the relative size of PTV to the lung. Thus, we used the "PTV/lung ratio" to quantify the relative size of PTV. We measured total length of the normal lung and PTV in the direction of the superior-inferior (SI), left-right (LR), anterior-posterior (AP) axis. If part of the PTV was outside of the lung length, only the portion of the PTV that overlapped with the lung length was defined as the PTV length (Figure 1).

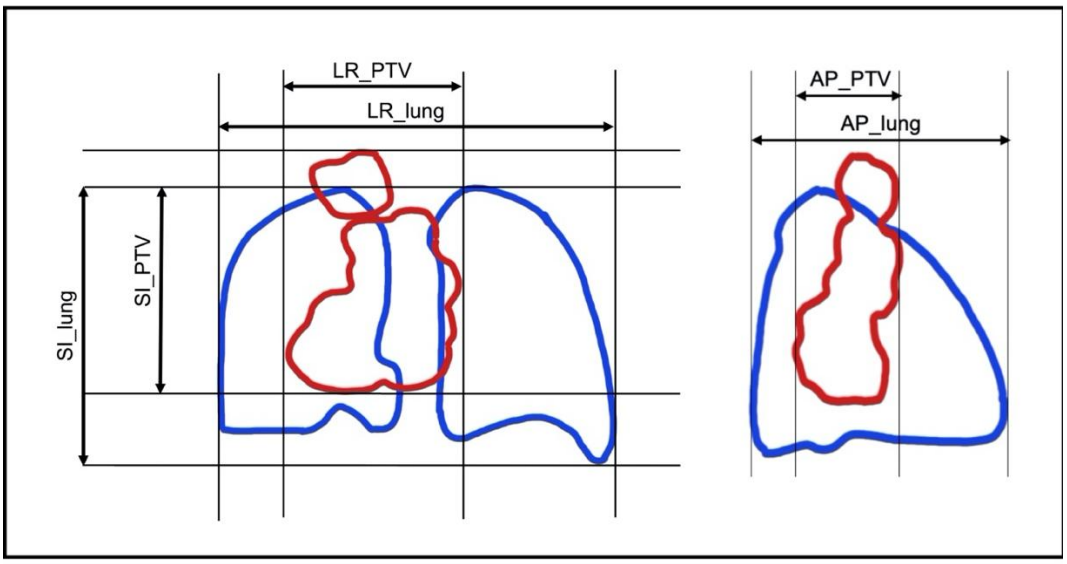

Figure 1. Schematic diagrams represent that measurement method of the planning target volume (PTV) and lung length in each axis.

The PTV/lung ratio of each axis was calculated as follows;

$$PTV/Lung \text{ Ratio} = \frac{PTV\ \ length}{Lung\ \ length}$$

The average cumulative dose volume histogram (DVH) curves of each treatment technique were generated using the individual patient's DVHs. Paired two tailed t-tests were used to verify differences between the two techniques. Statistical analysis was performed using SPSS (IBM SPSS version 24.0, New York, USA), and differences were considered statistically significant if the *p*-value was less than 0.017 according to the Bonferroni correction. Follow-up duration was calculated from the RT end date and survival analysis was performed using Kaplan-Meier method. The log rank test was used to statistically compare the survival curves between stage IIIA and IIIB. We evaluated the frequency of adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [14]. This study was approved by the Institutional Review Board.

RESULTS

The characteristics of the 32 included patients is shown in Table 1. Twelve patients were stage IIIA (AJCC 6th edition) and remaining 20 patients were stage IIIB. Pathologic type was squamous cell carcinoma in 13 patients, adenocarcinoma in 8 patients and small cell carcinoma in 9 patients. The goal of dose prescription was delivering 66Gy in 30 or 33 fractions to PTV. However, only 24 patients were treated with this aimed dose. Other 7 patients were treated with 60Gy in 30 fractions or 59.4Gy in 33 fractions, and one patient received 56Gy in 28 fractions because of the lung dose criteria. Twenty-five patients (84.4%) received concurrent chemo-radiation therapy (CCRT), four patients (12.5%) were treated with sequential chemo-radiation therapy and remaining one patient (3.1%) received radiation therapy alone.

Table 1. Patient characteristics

Median age	65 (49~80)
Gender	
Male	28 (87.5%)
Female	4 (12.5%)
Chronic lung disease	
No	27 (84.4%)
COPD	4 (12.5%)
IPF	1 (3.1%)
Stage	
IIIA	12 (37.5%)
IIIB	20 (62.5%)
Histology	
Adenocarcinoma	8 (25.0%)
Squamous cell carcinoma	13 (40.6%)
Non-small cell carcinoma	2 (6.3%)
Small cell carcinoma	9 (28.1%)
Chemotherapy	
Concurrent	27 (84.4%)
Sequential	4 (12.5%)
No	1 (3.1%)
Median dose (Gy)	66 (56 ~ 66)
66 Gy	24 (75.0%)
60 ~ 59.4 Gy	7 (21.9%)
56 Gy	1 (3.1%)

COPD; chronic obstructive pulmonary disease, IPF; idiopathic pulmonary fibrosis

The mean volume of PTV was 408.2 (range: 171.9 ~ 1092.5) cm^3 and the mean PTV/lung ratios of the SI, LR, and AP axes were 0.54 (range: 0.33 ~ 0.81), 0.43 (range: 0.32 ~ 0.58), and 0.54 (range: 0.39 ~ 0.83), respectively. The correlation analysis between the volumetric parameters of PTV (PTV/lung ratios for each axis, PTV volume) and the dosimetric parameters of the lung (V_5, V_{10}, V_{20}, MLD) found that there was no significant correlation between the PTV volume and the lung dose (Table 2). There was no significant correlation between PTV volume and lung dose. However, the PTV/lung ratio of the SI axis showed significantly strong correlations with the lung dose (correlation coefficient: 0.66 ~ 0.81, *p*-value < 0.001, Figure 2). Therefore, we divided the patients into two groups based on the median SI ratio (0.55: group A < 0.55, group B ≥ 0.55) to compare the average DVH curves and dosimetric parameters between two groups according to the PTV/lung ratio of SI axis.

Table 2. Correlation analysis between volumetric parameters of PTV and lung dose.

		MLD			V20			V10			V5		
		hVMAT	VMAT	3DCRT	hVMAT	VMAT	3DCRT	hVMAT	VMAT	3DCRT	hVMAT	VMAT	3DCRT
PTV/lung SI	P-coefficient	**0.746**	**0.770**	**0.746**	**0.660**	**0.714**	**0.675**	**0.741**	**0.805**	**0.749**	**0.792**	**0.800**	**0.781**
	p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
PTV/lung LR	P-coefficient	**0.481**	**0.409**	**0.427**	**0.500**	**0.465**	**0.391**	**0.400**	**0.355**	0.296	0.332	0.324	0.344
	p-value	0.005	0.020	0.015	0.004	0.007	0.027	0.023	0.046	0.099	0.063	0.070	0.054
PTV/lung AP	P-coefficient	0.069	0.042	0.004	0.030	-0.117	-0.141	-0.092	-0.001	-0.065	0.041	0.046	-0.041
	p-value	0.707	0.821	0.983	0.871	0.523	0.440	0.618	0.996	0.722	0.824	0.804	0.822
PTV volume	P-coefficient	0.172	0.174	0.112	0.142	0.185	0.020	0.154	0.098	0.068	0.062	0.029	0.053
	p-value	0.347	0.341	0.541	0.438	0.311	0.915	0.402	0.595	0.712	0.736	0.875	0.772

MLD; mean lung dose, hVMAT; hybrid volumetric modulated arc therapy, VMAT; volumetric modulated arc therapy, 3DCRT; 3-dimensional conformal radiation therapy, PTV; planning target volume, P-coefficient; Pearson coefficient, SI; superior-inferior, LR; left-right, AP; anterior-posterior

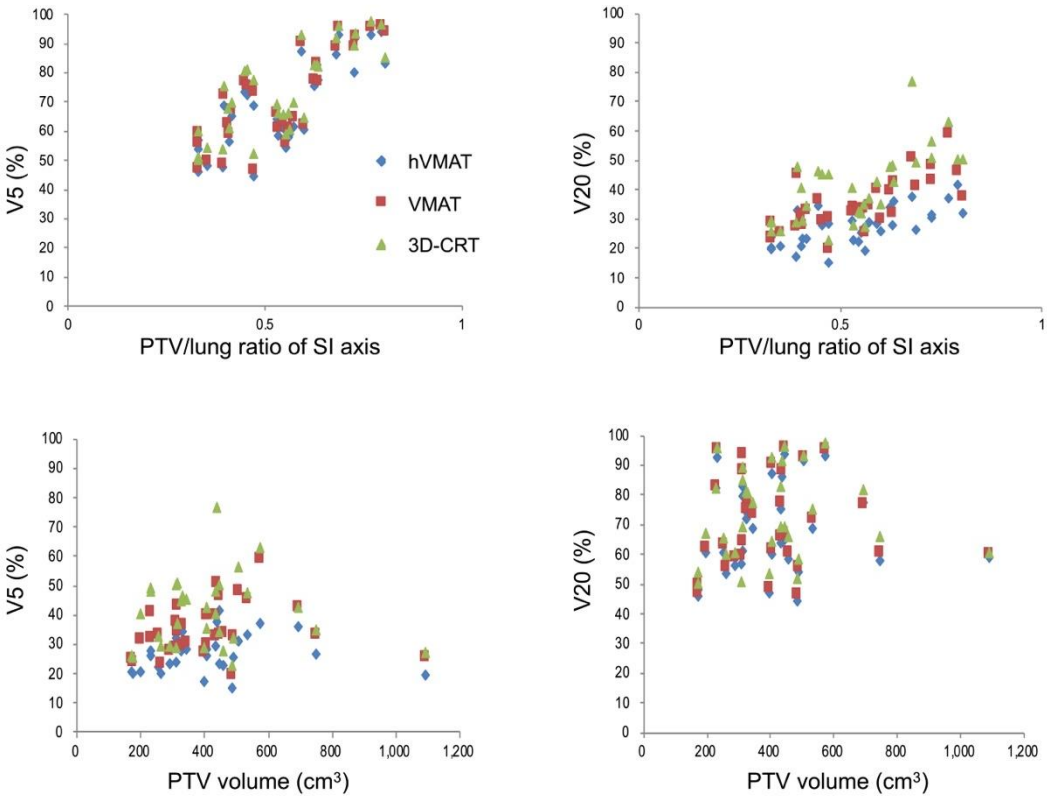

Figure 2. Scatter plots of the V_5 and V_{20} of the lung according to the PTV/lung ratio of the SI axis and PTV volume. (PTV; planning target volume, SI; superior-inferior)

The difference in the values for V_5 and V_{20} of the lung for the two techniques are demonstrated in Figure 3. Correlation analysis revealed that there was a significant correlation between the V_{20} difference and the SI ratio (correlation coefficient was -0.511 for hVMAT ~ 3DCRT and -0.431 for hVMAT ~ VMAT). Namely, if the patient has a large PTV/lung ratio of the SI axis, the V_{20} of lung was reduced even more by the hVMAT plan. However, the correlation between the V_5 difference and the ratio of the SI axis was not statistically significant (Table 3).

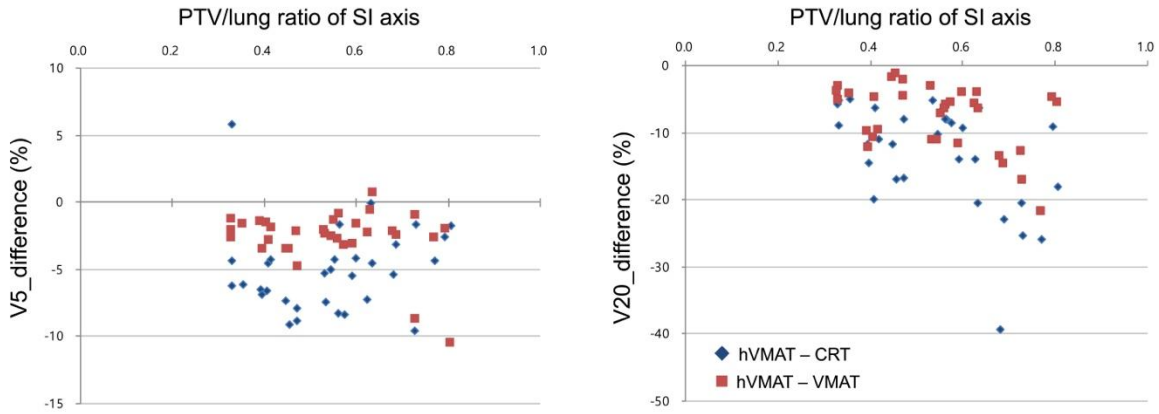

Figure 3. Scatter plots of the V_5 and V_{20} difference between hVMAT and CRT or hVMAT and VMAT plan according to the PTV/lung ratios of the SI axis. (CRT; conformal radiation therapy, VMAT; volumetric modulated arc therapy, hVMAT; hybrid volumetric modulated arc therapy, PTV; planning target volume, SI; superior-inferior)

Table 3. Correlation analysis between dosimetric parameters of lung and PTV/lung ratio of the SI axis.

		V_{20}		V_5	
		Difference between hVMAT and 3DCRT	Difference between hVMAT and VMAT	Difference between hVMAT and 3DCRT	Difference between hVMAT and VMAT
PTV/LUNG ratio of the SI axis	Pearson coefficient	**-0.511**	**-0.431**	0.113	-0.289
	p-value	0.003	0.014	0.539	0.109

3DCRT; 3-dimensional conformal radiation therapy, hVMAT; hybrid volumetric modulated arc therapy, VMAT; volumetric modulated arc therapy, PTV; planning target volume, SI; superior-inferior

Pretreatment QA for each hVMAT plan was performed, and gamma evaluation with 3%/3 mm criteria showed an average (± standard deviation) gamma passing rate of 99.75 ± 0.27%. Figure 4 shows the typical isodose distribution for each treatment plan of stage IIIB (cT2N3M0) patient with large PTV (volume of PTV was 574.5 cm^3, PTV/lung ratio of the SI axis was 0.77). The isodose line from the hVMAT plan shows the best dose distribution regarding the irradiated volume of the lung.

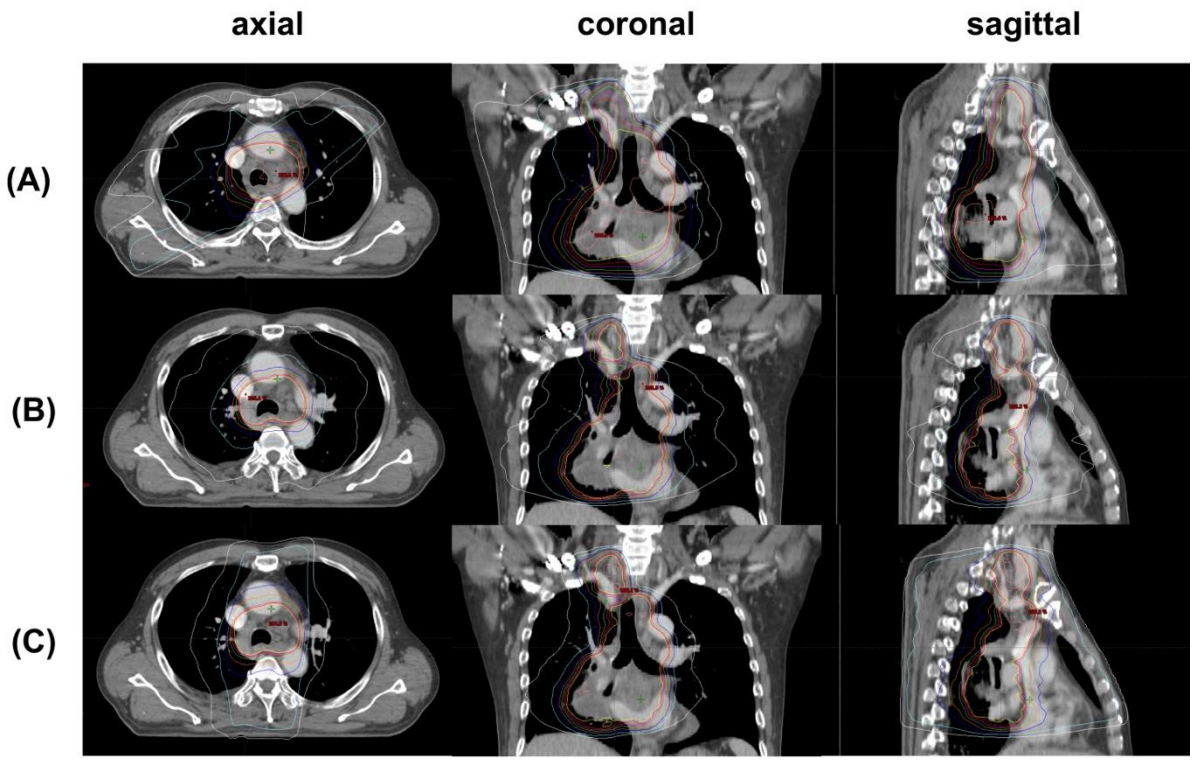

Figure 4. Dose distributions: each isodose line represent 30% (white), 50% (light blue), 70% (navy blue), 100% (yellow). (A): 3-dimensional conformal radiation therapy (3DCRT) plan, (B): volumetric modulated arc therapy (VMAT) plan, (C) hybrid-volumetric modulated arc therapy (hVMAT) plan.

The average DVH curves for PTV and lung are shown in Figure 5. Figure 5-(A) and 5-(B) represent the average DVH of group A and group B, respectively. The average DVH curves from all patients are shown in Figure 5-(C).

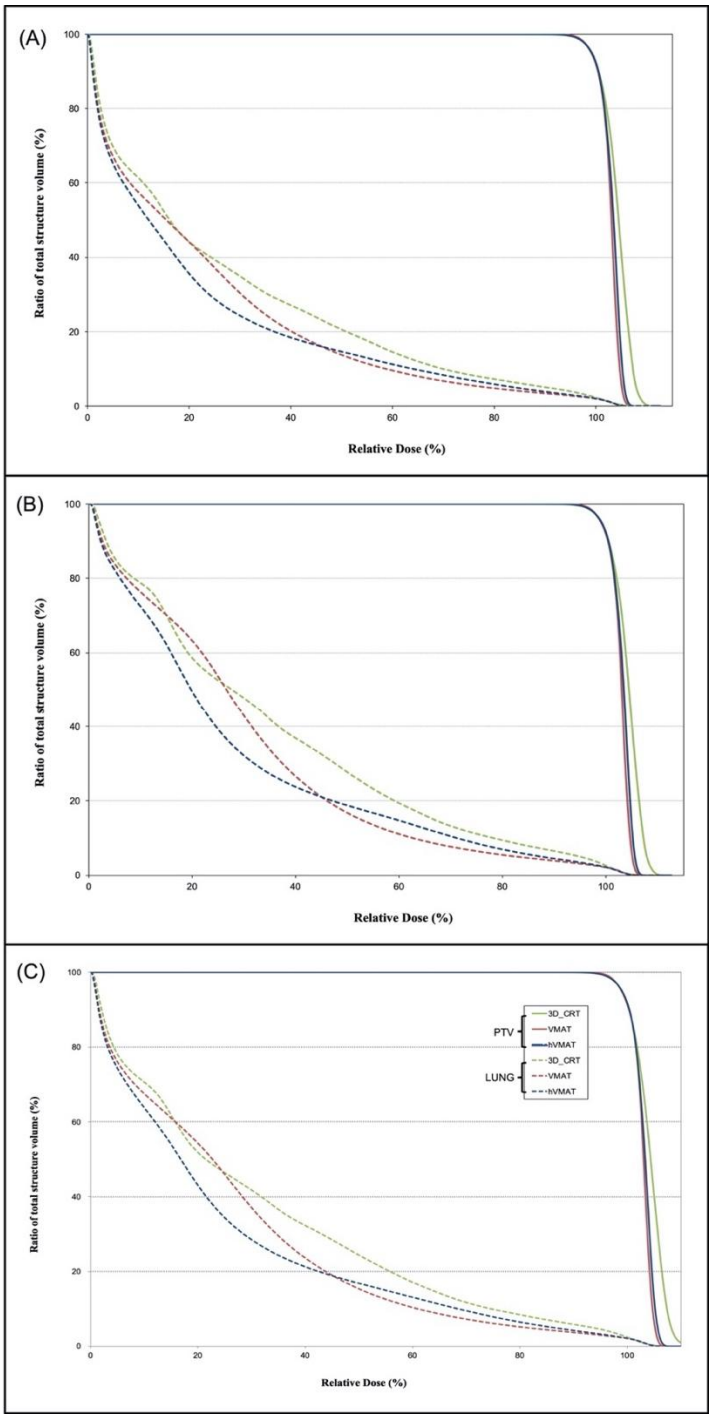

Figure 5. Comparison of average dose volume histograms (DVH) for planning target volume (PTV) and normal lung. (A): group A (PTV/lung ratio of the SI axis < 0.55), (B): group B (PTV/lung ratio of the SI axis ≥ 0.55), (C): all patients. (SI; superior-inferior)

The comparison of dosimetric data from the 3DCRT, VMAT, and hVMAT plans are summarized in Table 4. According to the CI, CN and HI, the VMAT and hVMAT plans had significantly improved conformity and homogeneity compared with the 3DCRT plan. Although the *p*-values for CI, CN, and HI were statistically significant, the absolute differences between VMAT and hVMAT were negligible. Thus, dose conformity and homogeneity of hVMAT may be not inferior to VMAT in clinical situation. The mean V_{20} of the lung of the hVMAT plans (27.2%) was significantly lower than 3DCRT plans (40.5%%; $p < 0.001$) and VMAT plans (35.0%%; $p < 0.001$). Additionally, the mean V_{10}, V_5 of the lung and MLD of the hVMAT plans were also significantly lower than 3D CRT and VMAT plans. The average D_{max} of the spinal cord of the hVMAT plans was higher than VMAT, but each D_{max} of all hVMAT plans was below the cord dose constraint of 50Gy. The D_{max} of the esophagus of the hVMAT and VMAT plans were slightly but significantly lower than 3DCRT, and the mean V_{60} of esophagus from hVMAT and VMAT plans were also lower than 3DCRT. The mean V_{40} of the heart were negligible in all three plans, nevertheless the mean dose of heart in hVMAT and VMAT plans showed better results than 3DCRT plans.

Table 4. Comparison of dosimetric parameters from 3DCRT, VMAT and hVMAT plan

	3D-CRT	VMAT	hVMAT	3DCRT vs. VMAT	3DCRT vs. hVMAT	VMAT vs. hVMAT
	Mean ± SD	Mean ± SD	Mean ± SD	(*p* value)	(*p* value)	(*p* value)
CI	0.73 ± 0.08	0.93 ± 0.02	0.91 ± 0.02			
CN	0.66 ± 0.08	0.81 ± 0.04	0.81 ± 0.03			0.002
HI	0.10 ± 0.01	0.07 ± 0.01	0.08 ± 0.01			
Lung						
V_{20} (%)	40.5 ± 12.1	35.0 ± 8.8	27.2 ± 6.4			
V_{10} (%)	60.9 ± 14.7	59.9 ± 14.9	52.7 ± 13.2	0.304		
V_5 (%)	73.3 ± 14.8	70.8 ± 15.6	68.2 ± 15.0			
Mean (Gy)	19.9 ± 4.1	17.3 ± 3.3	16.1 ± 3.1			
Spinal cord						
D_{max} (Gy)	43.5 ± 7.6	31.5 ± 5.4	43.7 ± 3.5		0.847	
Esophagus						
V_{60} (%)	30.6 ± 16.7	19.3 ± 15.8	20.0 ± 16.3			0.011
D_{max} (%)	106.0 ± 2.4	104.0 ± 6.3	104.0 ± 4.4	0.003		0.080
Heart						
V_{40} (%)	8.2 ± 7.8	3.2 ± 3.5	6.7 ± 9.4		0.002	
Mean (Gy)	12.3 ± 8.8	8.7 ± 6.8	9.8 ± 8.1			0.005

3DCRT; 3-dimensional conformal radiation therapy, VMAT; volumetric modulated arc therapy, hVMAT; hybrid VMAT, CI; conformity index, CN; conformation number, HI; homogeneity index

(blank p-values represent $p < 0.001$)

We also compared the dose parameters of group A (relatively small) and group B (relatively large) separately according to PTV/lung ratio of SI axis (Table 5). Both groups generally showed similar results in the CI, CN, and HI. Although the lung sparing effect of hVMAT was greater in group B, hVMAT showed significantly improved lung protection in group A as well.

Table 5. Comparison of dosimetric parameters from 3DCRT, VMAT and hVMAT plan according to PTV/lung ratio of the SI axis

	Group	3DCRT	VMAT	hVMAT	3DCRT vs. VMAT	3DCRT vs. hVMAT	VMAT vs. hVMAT
		Mean ± SD	Mean ± SD	Mean ± SD	(*p* value)	(*p* value)	(*p* value)
CI	A	0.74 ± 0.07	0.93 ± 0.02	0.91 ± 0.02			
	B	0.72 ± 0.08	0.93 ± 0.02	0.91 ± 0.03			
CN	A	0.68 ± 0.07	0.82 ± 0.03	0.81 ± 0.03			
	B	0.64 ± 0.08	0.80 ± 0.04	0.80 ± 0.03			0.322
HI	A	0.10 ± 0.01	0.07 ± 0.01	0.08 ± 0.01			
	B	0.10 ± 0.02	0.08 ± 0.01	0.09 ± 0.01		0.006	
Lung							
V_{20} (%)	A	34.5 ± 8.4	30.2 ± 6.1	24.0 ± 5.4	0.010		
	B	46.6 ± 12.4	39.8 ± 8.7	30.5 ± 5.6	0.001		
V_{10} (%)	A	52.6 ± 9.6	50.3 ± 8.1	44.7 ± 7.1	0.063		
	B	69.2 ± 14.3	69.6 ± 14.0	60.7 ± 13.1	0.829		
V_5 (%)	A	64.7 ± 10.6	61.5 ± 10.1	59.0 ± 9.4	0.002		
	B	81.8 ± 13.6	80.1 ± 14.8	77.3 ± 14.2	0.058		0.002
Mean (Gy)	A	17.7 ± 3.2	15.4 ± 2.6	14.3 ± 2.5			
	B	22.1 ± 3.6	19.2 ± 2.9	17.9 ± 2.7			
Spinal cord							
D_{max} (Gy)	A	42.2 ± 6.4	30.3 ± 6.4	43.3 ± 3.6		0.448	
	B	44.7 ± 8.8	32.6 ± 4.1	44.1 ± 3.4		0.782	

Table 5. Continued

Esophagus							
V_{60} (%)	A	28.1 ± 14.8	18.8 ± 14.0	19.7 ± 14.6			0.051
	B	33.2 ± 18.5	19.9 ± 18.0	20.3 ± 18.3			0.117
D_{max} (%)	A	105.5 ± 1.9	103.5 ± 5.2	103.5 ± 5.2	0.275	0.141	0.765
	B	106.7 ± 2.7	104.9 ± 4.6	104.4 ± 3.6	0.023	0.002	0.264
Heart							
V_{40} (%)	A	7.0 ± 8.1	2.5 ± 3.2	4.9 ± 6.8	0.003	0.012	0.021
	B	9.3 ± 7.6	3.8 ± 3.9	8.5 ± 11.4		0.684	0.041
Mean (Gy)	A	9.3 ± 7.7	6.2 ± 5.5	7.2 ± 6.6		0.001	0.020
	B	15.3 ± 9.0	11.2 ± 7.3	12.8 ± 8.7		0.025	0.119

Group A; PTV/lung ratio of SI axis < 0.55, Group B; PTV/lung ratio of SI axis ≥ 0.55, 3DCRT; 3- dimensional conformal radiation therapy, VMAT; volumetric modulated arc therapy, hVMAT; hybrid VMAT, CI; conformity index, CN; conformation number, HI; homogeneity index (blank p-values represent $p < 0.001$)

The median follow-up duration was 14.4 (range: 0.8 ~ 60.2) months for all 32 patients, and 34.4 (range: 10.8 ~ 60.2) months for the 11 surviving patients at the time of the analysis. Seventeen patients achieved partial response, while 13 achieved complete response. The most common first recurrent site was distant metastasis which had been occurred in 20 patients (62.5%). Solitary local failure as the first recurrence occurred in 2 patients (6.3%), and simultaneous local and distant recurrence occurred in 3 patients (9.4%). 7 patients (21.9%) have maintained NED (no evidence of disease) status during whole follow up period. According to complication analysis using CTCAE version 5.0 [14], radiation induced esophagitis occurred in 25 (78.1%) patients, and radiation pneumonitis occurred in 23 (71.9%) patients. However, grade 3 esophagitis occurred in two patients and grade 3 pneumonitis occurred in only one patient. All patients suffering from Grade 3 esophagitis recovered within 2 months of the end of treatment without sequelae. There were no cases of grade 4 or 5 toxicity (Table 6). One patient was diagnosed with idiopathic pulmonary fibrosis (IPF) before RT, but this patient developed grade 1 pneumonitis after RT. And he

died 14.6 months after treatments, the cause of death was cancer progression (brain metastasis) not lung complication.

Table 6. Incidence of radiation induced complications according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Grade	Esophagitis	Pneumonitis
0	7 (21.9%)	9 (28.1%)
1	9 (28.1%)	18 (56.3%)
2	14 (43.8%)	4 (12.5%)
3	2 (6.3%)	1 (3.1%)
4	0 (0%)	0 (0%)
5	0 (0%)	0 (0%)

The median progression free survival (PFS) time was 7.1 months and the 1-year PFS rate was 22.5%. The mean overall survival time was 26.1 months and the 1-year overall survival rate was 58.7%. Based on clinical stage, the mean overall survival time of stage IIIA and stage IIIB was 21.0 and 26.4 months, and the 1-year overall survival rate of stage IIIA and IIIB was 66.7% and 53.8%. These survival differences between stage IIIA and IIIB were not statistically significant (p=0.466) (Figure 6).

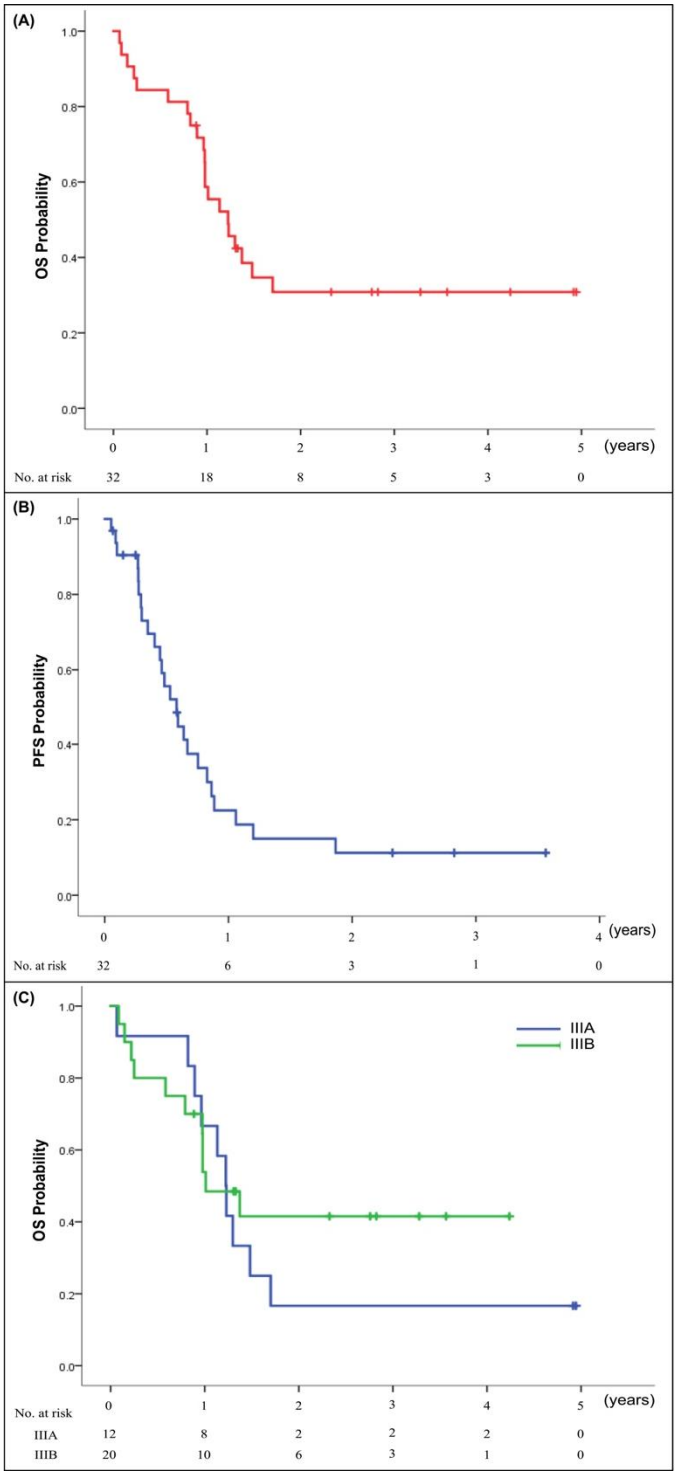

Figure 6. Kaplan–Meier survival curves. (A): overall survival (OS), (B) progression free survival (PFS), (C): overall survival curves according to stage.

DISCUSSION

It may not be possible to irradiate sufficient dose in some patients with stage III lung cancer due to surrounding normal tissue, especially lung dose constraint. Therefore, several researchers have attempted to develop a hybrid RT technique that combines CRT with IMRT or VMAT to reduce the irradiated lung volume for the treatment of lung cancer (Table 7) [5-10]. Mayo et al. reported a planning study in which hIMRT plans had a better dose distribution than IMRT plans [9]. In this study, they included 12 lung cancer patients and 6 esophageal cancer patients and compared separately. They included not only advanced stage but also early stage lung cancer patients, so the treatment volume was relatively smaller than other studies (the mean PTV was 179 cm^3). Chan et al. showed the superiority of the hVMAT plan over the VMAT and 3DCRT plans in the treatment of stage III non-small cell lung cancer (NSCLC) [6]. They included 24 patients, and the mean PTV was 508 cm^3. In this study, the hVMAT was composed of two static beams (about half dose) and two arcs (about half dose), and the prescription dose was 60Gy. The hVMAT plan showed a better D_{max} of spinal cord,

MLD compared to 3DCRT. Additionally, hVMAT also showed a better V_{20} of lung than VMAT or 3DCRT, and V_5 and V_{10} of the lung were smaller in hVMAT and 3DCRT plan than VMAT. Verbakel et al. compared the hIMRT technique with the 3DCRT, IMRT, VMAT, and hVMAT in the treatment of 14 patients with stage III NSCLC [7]. Compared to the two previous studies (Mayo et al. and Chan et al.), the PTV were relatively large (the mean PTV was 779 cm^3). The hIMRT plan was composed of 3-fields static component (89% dose) and 3-fields IMRT component (11% dose), and the hVMAT was composed of single partial arc rather than two arcs. This study did not use a statistical comparison; it just showed the differences between the five plans. The V_{20} of total lung was better in VMAT (30.3%), hIMRT (30.3%) and hVMAT (30.1%) than CRT (33.4%) or IMRT (33.4%). The V_5 of contralateral lung was the best in hIMRT (35.6%) than other plans (36.2% ~ 54.5%). They also reported clinical results; grade 3 radiation induced esophagitis occurred in five (35.7%) patients and grade 3 pneumonitis occurred in three (21.4%) patients; these complication rates were higher than our results. Silva et al. reported the clinical and dosimetric results of 11 patients with stage III lung cancer [8]. The mean PTV was 513 cm^3, and they compared

hVMAT plan with 3DCRT and VMAT plan. The hVMAT plan combined static beams (60% dose) and arcs (40% dose), dosimetric comparison showed similar findings to those previously reported and there were no severe complications (≥ grade 3) after hVMAT treatment. Agapito et al. also reported the planning study using hVMAT in 8 patients with NSCLC [5]. In this study, the mean PTV was relatively small (196 cm^3) because 2 patients with stage IB were also included. This study compared the dosimetric parameters between the 3DCRT and hVMAT. The V_{20} and V_{10} of lung, MLD were better in the hVMAT plan.

Table 6. Comparison of hybrid planning studies for lung cancer.

Author	Number of patients	Stage	Real treatment modality	Prescribed dose (Gy)	Mean PTV volume (cm^3)	Definition of lung	Dose contribution of static component (%)	Comparison techniques	TL_V_{20} (%)	TL_V_5 (%)	CL_V_5 (%)	MLD (Gy)
Mayo	12	I-III	hIMRT	59.4 ~ 75.6	179 (30 ~ 597)	lung - PTV	66	3DCRT	25.0	40.5	28.2	14.2
								IMRT (4~5 fields)	23.1	49.0	43.1	13.2
								IMRT (9 fields)	26.7	54.0	49.5	14.3
								hIMRT	20.6	44.2	32.2	13.7
Chan	24	III	n/a	60	508 (170 ~ 993)	lung - PTV	47	3DCRT	25.0	57.2	n/a	14.6
								VMAT	25.4	64.0	n/a	14.4
								hVMAT	23.3	59.5	n/a	14.0

Table 6. Continued

Verbakel	14	III	hIMRT	62 ~ 66	779 (591 ~ 1258)	lung - PTV	89	3DCRT	33.4	n/a	54.5	n/a
								IMRT	33.4	n/a	47.3	n/a
								VMAT	30.3	n/a	44.6	n/a
								hIMRT	30.3	n/a	35.6	n/a
								hVMAT	30.1	n/a	36.2	n/a
Agapito	8	IB-IIIA	3D-CRT	60 ~ 66	196 (76~302)	**lung - GTV**	54	3DCRT	22.2	39.9	n/a	13.6
								hVMAT	19.3	38.5	n/a	11.7
Silva	11	III	hVMAT	59.4 ~ 66	513 (213 ~ 952)	lung - PTV	60	3DCRT	31	65	60	18.5
								VMAT	32	57	45	16.9
								hVMAT	29	58	37	17.9
Present study	**32**	III	hVMAT	56 ~ 66	408 (171 ~ 1093)	**lung - GTV**	**20**	3DCRT	40.5	73.3	n/a	19.9
								VMAT	35.0	70.8	n/a	17.3
								hVMAT	27.2	68.2	n/a	16.1

PTV; planning target volume, GTV; gross tumor volume, TL; total lung, CL; contralateral lung, MLD; mean lung dose, 3DCRT; 3-dimensional conformal radiation therapy, IMRT; intensity modulated radiation therapy, hIMRT; hybrid IMRT, VMAT; volumetric modulated arc therapy, hVMAT; hybrid VMAT

According to the RTOG and European Society for Radiotherapy and Oncology (ESTRO) guidelines [11,15], the recommended definition of the lung is as “lung minus GTV”. The PTV is made by adding margin to CTV to account for the geometric uncertainties. Thus, if the lung is defined as “lung minus PTV” instead of a “lung minus GTV”, the irradiated lung volume (V_{20}, V_{10}, V_5, and MLD etc.) will be smaller because the volume of the added margin is not included in the dose calculation as the lung volume. With the exception of Agapito et al.’s study, the previous four studies defined the lung volume as a "lung minus PTV". Therefore, in these four studies, the irradiated lung volume would have been calculated smaller than the real irradiated lung volume. For example, although Verbakel et al. included only large tumors (PTV> 500 cm^3), the V_{20} of the lung was about 30% even in 3DCRT. Other previous studies also showed similar dosimetric results which are within the acceptable lung dose level according to National Comprehensive Cancer Network (NCCN) guideline for lung cancer RT even in 3DCRT without the use of the hybrid technique [16]. In Agapito et al.’s study, the definition of the lung was a “lung minus GTV”, but the mean PTV was relatively small (196 cm^3) because this study included stage IB patients. Thus, the V_{20} of the lung were

as low as 22.2% in the 3DCRT plan and 19.3% in the hVMAT plan. In the present study, we used the "lung minus GTV" definition for lung dose calculation to meet the RTOG, ESTRO guidelines. We included only stage III patients and in particular 62.5% of patients were stage IIIB. Therefore, dosimetric results of the lung from the 3DCRT and VMAT plans were higher than those reported in previous studies and out of the acceptable range in some patients. However, all dosimetric parameters from the hVMAT plan were within the acceptable range.

Studies about the pulmonary function reported lung volume in the Caucasian group was larger than in the Asian group [17,18]. Although previous hybrid RT studies did not disclose racial information, but since the institutions of these studies were in the United States or Europe, the hypothesis that most patients involved in these studies were either American or European may be reasonable. Consequently, because patients in previous studies had relatively large lung size, overall PTV/lung ratio could be small even with large PTV. On the other hand, we included only Asian patients in present study, so the absolute lung volume may be smaller than other studies. In addition, since most patients (62.5%) in our study were

stage IIIB, overall PTV/lung ratio could be larger than other studies. Therefore, the dosimetric parameters of the lung from our study were higher than other studies because patients had relatively small lung volume due to Asian race characteristic and relatively large tumor volume due to more advanced stage. Lung dose parameters from half of patients with small PTV/lung ratio (group A) were similar to previous studies (Table 5, Table 7), which may be another evidence for the hypothesis that the overall PTV/lung ratios in our study were larger than previous studies. In summary, we used the "lung minus GTV" definition for lung volume and the PTV/lung ratios of our study were relatively large due to relatively small lung volume and more advanced stage. In other words, more difficult cases were included in our study to make acceptable RT plan. Therefore, for these reasons, it can be thought that lung dose parameters were higher in our study.

According to correlation analysis, the absolute volume of PTV was not correlated with the lung dose parameters (Table 2, Figure 2). Therefore, the absolute volume of PTV was not sufficient to represent the relative size of PTV to the lung volume, so we used the concept of the "PTV/lung ratio" to represent the relative PTV volume; the ratio of the SI axis had a

significantly strong correlation with all of the lung dose parameters. Thus, based on the median PTV/lung ratio of the SI axis, we divided patients into group A (relatively small) and group B (relatively large) to compare dosimetric parameters according to the relative volume of PTV. According to the sub-group analysis, although the dosimetric benefit of hVMAT was greater in group B than group A, but there was significant improvement in group A as well (Table 5). That is, the hVMAT plan significantly reduced all dosimetric parameters of the lung even in the patients with relatively small PTV. Therefore, the hVMAT plan might also be useful for the treatment of stage III lung cancer with a relatively small tumor volume. All previous hybrid planning studies made their hIMRT or hVMAT plans by adding IMRT or VMAT components to the base static plan. The dose contribution of the static component ranged from 50% to 90%, so most of the radiation dose was delivered through static beams in these studies. The IMRT or VMAT component of the hybrid plan just played a secondary role to increase conformity. The authors from the previous studies explained that the reason for using a small proportion of the IMRT or VMAT components was to reduce the uncertainty of IMRT or VMAT. The uncertainty of the IMRT or VMAT plan can be

increased in moving tumor treatment; this is called an “interplay effect”. The interplay effect should be considered in stereotactic body radiation therapy (SBRT) which uses flattening filter free (FFF) beams and high dose rate. However, if radiation is delivered in multiple fractions and at a low dose rate with flattened beams then the interplay effect will be averaged out [19-22]. Thus, the interplay effect can be ignored in conventional RT with a large number of fractions. For this reason, we used VMAT as the base plan, and added the small weight of two static beams to the original VMAT plan to make the hVMAT plan. As a result, the dose contribution of CRT was approximately 20%; this ratio was the opposite to that used in other hybrid studies and most of the radiation dose was delivered through VMAT. This unique hybrid ratio was able to significantly reduce the irradiated lung volume while maintaining dose conformity and homogeneity similar to observed in the original VMAT plan. In other words, the results of CI and HI from hVMAT plans were not inferior than VMAT plans. Through this novel technique, all dosimetric parameters of the lung (V_5, V_{10}, V_{20}, MLD) were improved while maintaining a proper spinal cord dose, esophageal dose, and heart dose. Each spinal cord D_{max} of all hVMAT plans was below the cord dose

constraint of 50Gy and the heart dose were negligible in all three plans. Although the high dose lung volume in the hVMAT plan is increased than the VMAT plan, the decrease in the low dose volume through the hVMAT plan is greater than the increase. In addition, since it is known that the generation of radiation pneumonitis is correlated with the low dose lung volume, we believe that the incidence of radiation pneumonitis can be reduced by reducing the low dose lung volume using hVMAT technique [23]. Even though 62.5% of patients included in this study were stage IIIB, severe esophagitis and pneumonitis occurred in only 3 (6.3%) and 1 (3.1%) patients, respectively. And most complications were mild and there was no grade 4 or 5 complication. Therefore, acceptable plans can be made using hybrid technique even in the patients who cannot receive a proper dose through the 3DCRT or VMAT plans. If such patients are treated with an existing 3DCRT or VMAT plan, they will not be treated with a high enough radiation dose as the curative intended treatment.

The limitation of this study is its retrospective nature. However, even though statistical analysis was conducted retrospectively, all three plans were generated for comparison and selection prior to treatment. Thus, the present study may have less bias than previous hybrid

studies that made rival plans for plan comparison at analysis after RT completion.

Furthermore, this study is not just a plan comparison study. In reality, all patients were treated with a novel hVMAT technique. Therefore, this study provides the first clinical and dosimetric results from the treatment of stage III lung cancer using the new hybrid treatment technique consisting of a basic VMAT component and a small amount of static component.

Another limitation of this study was that the results of dosimetric results of lung doses were improved, but the improvement in dose distribution did not lead to improved survival.

CONCLUSION

This novel hVMAT technique based on the VMAT plan can be simply made by adding two static beams to the original VMAT plan and adjusting the static beam weight to be approximately 20% of the total dose. Compared with the 3DCRT and VMAT, this easy hybrid technique can produce optimal dose distribution for PTV and OARs. In addition, despite the static beams were arranged in anterior-posterior direction, the irradiated dose of the spinal cord, esophagus, and heart can be maintained at an acceptable level. Therefore, this new hVMAT technique might be a solution for the patients with stage III lung cancer who cannot receive a sufficient radiation dose with the existing 3DCRT or VMAT plans.

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국문요약

목적 : III 기 폐암 환자에서 기존의 3 차원 입체조형방사선치료 (3-dimensional conformal radiation therapy, 3DCRT), 세기조절방사선치료 (intensity modulated radiation therapy, IMRT) 또는 체적조절호형방사선치료 (volumetric modulated arc therapy, VMAT) 기술을 사용하여 충분한 방사선량을 조사하기 어려운 경우가 있습니다. 이 문제를 해결하기 위해 새로운 하이브리드 VMAT (hVMAT) 기술을 개발했습니다. 이 연구의 목표는 III 기 폐암 치료에서 새로운 hVMAT 기술의 유용성을 입증하는 것입니다.

방법 : hVMAT 으로 치료받은 III 기 폐암 환자 32 명을 대상으로 분석하였습니다. hVMAT 계획은 기존 VMAT 계획에 두 개의 정적 빔을 추가하여 만들었습니다. hVMAT 계획의 유용성을 평가하기 위해 conformity index (CI), conformation number (CN), homogeneity index (HI) 및 정상 장기 (organ at risk, OAR)의 선량 변수 등을 사용하여 3 가지 치료 계획 (3DCRT 대 VMAT 대 hVMAT)을 비교했습니다.

결과 : 폐의 평균 V_{20}은 hVMAT 계획(27.2 %)에서 3DCRT 계획(40.5 %) 및 VMAT 계획(35.0 %)보다 유의하게 낮았습니다. 또한, hVMAT 계획은 척수, 식도 및 심장에 대해 허용되는 수준으로 조사 선량을 유지하면서 폐에 대한 선량 변수 (V_5, V_{10}, mean lung dose)에서 최상의 결과를 보여줬습니다. 또한 hVMAT 는 VMAT 계획과 비교하여 CI, CN 및 HI 에 대해 열등하지 않은 결과를 보여줬습니다.

결론 : 새로운 hVMAT 치료 계획은 모든 폐 선량 변수를 향상시키면서 다른 장기에 조사되는 선량을 허용범위 이하로 유지할 수 있습니다. 따라서 hVMAT 은 III 기 폐암 치료에 유용한 치료계획 방법이 될 수 있으며, 기존 3DCRT 또는 VMAT 계획으로 충분한 선량을 조사 할 수 없는 환자에 대한 해결방법이 될 수 있습니다.