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Avoiding Dosimetric Risk Factors for Complications in Neoadjuvant Chemoradiotherapy for Lung Cancer: Conventional Radiotherapy *Versus* Intensity-modulated Radiotherapy

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Abstract. *Background/Aim: We compared three-dimensional conformal radiotherapy (3D-CRT) with intensity-modulated radiotherapy (IMRT) for avoiding dosimetric risk factors related to pulmonary complications after neoadjuvant chemoradiotherapy followed by surgery (NACRT-S) for non-small cell lung cancer (NSCLC). Patients and Methods: We performed simulations in 11 patients with dosimetric risk factors during their treatment with NACRT-S for NSCLC. Radiation treatment plans were generated using 3D-CRT and IMRT to avoid dosimetric risk factors. Regarding dose–volume histogram (DVH) parameters, we calculated the percentage of lung volume that received more than x Gy (V_x) using 1) the total lung volume minus gross tumor volume (DVH_g), 2) the lung volume remaining after surgery (DVH_r), and 3) the contralateral lung volume (DVH_c). We analyzed the dosimetric differences between 3D-CRT and IMRT. Results: V_{35g} and V_{40g} were significantly lower with IMRT than with 3D-CRT (p=0.001 each); the median V_{35g} and V_{40g} were 16.1% and 14.9% with 3D-CRT versus 12.0% and 9.2% with IMRT, respectively. Overall, 0% and 55% of the patients were able to avoid all dosimetric risk factors with 3D-CRT and IMRT, respectively (p=0.006). Even with IMRT, tumor location and length of the planning target volume (PTV) significantly affected the avoidance of all dosimetric risk factors (p=0.015 and 0.022, respectively). Conclusion: IMRT is more useful than 3D-CRT for avoiding dosimetric risk factors in NACRT-S for NSCLC. For further improvements in avoiding these factors, respiratory motion managements to reduce the length of the PTV may be required for patients with middle or lower lobe tumors.*

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According to the National Comprehensive Cancer Network (NCCN) guidelines, neoadjuvant chemoradiotherapy followed by surgery (NACRT-S) is recommended for patients with resectable superior sulcus tumors, and is an alternative option for patients with resectable stage IIIA non-small cell lung cancer (NSCLC) (1). However, neoadjuvant therapy is a major risk factor for postoperative broncho-pleural fistula (BPF) and respiratory failure (2). From the perspective of radiotherapy (RT), several studies have reported dosimetric risk factors using dose–volume histogram (DVH) parameters related to pulmonary complications after NACRT-S for NSCLC (3-6). In definitive chemoradiotherapy for locally advanced NSCLC, intensity-modulated radiotherapy (IMRT) has been more useful than three-dimensional conformal radiotherapy (3D-CRT) in reducing lung toxicities (7, 8). The usefulness of IMRT in the setting of NACRT-S remains unknown. Therefore, in this planning study, we compared 3D-CRT with IMRT to avoid the dosimetric risk factors of NACRT-S for NSCLC.

Patients and Methods

Patients. This retrospective study was approved by the institutional ethics committee (approval number: 2019-053). The eligibility criteria for this study were as follows: 1) patients who underwent NACRT-S for NSCLC between 2016 and 2019 at our institution; 2) patients who underwent 3D-CRT with a dose of 50 Gy in 25 fractions; and 3) patients with dosimetric risk factors in the clinical treatment using NACRT-S.

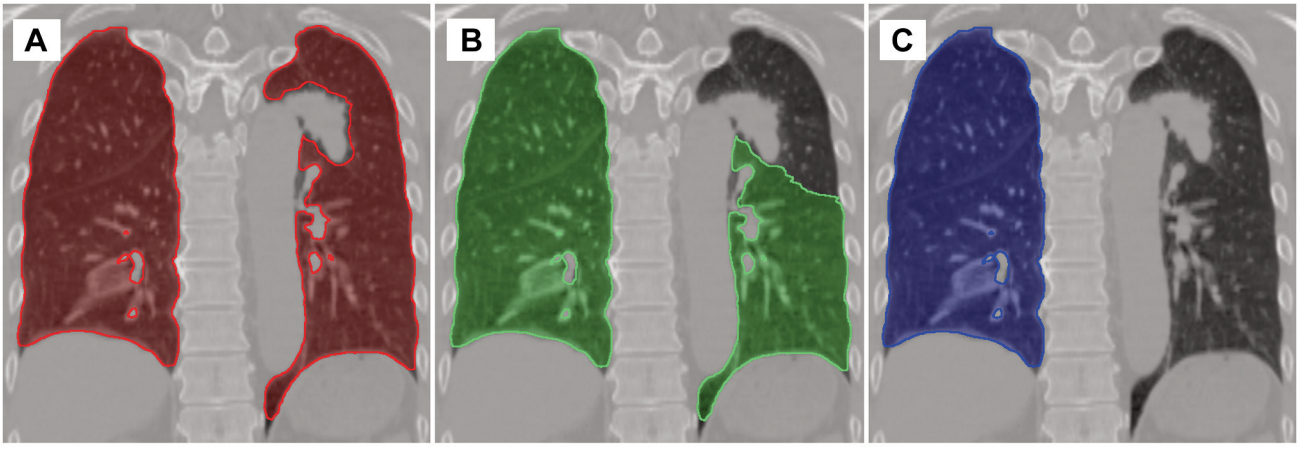

Figure 1. *The lung volumes were generated for dose–volume histogram (DVH) parameters using: A) the total lung volume minus GTV (DVH_g, red); B) the lung volume remaining after surgery (DVH_r, green); and C) the contralateral lung volume (DVH_c, blue).*

Radiation treatment planning. Four-dimensional computed-tomographic images of free breathing were obtained for radiation treatment planning. Primary tumors and clinically positive lymph nodes (LNs) were defined as the gross tumor volumes (GTVs). The clinical target volume (CTV) was defined as the GTV with a 5 mm margin and the nodal station to which the clinically positive LNs belonged. Elective nodal irradiation was not performed to the non-metastatic stations. The planning target volume (PTV) was defined as the CTV with a 5 mm margin.

Regarding the DVH parameters, we calculated the percentage of the lung volume that received more than x Gy (V_x) and the mean lung dose (MLD) using: 1) the total lung volume minus the GTV (DVH_g: Figure 1A); 2) the lung volume remaining after surgery (DVH_r: Figure 1B); and 3) the contralateral lung volume (DVH_c: Figure 1C). Previous reported dosimetric risk factors in NACRT-S (3-6) were as follows: 1) for DVH_g, V_{20g}≥21%, V_{20g}≥23%, V_{35g}≥19%, V_{40g}≥16%, MLD_g≥10 Gy, and MLD_g≥10.8 Gy; 2) for DVH_r, V_{20r}≥10%, V_{20r}≥12%, and MLD_r≥5.6 Gy; and 3) for DVH_c, V_{10c}≥20% and V_{20c}≥7%.

In this study, we generated radiation treatment plans using 3D-CRT and IMRT to avoid the aforementioned dosimetric risk factors for the lungs and achieve common dose constraints for the spinal cord based on the NCCN guidelines (1). We were careful not to broaden the low doses to the lungs during beam arrangement. The prescribed doses that were normalized to 50% of the volume of the PTV were 50 Gy in 25 fractions.

Statistics. We analyzed the dosimetric differences between 3D-CRT and IMRT using the Wilcoxon rank-sum test and Fisher's exact test. A p-value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using JMP Pro ver. 15 (SAS Institute, Cary, NC, USA).

Results

Eleven patients met the eligibility criteria, and their tumor characteristics are listed in Table I. Dosimetric differences between 3D-CRT and IMRT are listed in Table II. V_{35g} and V_{40g} were significantly lower with IMRT than with 3D-CRT (p=0.001 each). As for each dosimetric risk factor (Table III), 9% and 55% of the patients were able to avoid MLD_g≥10 Gy with 3D-CRT and IMRT, respectively (p=0.032). Overall, 0% and 55% of the patients were able to avoid all dosimetric risk factors with 3D-CRT and IMRT, respectively (p=0.006).

Additional analyses were performed for IMRT with or without avoiding all dosimetric risk factors (Table IV).

Table I. *Tumor characteristics*.

Characteristics			%
Laterality	Right	7	64
	Left	4	36
Lobe	Upper	7	64
	Middle	2	18
	Lower	2	18
Histology	Squamous cell carcinoma	6	55
	Adenocarcinoma	5	45
cT-status*	1b	1	9
	1c	1	9
	2a	2	18
	2b	2	18
	3	2	18
	4	3	27
cN-status*	1	1	9
	2	10	91
c-stage*	IIIA	8	63
	IIIB	3	27
PTV size (cc)	Median	356	
	Range	187-888	
PTV length (cm)	Median	12.8	
	Range	7.8-16.4	

*Based on 8th edition of the Union for International Cancer Control. PTV: Planning target volume.

Table II. *Dosimetric differences between three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT).*

Structures	DVH parameters	3D-CRT [median (range)]	IMRT [median (range)]	*p*-Value
PTV	$D_{95\%}$ (Gy)	46.5 (45.7-47.6)	46.4 (45.1-47.5)	0.793
Spinal cord	D_{max} (Gy)	40.7 (33.5-44.8)	40.1 (32.5-45.6)	0.554
Lung	V_{5g} (%)	31.9 (24.4-55.5)	33.0 (24.3-56.9)	0.412
	V_{20g} (%)	19.7 (12.3-26.8)	19.4 (11.7-25.9)	0.646
	V_{35g} (%)	16.1 (9.5-20.8)	12.0 (9.2-14.4)	0.001
	V_{40g} (%)	14.9 (8.5-17.0)	9.2 (5.6-13.3)	0.001
	MLD_g (Gy)	10.6 (7.8-14.8)	9.8 (6.6-12.9)	0.088
	V_{20r} (%)	10.0 (5.4-24.9)	9.0 (5.1-22.4)	0.718
	MLD_r (Gy)	5.9 (4.3-13.8)	5.3 (3.8-11.9)	0.470
	V_{10c} (%)	8.2 (1.1-12.3)	5.8 (2.2-10.6)	0.490
	V_{20c} (%)	1.3 (0.0-3.1)	1.4 (0.1-4.6)	0.449

DVH: Dose-volume histogram; PTV: planning target volume; $D_{n\%}$: irradiated dose to *n*% of volume of the structure; $V_{n\text{Gy}}$: percentage of volume of the structure at least irradiated $_n$ Gy; MLD: mean lung dose.

Table III. *Avoiding dosimetric risk factors between three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT).*

Dosimetric risk factors		3D-CRT	IMRT	*p*-Value
V_{20g}	≥21%	4/11 (36%)	4/11 (36%)	0.670
	<21%	7/11 (64%)	7/11 (64%)	
V_{20g}	≥23%	4/11 (36%)	3/11 (27%)	0.500
	<23%	7/11 (64%)	8/11 (73%)	
V_{35g}	≥19%	3/11 (27%)	0/11 (0%)	0.107
	<19%	8/11 (73%)	11/11 (100%)	
V_{40g}	≥16%	3/11 (27%)	0/11 (0%)	0.107
	<16%	8/11 (73%)	11/11 (100%)	
MLD_g	≥10 Gy	10/11 (91%)	5/11 (45%)	0.032
	<10 Gy	1/11 (9%)	6/11 (55%)	
MLD_g	≥10.8 Gy	4/11 (36%)	4/11 (36%)	0.670
	<10.8 Gy	7/11 (64%)	7/11 (64%)	
V_{20r}	≥10%	6/11 (55%)	5/11 (45%)	0.500
	<10%	5/11 (45%)	6/11 (45%)	
V_{20r}	≥12%	4/11 (36%)	4/11 (36%)	0.670
	<12%	7/11 (64%)	7/11 (64%)	
MLD_r	≥5.6 Gy	6/11 (55%)	5/11 (45%)	0.500
	<5.6 Gy	5/11 (45%)	6/11 (45%)	
V_{10c}	≥20%	0/11 (0%)	0/11 (0%)	1.000
	<20%	11/11 (100%)	11/11 (100%)	
V_{20c}	≥7%	0/11 (0%)	0/11 (0%)	1.000
	<7%	11/11 (100%)	11/11 (100%)	

$V_{n\text{Gy}}$: Percentage of volume of the structure at least irradiated $_n$ Gy; MLD: mean lung dose.

Tumor location and the length of PTV significantly affected the avoidance of all dosimetric risk factors (p=0.015 and 0.022, respectively). As for the relationship between PTV length and tumor location, the PTV length of the middle or lower lobe tumors was significantly longer than that of the upper lobe tumors: median, 14.2 cm and 10.0 cm, respectively (p=0.013).

Discussion

NACRT-S is a well-known risk factor of pulmonary complications during NSCLC treatment (2, 11). To reduce the toxicity, improvements were explored from the perspective of RT. Regarding the dosimetric risk factors of NACRT-S for NSCLC, V_{20r}≥12%, V_{35g}≥19%, and

Table IV. *Additional analyses for intensity-modulated radiotherapy with or without avoiding all dosimetric risk factors.*

Characteristics		With avoiding all dosimetric risk factors	Not avoiding at least one dosimetric risk factor	*p*-Value
Laterality	Right	3/7 (43%)	4/7 (57%)	0.546
	Left	3/4 (75%)	1/4 (25%)	
Lobe	Upper	6/7 (86%)	1/7 (14%)	0.015
	Middle or lower	0/4 (0%)	4/4 (100%)	
Histology	Squamous cell carcinoma	3/6 (50%)	3/6 (50%)	1.000
	Adenocarcinoma	3/5 (60%)	2/5 (40%)	
cT-status*	1-2	4/6 (67%)	2/6 (33%)	0.567
	3-4	2/5 (40%)	3/5 (60%)	
c-stage*	IIIA	4/8 (50%)	4/8 (50%)	
	IIIB	2/3 (67%)	1/3 (33%)	1.000
PTV size (cc)	Median (range)	358 (187-888)	305 (252-538)	0.784
PTV length (cm)	Median (range)	9.6 (7.8-13.2)	13.8 (12.8-16.4)	0.022

*Based on 8th edition of the Union for International Cancer Control. PTV: Planning target volume.

V_{40g}≥16% were first proposed as significant factors affecting the incidence of radiation pneumonitis (RP) and BPF or pulmonary fistulas (3). Second, V_{20r}≥10% and MLD_r≥5.6 Gy have been reported to be significant predictors of RP (4). Third, V_{10c}≥20% and V_{20c}≥7% were significant factors affecting the incidence of pulmonary toxicity (5). Finally, V_{20g}≥21% and MLD_g≥10 Gy have been reported to be significant predictors of RP (6).

In this planning study, we compared 3D-CRT with IMRT to avoid the dosimetric risk factors associated with NACRT-S for NSCLC. IMRT significantly reduced V_{35g} and V_{40g} compared to 3D-CRT. Among the dosimetric risk factors, MLD_g≥10 Gy was significantly avoided using IMRT. Overall, 0% and 55% of the patients were able to avoid all dosimetric risk factors with 3D-CRT and IMRT, respectively. In the treatment of definitive chemoradiotherapy for locally advanced NSCLC, IMRT has been useful in reducing the radiation dose to the lungs compared to 3D-CRT (7, 8). We confirmed that IMRT is more useful than 3D-CRT in reducing the irradiated dose to the lungs in the NACRT-S setting, as with the definitive setting.

However, even with IMRT, all of the four patients with middle or lower lobe tumors had at least one dosimetric risk factor. Tumor location and PTV length significantly affected the avoidance of all dosimetric risk factors. The PTV of the middle and lower lobe tumors was significantly longer than that of the upper lobe tumors. One possible reason for this is the respiratory motion of the tumor. Respiration-induced tumor motion in the superior-inferior direction was greater in the lower lobe and lower pulmonary zone tumors compared with apical tumors (9). Respiratory motion management is recommended to spare the normal tissue when patients can tolerate the procedure (10). To further improve the avoidance of dosimetric risk factors for NACRT-S, we should apply additional respiratory motion management, such as breath-holding, for patients with middle or lower lobe tumors.

Our study has some limitations, such as the small number of participants and the retrospective single-institutional design.

In conclusion, our findings suggest that IMRT is more useful than 3D-CRT for avoiding dosimetric risk factors in NACRT-S for NSCLC. For further improvements in avoiding these factors, respiratory motion managements to reduce the length of the PTV may be required for patients with middle or lower lobe tumors.

Conflicts of Interest

The Authors have no conflicts of interest regarding this study.

Authors' Contributions

This study was coordinated by ST and TS. The data were collected by ST, MA, TK, and TN. The collected data were analyzed by ST. This article was drafted by ST. Data interpretation and article revision were performed by all authors: ST, MA, TK, TN, and TS. All the Authors have approved the submitted manuscript.

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