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Original paper

Multi-institutional evaluation of knowledge-based planning performance of volumetric modulated arc therapy (VMAT) for head and neck cancer

Tatsuya Kamima[a], Yoshihiro Ueda[b], Jun-ichi Fukunaga[c], Yumiko Shimizu[d], Mikoto Tamura[e], Kazuki Ishikawa[f], Hajime Monzen[e,*]

[a] Radiation Oncology Department, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo 1358550, Japan
[b] Department of Radiation Oncology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 537-8567, Japan
[c] Divisin of Radiology, Department of Medical Technology, Kyushu University Hospital, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[d] Department of Radiology, Seirei Hamamatsu General Hospital, 2-12-12 Sumiyoshi, Naka Ward, Hamamatsu, Shizuoka 430-8558, Japan
[e] Department of Medical Physics, Graduate School of Medical Sciences, Kindai University, 377-2 Ohno-higashi, Osakasayama, Osaka 589-8511, Japan
[f] Department of Radiation Oncology, Faculty of Medicine, Kindai University, 377-2 Ohno-higashi, Osakasayama, Osaka 589-8511, Japan

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ABSTRACT

Purpose: The aim of this study was to investigate whether additional manual objectives are necessary for the RapidPlan (RP) with a single optimization. We conducted multi-institutional comparisons of plan quality for head and neck cancer (HNC) using the models created at each institute.

Methods: The ability of RP to produce acceptable plans for dose requirements was evaluated in two types of oropharynx cancers at five institutes in Japan. Volumetric modulated arc therapy plans created without (RP plan) and with additional manual objectives (M-RP plan) were compared in terms of planning target volume (PTV), brainstem, spinal cord and parotid glands in dosimetric parameters.

Results: There were no major dosimetric PTV differences between RP and M-RP plans. For the brainstem and spinal cord in the RP plans, only 40% and 30% of the plans achieved the dose requirements, while the M-RP plans with upper objective added to volume 0% at all institutes achieved them for 90% of the plans. For the L-parotid gland, there was no difference in the RP and M-RP plans (both were 40%) in achieving the acceptable criteria. For the R-parotid gland, 60% and 80% of the RP and M-RP plans achieved the constraint criteria, and in terms of the achievement rate, the RP plans were relatively high.

Conclusions: M-RP plans did not require reoptimization; only an upper objective was needed for the brainstem and spinal cord, while the parotid gland dose was reduced in both RP plans with the auto generated line objectives alone.

1. Introduction

Volumetric modulated arc therapy (VMAT) has been widely used in external beam radiation therapy for head and neck cancer (HNC) because of its rapid delivery of highly conformal dose distributions. In general, the treatment planning of HNC is a very complex inverse planning process with severe trade-offs between target coverage and organs at risk (OAR) sparing [1]. The increasing complexity of treatment planning has made it difficult to produce consistent treatment plans, and the treatment plans also depend on the planner or institution experience and skills [2–6]. Recently, a new commercial knowledge-based planning (KBP) optimization engine, RapidPlan (RP, Varian Medical Systems, Palo Alto CA, USA), was developed and released for clinical use. RP predicts achievable dose volume histograms (DVH) and automatically generates optimization objectives to achieve the prediction. There have been many reports of improvements in OAR sparing using KBP [7–11]. The mechanical performance and dosimetric accuracy of the KBP were also verified, showing the KBP could be safely used in clinical practice [12]. In addition, several published studies proposed KBP as a means of homogenizing treatment plan quality across institutions by transferring planning expertise from the experienced to the less experience institutions [13–16].

It has been reported that RP with a single optimization could produce clinically acceptable plans for 9 of 20 nasopharyngeal carcinoma cases. Reoptimization, denoted as “manual touch-up”, increased the number of acceptable plans to 19 [17]. In their report, they concluded that performance of a RP to achieve the dose constraints is still behind that of an experienced human planner, and manual touch-up is

* Corresponding author.
E-mail address: hmon@med.kindai.ac.jp (H. Monzen).

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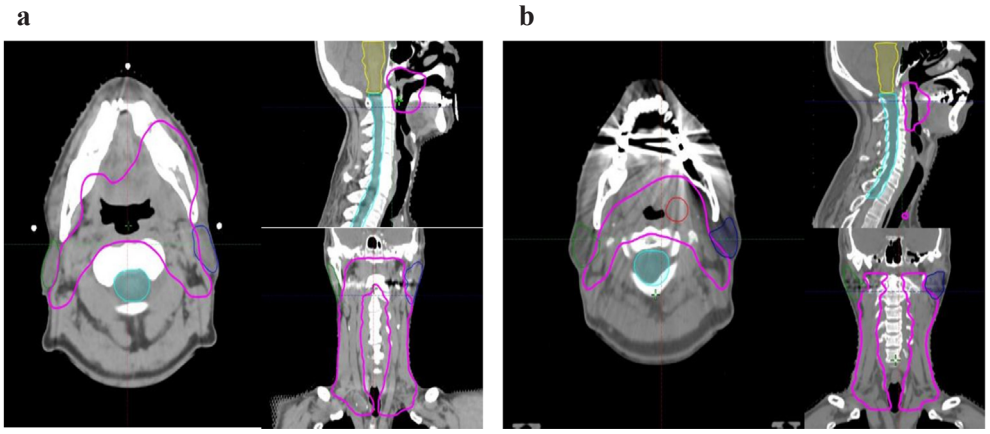

Fig. 1. Planning CT images of (a) Case 1 and (b) Case 2. Red, pink, yellow, light blue, blue, and green contours represent the GTV, PTV, brainstem, spinal cord, left parotid gland and right parotid gland, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

necessary. However, manual touch-up by the human planner may nullify RP's main advantage. Additionally, since their study was performed in a single institute and used a single model, it is unknown whether this result can be applied to other institutes. Ueda et al. reported that values calculated with KBP were influenced by plans registered in the model [18]. Thus, a multi-institutional study with multiple models would be helpful to evaluate the performance of RP.

The aim of this study was to investigate whether additional manual objectives were necessary for RP with a single optimization. We conducted a multi-institutional comparison of plan quality for HNC using the models created at each institute. We first created VMAT plans for two sets of CT data with only automatically generated line objectives by the RP (RP plan) and evaluated the performance. In the next step, the RP plan with additional objectives (M-RP plan) were created with a single optimization. Comparison between the RP plans and M-RP plans were performed in terms of dosimetric parameters for planning target volume (PTV), brainstem, spinal cord and parotid glands.

2. Material and methods

2.1. VMAT plan setting for HNC in each institute

In this multi-institutional study, five institutes (A–E) in Japan were enrolled. In each institute, VMAT plans were created using an Eclipse treatment planning system Ver 13.0 (Varian Medical Systems, Palo Alto, CA, USA) with an analytical anisotropic algorithm or Acuros XB. The dose prescription was based on the VMAT strategy of each institute. Institutes A and E used the 2-phase strategy. Institutes C and D had three PTV dose levels using a simultaneous integrated boost (SIB). Institute B introduced the original modified 2-phase VMAT (sequential SIB), wherein the first plan involves treatment of PTV_boost and PTV_elective using SIB and the second plan treatment of PTV_boost only [19].

2.2. RapidPlan model configuration

The RP algorithm was explained in detail by Fogliata et al. [20]. A sequence of three main steps is required to create the model. In the first step, model building, patients previously treated in clinical settings were registered. The second step was the extraction phase. In each structure of the registered plans, dosimetric and geometric data was extracted from the patient database into the model. The third step was the training step based on the information from the extraction phase. In this last step, a new DVH curve of each structure in the model was generated. Upper and lower limits of the estimated doses were obtained [18]. RP automates the optimization process by generating a line of optimization objectives just below the inferior boundary of the OAR DVH prediction range [21].

The number of registered cases at Institutes A, B, C, D, and E were 63, 28, 37, 178, and 33, respectively. The HNC model created at A, B, C, and D did not differentiate the location of the primary tumor. At Institute C, the ipsi- and contra-lateral parotids structures were merged into a single structure for training, but these were registered separately at other institutes.

In previous studies, the ability of model was shown by a quadratic regression curve of the overlap volume between the PTV and OAR of registered plans in the model [18]. To evaluate the performance in reducing the dose to OARs in each model, the volume of the irradiation field for the brainstem, spinal cord and overlapping volume with PTV for parotid glands were extracted from the model analytics data (https://ModelAnalytics.varian.com).

2.3. Evaluation of the RapidPlan performance

The performance of RP was evaluated using two sets of CT data and structures of oropharynx cancer patients at Institute A, which were anonymized and delivered to other institutes. Written informed consent was obtained from all patients, and the Institutional Ethics Committee approved this study (Kindai University review board number: 29–133). For each patient, a CT-scan was acquired with a 2.5 mm slice thickness and the field of view was 50 cm. The target and OARs were contoured by a physician according to the protocol of Institute A. Fig. 1 shows the PTV and OAR contours of Case 1 and Case 2 in three planes (axial, coronal and sagittal).

The details of the HNC model in each institute and the structures volume of Case 1 and Case 2 are shown in Table 1. Without additional manual objectives, VMAT plans were created with a single optimization (RP plan). The dose prescription was 50 Gy (in 25 fractions) in both Case 1 and Case 2, which was standardized at each institute. All plans were normalized such that 95% of the PTV volume received 100% of the prescribed dose ($D_{95\%}$ = 50 Gy). In OAR, only the line objective generated automatically was used for optimization and evaluation of the performance of DVH prediction. The line objective doses were automatically calculated for the brainstem, spinal cord (max dose) and parotid glands (mean dose).

2.4. Evaluation of the RapidPlan with additional manual objectives

The M-RP plans were created with additional manual objectives to clarify the weak points of the original RP plan. At the five institutes, there were planning variations including different treatment planning techniques and different planning settings for dose constraints. In this study, we referred to dose constraints of the Japan Clinical Oncology Group (JCOG) 1015 protocol [22] in order to use common acceptance criteria at each institute. Table 2 shows the dose constraints used at each institute and the dose constraints for the JCOG 1015 protocol.

Table 1
Patient data included in the RapidPlan model at each institution and the structures volume of Case 1 and Case 2.

					Parotid gland	
	Number	PTV	Spinal cord	Brainstem	Right	Left
		Volume ± SD [cm^3]				
			(Infield Vol. [%])		(Overlap vol. [%])	
Case 1		548.9	59.7 (100)	43.5 (60.5)	14.4 (1.73)	16.9 (5.16)
Case 2		433.1	56.8 (100)	45.6 (24.3)	16.5 (0.54)	14.9 (4.18)
A	63	461.0 ± 175.3	57.7 ± 13.1	41.4 ± 7.8	23.3 ± 10.6	21.4 ± 9.7
B	28	409.2 ± 112.1	21.3 ± 8.2	24.5 ± 5.2	27.3 ± 7.6	27.0 ± 6.4
C	37	343.2 ± 296.8	101.4 ± 64.8	23.9 ± 70.0	20.7 ± 8.9	
D	178	550.3 ± 206.8	99.1 ± 9.8	32.4 ± 4.8	37.7 ± 11.7	38.1 ± 12.8
E	33	774.5 ± 181.0	34.7 ± 9.8	21.8 ± 6.7	26.0 ± 8.2	27.0 ± 7.8
				D_{mean} ± SD [Gy]		
A	63	55.4 ± 12.6	16.4 ± 6.4	17.2 ± 8.5	21.6 ± 7.3	19.9 ± 6.9
B	28	48.0 ± 0.5	19.2 ± 3.3	6.0 ± 4.0	15.3 ± 5.9	17.9 ± 7.1
C	37	64.7 ± 5.2	31.5 ± 6.6	23.4 ± 9.0	31.8 ± 10.7	
D	178	55.2 ± 0.2	24.0 ± 1.9	14.1 ± 4.3	26.2 ± 8.1	27.9 ± 7.3
E	33	43.2 ± 5.3	21.9 ± 3.6	11.3 ± 5.6	21.3 ± 5.8	21.4 ± 4.5

PTV: planning target volume, D_{mean}: mean dose.

Table 3 shows the optimization objectives in the M-RP plan and the priority of line objectives in the RP plan. The same calculation algorithm and beam parameters were used in the RP and M-RP plans.

Comparisons between the RP and M-RP plans were performed on target coverage and OAR sparing to evaluate whether additional manual objectives were necessary for the RP. To evaluate target coverage, we analyzed $D_{2\%}$, $D_{98\%}$ and the homogeneity index (HI) for PTV among the two planning methods. HI was calculated as follows [23–25],

$$HI = \frac{D_{2\%} - D_{98\%}}{D_p} \quad (1)$$

Table 2
Dose constraints for treatment of head and neck cancer using volumetric-modulated arc therapy in each institution and dosimetric requirements for Japan Clinical Oncology Group 1015 protocol.

	Organs			Target	
	Brainstem	Spinal cord	Parotid glands	CTV	PTV
A	PRV $D_{max} < 64$	PRV $D_{max} < 54$	Each $D_{med.} < 24$		$D_{98} > 41.4$ $D_{50} < 49.2$ $D_{10} < 52.9$ $D_2 < 57.5$
B	Original $D_{max} < 54$ PRV $V_{60} < 0.1\,cm^3$	Original $D_{max} < 45$ PRV $V_{50} < 0.1\,cm^3$	Each $D_{mean} < 26$ Both $V_{50} < 30$		$D_{95} > 46$
C	Original $D_2 \leq 50$	Original PRV $D_2 \leq 40$	Contra lateral $D_{20} \leq 20$	Primary $72 \geq D_{50} \geq 69$ Subclinical $63 \geq D_{50} \geq 60$	Primary $71 \geq D_{50} \geq 69$ Subclinical $63 \geq D_{50} \geq 59$
D	Original $D_{max} < 54$ $D_1 < 60$ PRV $D_{max} < 54$ $D_1 < 60$	Original $D_{max} < 45$ $D_{1cm^3} < 50$ PRV $D_{max} < 45$ $D_{1cm^3} < 50$	Each $D_{mean} < 26$ $D_{50} < 30$		$D_{20} < 59.4$ $D_{90} > 51.3$ $D_{99} > 50.2$
E	PRV $D_{max} < 64$	PRV $D_{max} < 54$ $D_1 < 50$			$D_{98} > 37.3$ $D_{50} < 44.3$ $D_{10} < 47.6$ $D_2 < 49.7$
JCOG 1015	PRV $D_{max} < 38.8$	PRV $D_{max} < 35.9$ $D_1 < 33$	Each $D_{med.} < 14.4$ $D_{mean} < 18.7$		$D_{98} > 46.5$ $D_{95} = 50$ $D_{50} < 52.5$ $D_{10} < 55$ $D_2 < 60$

CTV: clinical target volume, PTV: planning target volume, PRV: planning organ-at-risk volume, D_{max}: maximum dose in Gy, D_{mean}: mean dose in Gy, $D_{med.}$: median dose in Gy, D_{99}, D_{98}, D_{95}, D_{90}, D_{50}, D_{20}, D_{10}, D_2 and D_1 the dose in Gy received by at least 99%, 98%, 95%, 90%, 50%, 20%, 10%, 2.0% and 1.0% of the volume, V_{60}, V_{50} the OAR volume that receives a dose exceeding 60 Gy, 50 Gy, D_{1cm^3}: dose in Gy to 1 cm^3 volume.

Table 3
Objectives for the M-RP plan and priority for line objective in the RP plan in each structure.

Structures	Institute	Objective	Vol. [%]	Dose [Gy]	Priority M-RP/RP	Vol. [%]	Dose [Gy]	Priority M-RP/RP
			Case 1			*Case 2*		
Brainstem	A	upper	0	31.5	200	0	31.5	200
		line			48/43			49/47
	B	upper	0	25	75	0	26.8	75
		line			43/43			47/47
	C	upper	0	31.5	200	0	31.5	200
		line			54/54			51/51
	D	upper	0	31.8	140	0	31.8	130
		line			90/90			53/53
	E	upper	0	30	110	0	30	120
		line			51/51			52/52
Spinal cord	A	upper	0	30	200	0	30	200
		upper	50	17.5	100	50	17.5	100
		upper	30	21.5	100	30	21.5	100
		line			49/66			46/62
	B	upper	0	32	75	0	29.3	75
		line			41/41			41/41
	C	upper	0	30	200	0	30	200
		upper	50	17.5	100	50	17.5	100
.		upper	30	21.5	100	30	21.5	100
		line			61/61			60/60
	D	upper	0	26.5	150	0	26.5	170
		line			130/130			100/100
	E	upper	0	30	110	0	30	120
		line			50/50			55/55
R-Parotid gland	A	upper	0	35	80	0	35	80
		mean		18	100		18	100
		line			37/37			35/41
	B	upper	67.9	5.2	50	56.7	5.2	50
		upper	51	10	50	18	14.1	50
		upper	31.2	20.4	50	5.3	21.3	50
		upper	9	31.9	50			
		line			60/39			40/40
	C	upper	0	35	80	0	35	80
		mean		12.9	100		12.9	100
		line			55/55			53/53
	D	upper	27	15.2	130	35	11.4	130
		upper	16	18.9	130	25	15.2	130
		upper	8	22.7	130	17	18.9	130
		upper	3	26.5	130	10	22.7	130
		line			70/70			70/70
	E	mean		18	70		10	70
		line			39/39			55/39
L-Parotid gland	A	upper	0	35	80	0	35	80
		mean		18	100		18	100
		line			39/39			37/42
	B	upper	53	13.4	50	71.9	5.5	50
		upper	34.4	14.6	50	32	17.7	50
		upper	23.3	30.3	50	12.2	30.8	50
		upper	7.2	38.5	50			
		line			60/41			41/41
	C	upper	0	35	80	0	35	80
		mean		12.9	100		12.9	100
		line			55/55			53/53
	D	upper	28	15.2	130	40	11.4	130
		upper	18	18.9	130	30	15.2	130
		upper	10	22.7	130	22	18.9	130
		upper	4	26.5	130	15	22.7	130
		line			70/70			70/70
	E	mean		18	70		18	70
		line			39/42			42/42

RP: RP plan, M-RP: M-RP plan.

where $D_{2\%}$ = the minimum dose to 2% of the target volume indicating the "maximum dose", $D_{98\%}$ = the minimum dose to the 98% of the target volume, indicating the "minimum dose" and D_p = the prescribed dose. The ideal value is zero and increases as the homogeneity decreases.

A comparison of OAR dose between RP plans ($D_{OAR,RP\ Plan}$) and M-RP plans ($D_{OAR,M-RP\ plan}$) inter-institutional and inter-OARs for both cases were performed to evaluate the OAR sparing. The mean (± 1 standard deviation: SD) dose difference between the RP plans and M-RP plans were calculated as follows,

$$\delta = D_{OAR,M-RP\ plan} - D_{OAR,RP\ plan}(Gy) \quad (2)$$

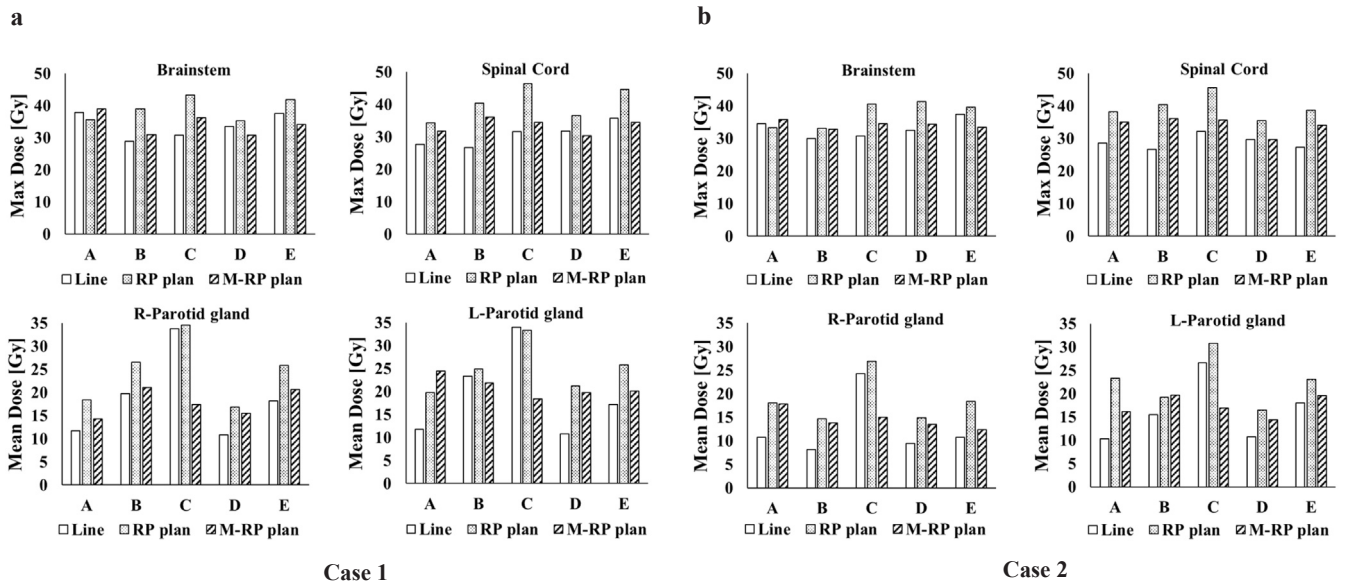

Fig. 2. Comparisons of OAR dose between line objective dose, RP plan and M-RP plan in (a) Case 1 and (b) Case 2.

3. Results

3.1. Inter-institutional comparisons for OARs (model evaluation)

For inter-institutional comparisons, the mean (± 1SD) dose differences of brainstem (max dose) between RP plans and M-RP plans for both cases were 3.1 ± 0.6 Gy, −4.1 ± 5.5 Gy, −6.5 ± 0.8 Gy, −5.7 ± 1.6 Gy, −6.9 ± 1.1 Gy for Institutes A, B, C, D, and E, respectively. The mean (± 1SD) dose differences of spinal cord (max dose) between RP plans and M-RP plans for both cases were −2.9 ± 0.4 Gy, −4.3 ± 0.0 Gy, −10.9 ± 1.3 Gy, −6.1 ± 0.2 Gy, −7.4 ± 4.1 Gy for Institutes A, B, C, D, and E, respectively. At most institutes, the OAR dose of the M-RP plans was reduced compared to the RP plans.

Fig. 2a and b show comparisons of the OAR dose between line objective dose, RP and M-RP plans for Case 1 and Case 2, respectively. There were only a slight difference in line objective dose between the RP and M-RP plans in the inter-institutional comparisons for the brainstem and spinal cord. Quadratic regression curves between the maximum dose of registered plans in the model and volume in the irradiation field for the brainstem and spinal cord are shown in Fig. 3a and b. For the brainstem and spinal cord, the regression curves were nearly horizontal except in the brainstem at Institute B, indicating there is no difference in the ability of each model.

For inter-institutional comparisons, the mean (± 1SD) dose differences of R-parotid gland (mean dose) between RP plans and M-RP plans for both cases were −2.2 ± 2.8 Gy, −3.2 ± 3.2 Gy, −14.5 ± 3.7 Gy, −1.4 ± 0.1 Gy, −5.6 ± 0.5 Gy for Institutes A, B, C, D, and E, respectively. The mean (± 1SD) dose differences of L-parotid gland (mean dose) between RP plans and M-RP plans for both cases were −1.3 ± 8.4 Gy, −1.3 ± 2.5 Gy, −14.4 ± 0.8 Gy, −1.8 ± 0.4 Gy, −4.6 ± 1.6 Gy for Institutes A, B, C, D, and E, respectively. At all institutes, the OAR dose of the M-RP plans was reduced compared to the RP plans.

As shown Fig. 2a and b, there was a large difference in line objective dose and the RP plan in the inter-institutional comparisons for R-L-parotid glands. At Institute C, the dose sparing of the parotid glands in line objective dose and RP plan were worse than the other institutes. Alternatively, at Institute D, dose sparing of the R-L-parotid glands in both cases were better than the other institutes. Quadratic regression curves between the mean dose for parotid glands of registered plans in the model and overlapping volume with PTV for the parotid glands are shown in Fig. 3c and d. The slope of the curves varied according to the institutes. Institute C had a regression curve with a mean dose that tended to be greater than the other institutes, while Institute D had a gentle regression curve with mean dose that tended be less than the other institutes. The Institute A model had little overlap volume between the PTV and parotid glands. Therefore, Institute A had an insufficient regression curve.

3.2. OAR dose comparison (Line objective dose vs. RP plan vs. M-RP plan)

The DVH predictions for each model were evaluated using line objective dose and the overall RP performance evaluated using RP plans. As shown in Fig. 2a and b, the percentage of RP plans in which the OAR dose could not be reduced below the line objectives dose were 80%, 100% and 95% for the brainstem, spinal cord and parotid glands, respectively. Alternatively, the percentage of M-RP plans in which the OAR dose could not be reduced below the line objective dose was 70%, 70% and 75% for the brainstem, spinal cord and parotid glands, respectively. In the inter-OARs comparisons, the mean (± 1SD) dose differences between RP plans and M-RP plans in all institutes for both cases were −4.0 ± 4.3 Gy, −6.3 ± 3.2 Gy, −5.4 ± 5.4 Gy, −4.7 ± 6.1 Gy for the brainstem, spinal cord (max dose), R and L parotid gland (mean dose), respectively. In the M-RP Plan, all OAR dose could be reduced. Therefore, the M-RP plans with additional manual objectives had better OAR sparing than the RP plans.

Table 4 shows the proportions of plans achieving the acceptable criteria of the JCOG 1015 protocol in Case 1 and Case 2. For the brainstem and spinal cord, most of the RP plans could not achieve the primary objective, while the M-RP plans achieved them for 90% of the plans. As shown in Table 3, in the M-RP plans, an upper objective was added to volume 0% at all institutes. Alternatively, for the L-parotid gland, the number of M-RP plans achieving the acceptable criteria remained the same as that for the RP plans. For the R-parotid gland, M-RP plans performed slightly better than the RP plans (60%–80%). However, even in the RP plan, the number of plans achieving the acceptable criteria were more than half. Fig. 4 shows the relationship between the line objectives dose and mean dose of the parotid glands in the RP and M-RP plans. Coefficients of determination (R^2) between the line objectives dose and mean dose of the parotid glands for RP and M-RP plans were 0.871 and 0.072, respectively. There was strong correlation for the RP plan. In the RP plan, the lower the generated optimization objectives, the lower the mean dose of the parotid glands.

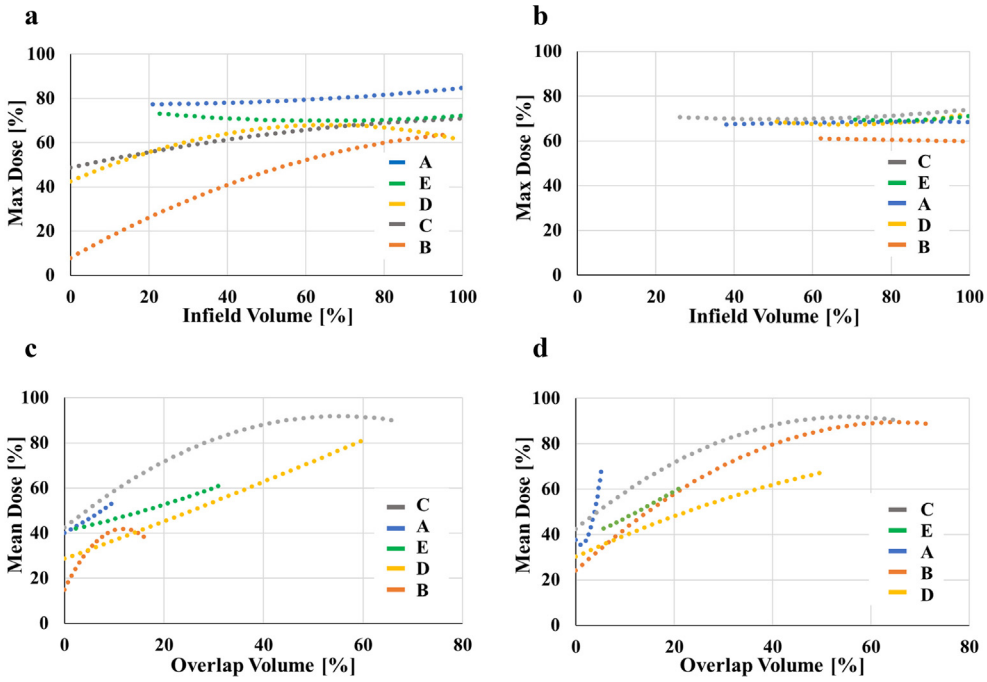

Fig. 3. Quadratic regressions curves between the maximum dose of registered plans in the model and volume in the irradiation field for the (a) brainstem and (b) spinal cord. Quadratic regression curves between mean dose for parotid glands of registered plans in the model and overlapping volume with PTV for (c) the R-parotid gland and (d) L-parotid gland. The colors of the dotted lines represent institutes (Blue: A, Orange: B, Gray: C, Yellow: D, and Green: E). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Proportions of plans achieving the acceptable criteria for organs at risk in Case 1 and Case 2.

Structures	Primary objective	RP plan	M-RP plan
Brainstem (PRV)	D_{max} < 38.8 Gy	40%	90%
Spinal cord (PRV)	D_{max} < 35.9 Gy	30%	90%
R-Parotid gland	D_{mean} < 18.7 Gy	60%	80%
L-Parotid gland	D_{mean} < 18.7 Gy	40%	40%

PRV: planning organ-at-risk volume, D_{max}: maximum dose, D_{mean}: mean dose.

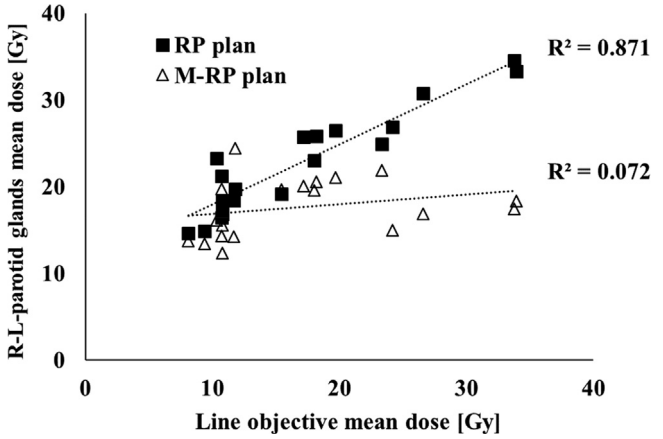

Fig. 4. Relationship between the line objective dose and mean dose of the R-L-parotid glands in the RP plan and M-RP plan in case 1 and case 2 at all institutes.

3.3. Target dose comparison (RP plan vs. M-RP plan)

Table 5 summarizes the dosimetric results for PTV at each institute for the RP and M-RP plans. Inter-institutional comparisons of PTV homogeneity in both cases showed there were no differences between the institutes, except Case 1 at Institute B. In the comparison between RP and M-RP plans at each institute, there were no influence on PTV dose by additional manual objectives. Additionally, all RP and M-RP plans achieved the PTV dose requirement of the JCOG 1015 protocol.

4. Discussion

This study evaluated whether additional manual objectives were necessary for the RP using the quality of treatment planning created for two cases by various models of five institutes. By analyzing five institutional KBP models, we determined that the dose sparing of M-RP plans were better than the RP plan at most institutes for the brainstem and spinal cord. Especially, additional manual objectives were required to decrease the maximum dose for OARs. Additionally, the mean dose difference between RP plan and M-RP plan in spinal cord and brainstem (max dose) was −4.0 Gy and −6.3 Gy, respectively. In HNC, the most common form of treatment failure after radiotherapy is locoregional recurrence, and around 20–50% of patients develop locoregional recurrence. Reirradiation for the treatment of recurrent HNC is feasible and effective, with acceptable toxicity [26]. However, it is very important for safe delivery of reirradiation to reduce the OARs dose as much as possible in the first radiotherapy. Therefore, the dose sparing of M-RP plan is a clinical advantage.

Although previous literature shows RP improves plan quality [7,20,21,27], the present study is the first to evaluate whether additional manual objectives are necessary for the RP in a multi-institutional validation. In this study, five clinically-approved models for HNC were collected from multiple institutes, indicating there were varying patient characteristics and different planning variations, including different treatment planning techniques, different planning settings for dose-volume constraints, and different dose prescription strategy. A multi-institutional validation was previously conducted to evaluate the RP performance and model sharing among different institutes [18,28,29]. Thus, our results would be helpful for evaluating the potential performance of a RP and for setting optimization objectives accompanying the RP.

The achievement rates of dose constraints for the JCOG 1015 protocol were also improved significantly with the M-RP plans. The RP plans using only a line objective achieved the constraints for 30% to 40% of each organ. It has been found that most of the RP-based plans (≥70%) without manual touch-up could not achieve the primary objectives of the brainstem, spinal cord, and optic chiasm, whereas manual reoptimized plans could achieve them for at least half of nasopharyngeal cancer patients (50% to 80%) [17]. As shown in Table 3 and Fig. 2, even at Institute D that set a high priority to spinal cord, the

Table 5
Detailed results for the PTV.

Institute	Case 1						Case 2					
	RP plan			M-RP plan			RP plan			M-RP plan		
	D_{98}	D_2	HI	D_{98}	D_2	HI	D_{98}	D_2	HI	D_{98}	D_2	HI
A	48.9	54.6	0.11	49.4	56.5	0.14	49.5	55.9	0.13	49.1	54.0	0.10
B	47.6	57.1	0.19	47.5	57.3	0.20	49.3	54.4	0.10	49.3	54.6	0.11
C	49.2	52.6	0.07	48.8	54.5	0.12	49.5	52.3	0.06	49.2	53.6	0.09
D	48.4	55.3	0.14	48.3	55.4	0.14	48.8	55	0.13	48.7	55.2	0.13
E	48.3	54.9	0.13	48.2	54.8	0.13	49.1	53.9	0.10	49	54.1	0.10

D_{98}, D_2 the dose in Gy received by at least 98%, 2.0% of the volume, HI: homogeneity index.

dose of the RP plan was greater than the line objective dose, indicating that the dose of the brainstem and spinal cord could not be reduced by constraints of the line objective alone.

The maximum dose is generally the most appropriate parameter for dosimetric evaluation of serial organs such as the brainstem and spinal cord. [30,31]. Serial organs can tolerate low doses to the whole organ, but cannot tolerate high doses to a small volume [32]. Therefore, since the plans registered in the model were evaluated only with the maximum dose, as shown by the regression curve in the Fig. 3a and b, there was no difference in the ability of each model. Alternatively, as shown in Table 1, there are large variations in the registered structure volumes of brainstem and spinal cord, and registered numbers of cases were small in Institute C. As shown in Fig. 2, this model didn't have the negative effect for plan quality of Case 1 and Case 2 in this study. However, it has also been reported that when the number of model registration cases is small, the DVH prediction performance is deteriorated and affected by the selected cases [33]. Thus, the model configuration might be taken care in the case of the large structure volume variations and small registered cases since the RP predicts achievable DVHs based on correlation between dosimetric and geometric data of registered plans in the model. Some previous studies have shown high planning quality and higher efficiency using RP [4,14,17,34,35]. Other study described that the choice of the type and value of the optimization objectives is of great importance [1]. However, there has been no report on the specific setting of optimization objectives accompanying the RP. In this study, in M-RP plans, an upper objective was added to volume 0% for the brainstem and spinal cord at all institutes. This result suggests that for serial organs, additional manual objectives is necessary, and only the upper objective is needed.

As shown in Table 5, with or without additional manual objectives did not influence the PTV dose, and all RP and M-RP plans achieved the PTV dose requirement of the JCOG1015 protocol. In the inter-institutional comparisons of PTV homogeneity, the homogeneity of Case 1 in Institute B was slightly worse than that of other institutes, but there were no major differences. Thus, in this study, the OAR dose of RP and M-RP plans was comparable while maintaining the PTV dose.

As shown in Table 4, the number of M-RP plans achieving the acceptable criteria for the L-parotid gland remained the same as that for the RP plans. The gross tumor volume location was on the left side in both cases as shown in Fig. 1. Thus, in order to obtain a sufficient target dose, the dose of the L-parotid gland could not be reduced even in the M-RP plans. Alternatively, in terms of the achievement rate, the R-parotid gland was relatively high with constraints of line objectives alone. In pelvic region, it has been reported that the RP model is able to generate high-quality plans, at least comparable to previously optimized clinical plans, without any interaction with the planner [11]. There are also similar reports in the parotid glands for head and neck region [17]. Therefore, it is possible to create a plan that achieves the dose constraints using only automatically generated optimization objectives.

Quadratic regression curves between the mean dose for parotid glands of registered plans in the model and overlapping volume with PTV for parotid glands (Fig. 3c and d) had various slopes according to the institute, indicating there is difference in the ability of each model. It has been reported that the calculated OAR dose with RP depended on the registered plans in the model and strongly correlated with OARs volumes in the PTV [18]. Quadratic regression curves showing the mean dose of parotid glands in Institute C was the highest of all overlapping volume with PTV for parotid glands. Institute D had a regression curve in which the mean dose tended to be less than the other institutes. These trends are similar to the line objective dose and RP plan as shown in Fig. 2. In addition, as shown in Fig. 4, there is a strong linear correlation between the line objective dose and mean dose of the parotid glands in the RP plans. Tol et al. [21] found that there was strong linear correlation between the estimated and achieved mean doses for parotid glands in the RP. Compared with their results, our multi-institutional study showed similar good linear correlation. Therefore, in order to get good dose sparing of the parotid glands using the RP plan, it is necessary to improve the plan quality registered in the model. This shows the feasibility of achieving the acceptable criteria for parotid glands using the line objective constraint alone.

The planning quality evaluation was conducted only for oropharynx cancer patients and there is a limitation that this study cannot cover treatment plans by RP in other anatomical sites. Moreover, there were only two cases for evaluation. Therefore, it is necessary to investigate more cases for various sites.

5. Conclusions

This inter-institutional comparison found that M-RP plans with additional manual objectives performed better OAR sparing than RP plans for the brainstem and spinal cord without any touch-up. Additionally, to reduce the dose for parotid glands, additional manual objectives were not required except for the brainstem and spinal cord, and only an upper objective is needed for such serial organs to decrease the maximum dose up to dose constrains.

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