Dosimetric Comparisons of Volumetric Modulated Arc Therapy with Three-Dimensional Conformal Radiation Therapy for Locally Advanced Non-Small Cell Lung Cancer

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Purpose : To evaluate the dosimetric differences between volumetric modulated arc therapy (VMAT) and three-dimensional conformal radiation therapy (3D-CRT) for locally advanced non-small cell lung cancer (NSCLC).

Materials and methods : A planning study was performed with the data of 17 patients with inoperable NSCLC who actually underwent definitive radiotherapy. VMAT and 3D-CRT plans were created for each patient. The primary objectives of these plans were to prescribe 60 Gy in 30 fractions to 95% of the planning target volume and to limit the dose delivered to the spinal cord to less than 50 Gy. The secondary objectives were to keep the doses delivered to other risk organs as low as possible.

Results : The 3D-CRT plans for two patients did not achieve the primary objectives, although they were achieved by the VMAT plans for these patients. In a comparison of the acceptable plans, the VMAT plans improved the dose conformity, V_{20} and mean dose of the lung, and V_{35} of the oesophagus. There were no significant differences in V_{10} or V_5 of the lung, or the maximum dose and mean dose of the oesophagus.

Conclusion : The advantage of VMAT compared to 3D-CRT may facilitate appropriate use of VMAT for patients with locally advanced NSCLC. *Shinshu Med J 65 : 93—98, 2017*

(Received for publication October 31, 2016 ; accepted in revised form December 7, 2016)

Key words : non-small cell lung cancer, volumetric modulated arc therapy, three-dimensional conformal radiation therapy, treatment planning comparison

I Introduction

Radiotherapy plays a key role in the treatment of inoperable locally advanced non-small cell lung cancer (NSCLC)[1]. Although radiotherapy is recognized as the standard of care for advanced NSCLC, significant challenges remain regarding this therapy. The lungs are surrounded by critical organs, such as the spinal cord, oesophagus, and heart. Furthermore, the lung itself is vulnerable to radiation. Delivering the prescribed doses to the planning target volume (PTV) while preventing intolerable irradiation of the organs at risk (OAR) is often difficult to achieve. Although this dilemma has been partially resolved with the advent of three-dimensional conformal radiation therapy (3D-CRT), a number of problems remain. Intensity-modulated radiation therapy (IMRT) has been expected to solve some of these issues, and has recently been utilized in clinical settings[2)-4)]. Volumetric modulated arc therapy (VMAT) is an advanced form of IMRT that efficiently provides highly conformal dose distributions with rotation of the gantry. Several planning studies showed that VMAT, especially partial arc (PA)-VMAT, has some advantages compared with conventional IMRT in the treatment of locally advanced NSCLC[5)6)]. However, there have been few studies related to the benefits of VMAT compared with 3D-CRT in consecutive

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patients. In this study, we investigated the dosimetric differences between VMAT and 3D-CRT plans and evaluated whether VMAT is more beneficial than 3D-CRT in the treatment of locally advanced NSCLC.

Ⅱ Materials and Methods

The institutional review board of our hospital approved this retrospective study, and the requirement to obtain informed consent from study patients was waived. Seventeen patients with inoperable locally advanced NSCLC who underwent definitive radiotherapy between January 2013 and August 2014 at our institution were selected for this study. The patient characteristics are listed in **Table 1**. All patients were staged by the 7th edition of the UICC-TNM staging system. Ten of 17 patients were staged as T4 or N3. Computed tomography (CT) images were acquired for radiation treatment planning in all patients. The entire thorax was scanned in the supine position with both arms raised above the head. Respiratory movement was evaluated with either four-dimensional CT images or breath-held CT images at inhaling and exhaling positions.

On those planning CT images, we newly contoured target volumes and OARs according to the following definitions. The gross tumour volume (GTV) was defined as the primary lesion that was macroscopically identifiable and lymph nodes > 1 cm in diameter. Fluorodeoxyglucose-positron emission tomography (FDG-PET) images were utilized for delineation of GTV when available. The GTV was delineated considering respiratory movement. The clinical target volume (CTV) enclosed the GTV with a margin of 0.5－1 cm. The PTV enclosed the CTV with a margin of 0.5 cm. The OARs consisted of the lung, spinal cord, oesophagus, and heart. Planning organ at-risk volumes (PRVs) were extended as 0.3 cm to the spinal cord, oesophagus, and heart. The lung PRV included both ipsi- and contralateral lungs, but the GTV was excluded.

Both 3D-CRT and the VMAT plans were created on the Eclipse treatment planning system (version 11 ; Varian Medical Systems, Palo Alto, CA, USA) with 10-MV photon beams. Doses were calculated with the anisotropic analytical algorithm. The 3D-CRT plans typically consisted of four beams arranged with anterior-posterior (AP) opposed beams and oblique off-cord opposed beams. The VMAT plans typically consisted of two partial coplanar arcs. Irradiation was avoided on the lateral sectors (40°-140°, 220°-320°) to prevent excessive irradiation of the normal lung tissue.

The primary objectives of planning were to prescribe 60 Gy in 30 fractions to 95% of the PTV and to limit the dose delivered to the spinal cord PRV < 50 Gy. The secondary objectives were to keep the doses delivered to other PRVs as low as possible. The dose-volume constraints for the PRVs were set as follows : lung PRV, volume receiving > 20 Gy (V_{20}) < 35% and mean lung dose (MLD) < 20 Gy ; oesophagus PRV, mean dose (D_{mean}) < 34 Gy ; heart PRV, volume receiving > 40 Gy (V_{40}) < 80%. Plans in which both the primary and secondary objectives were achieved were considered acceptable.

To compare the VMAT with the 3D-CRT plans, the dose-volume histograms (DVHs) of the PTV and the PRVs were calculated in each plan. The homogeneity index (HI) and conformity index (CI) were computed from the data of DVH to assess the quality of planning. The HI was defined as the ratio of the maximum dose (D_{max}) over the minimum dose (D_{min}) in the PTV. Greater HI values indicated doses exceeding the prescription dose and a greater degree of dose heterogeneity in the PTV. The CI was defined as the ratio of the prescription-isodose volume over the PTV. Greater CI values indicated a greater volume of the prescription dose delivered outside the PTV.

The collected data were statistically analysed based on Wilcoxon's signed rank test using JMP (version 5.1.1 ; SAS Institute, Cary, NC, USA). In all analyses, a value of $P < 0.05$ was considered to be significant.

Ⅲ Results

The primary objectives were not achieved in the 3D-CRT plans for two patients (Patients 3 and 14). Delivery of 60 Gy to 95% of the PTV could not be

Table 1 Patient characteristics

Patient	TNM	Location	PTV (cm^3)	T4/N3 descriptor
1	T4N0M0	Right lower lobe	216	Invasion to the heart
2	T4N2M0	Right upper lobe	853	Invasion to the great vessels
3	T4N1M0	Right upper lobe	581	Invasion to the vertebral body
4	T4N2M0	Left upper lobe	251	Invasion to the oesophagus
5	T1N2M0	Right upper lobe	147	
6	T3N3M0	Right upper lobe	481	Metastasis in the ipsilateral supraclavicular lymph nodes
7	T3N2M0	Right upper lobe	280	
8	T4N2M0	Left hilus	58	Invasion to the carina
9	T4N2M0	Left upper lobe	611	Invasion to the heart
10	T3N2M0	Right upper lobe	508	
11	T1N1M0	Right upper lobe	147	
12	T2N2M0	Left lower lobe	273	
13	T1N3M0	Left upper lobe	281	Metastasis in the ipsilateral supraclavicular lymph nodes
14	T4N3M0	Left upper lobe	776	Invasion to the mediastinum/ metastasis in the contralateral mediastinal lymph nodes
15	T4N0M0	Left hilus	89	Invasion to the carina
16	T2N1M0	Left lower lobe	262	
17	T2N1M0	Left upper lobe	240	

PTV, planning target volume.

achieved within the limit of dose to the spinal cord PRV because their PTVs were near the spinal cord PRV and the off-cord fields could not encompass the entire PTVs. We were able to create acceptable VMAT plans with full arcs for these patients. In the remaining 15 patients, all of the created plans were considered acceptable. Further analyses were performed on the acceptable plans for these 15 patients.

Comparisons of the DVH-based parameters of the PA-VMAT with 3D-CRT plans for the 15 patients are shown in **Table 2**. The conformity of the dose distribution to the PTV was significantly improved in the PA-VMAT plans ($P < 0.001$). On the other hand, the homogeneity of the dose distribution to the PTV was significantly better in the 3D-CRT plans ($P = 0.041$). Compared with the 3D-CRT plans, the PA-VMAT plans significantly reduced the dose of V_{20} ($P = 0.003$) and mean dose of the lung ($P = 0.002$), V_{35} of the oesophagus ($P = 0.033$), and V_{40} of the heart ($P = 0.020$). There were no significant differences between 3D-CRT and PA-VMAT plans with regard to V_{10} ($P = 0.258$) and V_5 ($P = 0.923$) of the lung.

Ⅳ Discussion

This planning study was performed on the data of patients with inoperable NSCLC who underwent definitive radiotherapy at our institution. The majority of the patients were staged as T4 or N3, i.e. completely unresectable. This is thought to be the general case in clinical situations, so our study reflects the conditions in actual clinical practice. In this study, the 3D-CRT plans for two of 17 patients were considered unacceptable because the off-cord fields in the plans could not encompass the entire PTVs. The 3D-CRT plans were obviously inadequate for these cases, but the VMAT plans delivered sufficient dose to the PTV while maintaining the dose to the PRVs within acceptable levels.

In this study, the dose conformity was improved in the VMAT plans, although the dose heterogeneity increased. The dose distributions in IMRT/VMAT plans commonly have more hot and cold spots compared with 3D-CRT plans, which is not regarded

Table 2 Comparisons of dose distributions between VMAT and 3D-CRT plans

	Dose constraints	3D-CRT		VMAT		
		Median	Range	Median	Range	*P*-value
PTV						
D_{mean} (Gy)		63.7	62.6 - 64.6	63.7	62.5 - 64.9	0.916
HI		1.27	1.20 - 1.70	1.50	1.25 - 5.34	0.041
CI		2.04	1.54 - 2.93	1.33	1.08 - 2.05	< 0.001
Lung						
V_{20} (%)	< 35	19.0	7.8 - 29.8	14.3	5.3 - 28.9	0.003
MLD (Gy)	< 20	9.7	4.5 - 17.1	8.8	3.7 - 17.2	0.002
V_{10} (%)		22.9	12.0 - 33.8	20.1	8.7 - 36.7	0.258
V_5 (%)		31.0	15.8 - 44.2	27.9	13.6 - 48.5	0.923
Esophagus						
D_{mean} (Gy)	< 34	15.8	1.5 - 23.0	15.1	1.4 - 22.7	0.182
D_{max} (Gy)		64.6	23.6 - 66.3	62.9	13.2 - 65.3	0.241
V_{35} (%)		22.7	0.0 - 36.3	20.6	0.0 - 30.0	0.033
Heart						
V_{40} (%)	< 80	0.4	0.0 - 31.5	0.4	0.0 - 20.0	0.020

3D-CRT, three-dimensional conformal radiation therapy ; VMAT, volumetric modulated arc therapy ; PTV, planning target volume ; MLD, mean lung dose.

as a serious problem, although efforts to evaluate and optimize is needed, if precise inspections confirm that the IMRT/VMAT plans are clinically acceptable[7].

Radiation pneumonitis (RP) is a life-threatening adverse event occurring in 13%-37% of patients receiving thoracic radiotherapy for NSCLC[8]. DVH parameters, especially V_{20} and MLD, have been accepted as predictors of RP after radiotherapy for lung cancer[9)-12]. Other parameters, such as V_5 and V_{10}, were also reported to be associated with RP[13)14]. Our data showed that the VMAT plans resulted in better sparing of the lung, i.e. reducing V_{20} and MLD, compared with the 3D-CRT plans, while suppressing expansion of low-dose areas in the lung. The efficiency of VMAT in sparing of the lung was consistent with previous studies comparing VMAT plans with conventional IMRT plans[5)6]. We confirmed the superiority of VMAT to 3D-CRT, which has been utilized in actual clinical settings more frequently than conventional IMRT.

Radiation oesophagitis (RO) is a common acute and chronic toxicity, especially in the setting of concurrent chemoradiotherapy, and is known to adversely affect the quality of life (QOL) of patients[15]. Several DVH parameters, such as V_{35}, were reported to be potentially relevant for prediction of RO[16)17]. The present study indicated that VMAT plans potentially reduced the V_{35} of the oesophagus. Although there are some uncertainties in predicting RO, reduction of the dose to the oesophagus with VMAT may improve the QOL of NSCLC patients treated with radiotherapy.

In our study, the median doses of the heart were quite low in both 3D-CRT and VMAT plans. This was attributed to the inclusion of only a few patients with left lower lobe tumour in our study population. Therefore, we cannot conclude that the difference in heart dose between 3D-CRT and VMAT plans observed in the present study is clinically significant.

Although reports of the clinical usefulness of IMRT/VMAT are still sparse[18)-20], several planning studies indicated the advantages of IMRT/VMAT in the treatment of locally advanced NSCLC[2)5)6)21]. However, it is impractical to treat every patient with IMRT/VMAT as it usually requires more time for preparation than 3D-CRT. The dose verification and quality assurance required for IMRT/VMAT are burdensome for medical staff, especially in understaffed institutions. Therefore, prioritizing patients

should be considered. The results of the present study directly comparing VMAT plans with 3D-CRT plans represent meaningful information for such prioritization. Based on our findings, patients in whom off-cord fields in 3D-CRT plans cannot encompass their entire PTVs should be highly prioritized as candidates for VMAT.

This study had several limitations. First, we did not consider motion-reducing approaches, such as breath holding and respiratory gating, although the interplay effects may have only a small dosimetric impact on fractionated radiotherapy[22]. The number of the patients was small, the locations of the tumours in the lung were biased, and plans created with 10-MV photon beams and lower-energy photon beams, which may improve the dose distribution of lung cancer treatment, were not tested due to the limitations of our radiation therapy equipment.

We demonstrated the advantages of VMAT plans compared to 3D-CRT plans for locally advanced NSCLC. These findings may facilitate appropriate usage of VMAT for such cases.

V Acknowledgements

The authors are grateful to Mrs. I. Koiwai and Mrs. Y. Ogawa for technical assistance.

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(2016. 10. 31 received ; 2016. 12. 7 accepted)