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Original Article

The dosimetric comparison of the radiotherapeutic plans between composite and synchronous planning approaches in sequential IMRT for nasopharyngeal carcinoma

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Abstract: The aim of present study was to compare the dosimetric differences of the radiotherapeutic plans between synchronous and composite planning approaches in sequential intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma (NPC). Twelve patients with NPC treated by sequential IMRT were enrolled. Two planning approaches were used to design sequential IMRT plan. The first was composite planning approach, in which the initial and boost plans were designed and optimized independently. The second was synchronous planning approach, in which the boost IMRT plan was designed on foundation of the initial IMRT plan, and its optimization would be adjusted based on dose distributions of the initial IMRT plan. Dosimetric comparisons in IMRT plans between composite and synchronous planning approaches were analyzed to evaluate (1) dose coverage, conformity, and homogeneity of the planning target volume (PTV), (2) sparing of organs at risk (OARs), and (3) the number of segments and monitor units (MUs). The results showed that both of the summed plans for the entire treatment course were achieved according to the original planning goals, and the dose coverage, conformity and homogeneity for each PTV was similar. With regard to sparing brain stem, spinal cord and parotid glands, there was no significant difference in the summed plans between two planning approaches. However, the boost IMRT plan by composite planning approach tended to have a higher dose coverage (P = 0.000), conformity (P = 0.000), and homogeneity (P = 0.000) than that of the plan by synchronous planning approach. Moreover, the boost plan by composite planning approach reduced the MUs significantly (P = 0.000). The results indicated that the radiotherapeutic plan by composite planning approach provides better dose coverage, conformity and homogeneity for the PTV in the boost plan than that by synchronous planning approach, and reduced MUs in sequential intensity modulated radiotherapy.

Keywords: Dosimetric comparison, intensity modulated radiotherapy, sequential boost, nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma is sensitive to radiation therapy, which has been the main treatment method for patients with NPC. Growing reports have shown that the dosimetric superiority of IMRT applied in nasopharyngeal carcinoma can not only improve local control and even patient survival, but also effectively reduce the treatment side effects [1-4].

With the introduction of simultaneous integrated boost intensity-modulated radiation therapy (SIB-IMRT), several studies suggested that IMRT has the ability to provide much superior dose distributions when it is designed with the SIB-IMRT technique. However, the normal tissues within, or adjacent to, the boost regions may receive higher doses per fraction compared to the doses given by sequential-IMRT technique. Therefore, sequential-IMRT may be more appropriate than SIB-IMRT when the doses given to the adjacent critical structures or other normal tissues are the major concern [5-7].

For sequential radiotherapeutic plan, the normal tissue constrains typically apply to the

Table 1. Patient characteristics

Characteristics	No. of patients
Patients	12
Age (years)	Median 60 (range, 38-74)
Gender	
Male	10
Female	2
Pathologic diagnosis	
Poorly differentiated squamous carcinoma	12
Tumor classification*	
T_1	3
T_2	2
T_3	3
T_4	4
Node classification*	
N_1	2
N_2	6
N_3	4

*According to UICC/AJCC 2010 stage system.

Table 2. Planning objectives for organs at risk

Organs at risk	Dose constrain
Brain stem	Max dose < 54 Gy
Spinal cord	Max dose < 45 Gy
Parotid glands	V_{30} < 50% (at least on side)
Eyes	Max dose < 50 Gy
Optic nerves	Max dose < 54 Gy
Lenses	Max dose < 9 Gy
Cochleas	Mean dose < 45 Gy or V_{55} < 5%
Larynx	Mean dose < 45 Gy

Abbreviations: Max = maximum.

entire treatment course rather than the individual phase. Usually there were two approaches to be introduced to design sequential-IMRT plan in clinic. The first was composite planning approach, in which the initial and boost IMRT plans were designed and optimized independently. Then the two phase's plans were summed directly. The second was synchronous planning approach, in which the boost IMRT plan was designed on foundation of the initial IMRT plan. The optimization of the boost plan would be adjusted based on dose distributions of the initial IMRT plan. Different dose distribution would be produced in the boost plan between these two different design approaches. The purpose of present study was to compare the dosimetric difference and elucidate the dosimetric quality of the radiotherapeutic plans between synchronous and composite planning approach in sequential IMRT for nasopharyngeal carcinoma.

Methods

Patients

Twelve newly diagnosed patients with nasopharyngeal carcinoma treated with curative radiotherapy between February 2011 and July 2011 were consecutively recruited into the study. Patient characteristics were demonstrated on (**Table 1**).

Computed tomography scanning and target volume delineation

All patients were positioned, and immobilized from the head to the shoulder by a thermoplastic mask. Computed tomography (CT) with a 3-mm slice thickness of the head and neck region was obtained, and imported to the treatment planning system. The physician contoured the target volume and OARs for all patients. The target volume included the gross tumor volume (GTV), clinical target volume (CTV), and PTV. The GTV covered the visible primary tumor and neck metastasis lymph nodes shown on the CT/MRI image. The CTV1 encompassed high-risk structures surrounding primary tumor and high-risk neck region, and the CTV2 encompassed low-risk neck region. The PTVg, PTV1, and PTV2 consisted of a 3-mm margin in all directions around GTV, CTV1 and CTV2 respectively. The OARs included brain stem, spinal cord, parotid glands, lenses, eyes, optic nerves, chiasm, cochlea, mandible, oral cavity and larynx.

The prescribed dose and treatment planning

The Philips Pinnacle Planning System 9.0 was used for IMRT planning. The treatment plan with a standard coplanar 9-field gantry arrangement was designed in all patients and delivered on Siemens Primus Linac equipped with a 58-leaf MLC. Direct machine parameter optimization (DMPO) module was adopted for the

Table 3. The differences of dose coverage, conformity and homogeneity in the summed IMRT plans between synchronous and composite planning approaches in the entire treatment course

	Composite planning	Synchronous planning	t-value	*p*-value
PTVg				
$V_{100\%}$	95.65 ± 0.55	95.12 ± 0.30	2.912	0.008
D_{Mean} (Gy)	71.83 ± 0.31	71.59 ± 0.28	2.355	0.028
$D_{98\%}$ (Gy)	69.47 ± 0.13	69.41 ± 0.11	1.038	0.310
$D_{2\%}$ (Gy)	73.94 ± 0.66	73.41 ± 0.64	2.008	0.057
CI	0.80 ± 0.04	0.82 ± 0.03	-1.832	0.081
HI	0.06 ± 0.01	0.06 ± 0.01	1.635	0.116
PTV1				
$V_{100\%}$	95.54 ± 0.37	95.38 ± 0.44	1.663	0.125
CI	0.78 ± 0.03	0.79 ± 0.02	3.432	0.006
PTV'				
D_{Mean} (Gy)	62.17 ± 0.37	61.74 ± 0.27	10.408	0.000
$D_{98\%}$ (Gy)	57.97 ± 0.71	58.06 ± 0.79	2.032	0.067
$D_{2\%}$ (Gy)	65.97 ± 0.82	65.11 ± 0.57	10.152	0.000
HI	0.13 ± 0.02	0.11 ± 0.02	7.961	0.000
PTV2				
D_{Mean} (Gy)	55.52 ± 5.07	55.37 ± 5.10	0.069	0.945
$D_{98\%}$ (Gy)	51.26 ± 0.65	51.16 ± 0.67	0.383	0.705
$D_{2\%}$ (Gy)	59.11 ± 1.15	58.11 ± 1.56	1.784	0.088
HI	0.14 ± 0.03	0.13 ± 0.03	1.216	0.237

Abbreviations: $D_{2\%}$ = dose to 2% of the volume; $D_{98\%}$ = dose to 98% of the volume; D_{Mean} = mean dose; $V_{100\%}$ = volume receiving 100% prescription dose; HI = homogeneity index; CI = conformity index.

planning. The maximum number of segments was set to 80, minimum segment area was 5 cm^2, and minimum monitor unit (MU) was 5 MUs. A collapsed-cone convolution algorithm was used to calculate dosage, with a dose grid resolution of 3 mm. The prescribed dose included three levels: 70 Gy to the PTVg in 33 fractions, 60 Gy to the PTV1 in 33 fractions, and 50.9 Gy to the PTV2 in 28 fractions. So the IMRT plan was separated into two phases. In the initial plan, the PTVg, PTV1 and PTV2 were planned for 59.4, 50.9 and 50.9 Gy in 28 fractions. Then the PTVg and PTV1 were planned to boost 10.6 and 9.1 Gy in 5 fractions in the boost plan. The boost IMRT plans were designed by two different approaches as follows: In composite planning approach, the initial and boost IMRT plans were designed and optimized independently. In order to effectively restrict the doses to the OARs, the PTVg, PTV1 and PTV2 were planned for 70, 60 and 60 Gy in 33 fractions in the initial plan. After completing the optimization, the dose of PTVg, PTV1 and PTV2 were cut to 59.4, 50.9 and 50.9 Gy in 28 fractions. For the boost plan, the PTVg and PTV1 were planned for 70 and 60 Gy in 33 fractions. After completing optimization of the boost plan, the dose of PTVg and PTV1 were cut to 10.6 and 9.1 Gy in 5 fractions. In the end, two phase's plans were summed directly.

In synchronous planning approach, the initial IMRT plan was designed like in the composite planning approach. The boost IMRT plan was designed on foundation of the initial IMRT plan with the normal tissue constrains was considered for the entire treatment regimen. The optimization of the boost plan would be adjusted based on dose distributions of the initial IMRT plan.

The treatment goals for summed plan in the entire treatment course were that prescribed dose would cover 95% of the PTV volume, and the maximum dose would not exceed 110%. Regarding the OAR, the maximum doses to the brain stem and spinal cord were set as 54 Gy and 45 Gy, respectively. In addition, the dose to other normal tissues was minimized within a reasonable range without affecting the target coverage (**Table 2**).

Plan evaluation and statistical analysis

The evaluation of treatment plans was performed by means of standard dose-volume histograms (DVHs). Data were analyzed for PTVg, PTV1, PTV2 and PTV' (volume of PTV1 without including PTVg). The main comparing parameters were: minimum and maximum doses as defined by the values of $D_{98\%}$ and $D_{2\%}$ (dose received by the 98, and 2% of the volume), mean dose, and $V_{100\%}$ (volume of PTV receiving 100% prescribed dose). The conformity index (CI) for PTV was calculated as per the formula: $CI = TV_{PV}^2/(V_{PTV} \times V_{TV})$. V_{PTV} is the volume of PTV. V_{TV} is the treatment volume of the prescription isodose lines, and TV_{PV} is the volume of V_{PTV} within the V_{TV}. The higher CI is, the more conformal the plan is. The homogeneity index (HI) for the plans was defined as follows: $HI = (D_{2\%}-D_{98\%})/D_{50\%}$. $D_{2\%}-D_{98\%}$ is the dose of difference between the dose covering 2% and 98% of the

Table 4. The differences of dose coverage, conformity and homogeneity in the boost IMRT plans between synchronous and composite planning approaches in the second phase

	Composite planning	Synchronous planning	t-value	*p*-value
PTVg				
$V_{100\%}$	95.34 ± 1.15	51.26 ± 11.96	12.708	0.000
D_{Mean} (Gy)	10.89 ± 0.08	10.61 ± 0.15	5.837	0.000
$D_{98\%}$ (Gy)	10.51 ± 0.04	9.41 ± 0.14	13.724	0.000
$D_{2\%}$ (Gy)	11.21 ± 0.14	11.77 ± 0.19	-7.969	0.000
CI	0.78 ± 0.07	0.28 ± 0.12	12.778	0.000
HI	0.07 ± 0.02	0.22 ± 0.04	-13.296	0.000
PTV1				
$V_{100\%}$	94.90 ± 0.20	66.70 ± 8.27	11.737	0.000
CI	0.78 ± 0.03	0.44 ± 0.09	13.065	0.000
PTV'				
D_{Mean} (Gy)	9.43 ± 0.05	9.00 ± 0.13	9.123	0.000
$D_{98\%}$ (Gy)	8.77 ± 0.11	7.27 ± 0.39	12.620	0.000
$D_{2\%}$ (Gy)	10.02 ± 0.11	10.71 ± 0.19	21.064	0.000
HI	0.13 ± 0.02	0.38 ± 0.07	14.180	0.000

Abbreviations: $D_{2\%}$ = dose to 2% of the volume; $D_{98\%}$ = dose to 98% of the volume; D_{Mean} = the mean dose; $V_{100\%}$ = volume receiving 100% prescription dose; HI = homogeneity index; CI = conformity index.

PTV. $D_{50\%}$ is the dose covering 50% of the PTV. A higher HI indicates poorer homogeneity.

As regard the spinal cord and brain stem, given its serial structure, D_{Max} (maximum point dose) and $D_{Max\_1\%}$ (maximum dose encompassing 1% of the volume) were studied. For parotids, V_{30} Gy (volume of the parotids receiving 30 Gy) was reported. In addition, the number of segments and MUs also were investigated.

The SPSS version 18.0 software (SPSS Inc., Chicago, USA) was applied for statistical analysis. The paired sample t-test was used to analyze the differences between the synchronous and composite planning approaches. The two-sided $P < 0.05$ was considered to be statistical significance for all tests.

Results

The differences of dose coverage, conformity and homogeneity for PTV in the IMRT plans between synchronous and composite planning approaches

Both of the summed IMRT plans were achieved according to the original planning goals. For the PTVg, the summed IMRT plan by composite planning approach tended to have slightly higher dose coverage and mean dose than that of the plan by synchronous planning approach ($P = 0.008$, and $P = 0.028$). There were no significant differences in conformity, homogeneity, maximum and minimum doses of the PTVg in the summed plans between composite and synchronous approaches. The conformity of PTV1 in the summed IMRT plan by composite approach was lower than that of the plan by synchronous approach ($P = 0.006$), while no significant difference existed in $V_{100\%}$ for PTV1. The summed IMRT plan by composite planning approach tended to have a lower maximum ($P = 0.000$) and mean doses ($P = 0.000$), and a higher homogeneity ($P = 0.000$) in PTV' compared to the plan by synchronous planning approach, while no significant difference existed in minimum doses for PTV'. For PTV2, there were no significant differences in homogeneity, maximum, minimum and mean doses between the two different planning approaches (**Table 3**). For the PTVg, the boost IMRT plan by composite approach tended to have a higher dose coverage ($P = 0.000$), conformity ($P = 0.000$), homogeneity ($P = 0.000$), mean doses ($P = 0.000$) and minimum doses ($P = 0.000$), and a lower maximum doses ($P = 0.000$) than that of the plan by synchronous planning approach. The dose coverage and conformity of PTV1 in the boost IMRT plan by composite approach was higher than that of the plan by synchronous approach ($P = 0.000$, and $P = 0.000$). The boost IMRT plan by composite planning approach tended to have a high homogeneity ($P = 0.000$), minimum ($P = 0.000$) and mean doses ($P = 0.000$), and a lower maximum doses ($P = 0.000$) in PTV' compared to the plan by synchronous approach (**Table 4**).

The isodose curve distributions for a representative patient were shown in (**Figure 1**) and the DVHs were shown in (**Figure 2**). The isodose curve distributions of the boost IMRT plans between composite and synchronous planning approaches existed significant differences (**Figure 1C**, **1D**). Many high dose and low dose region existed in the result by synchronous approach, and the isodose curve appeared confused. With compared approach, the distribution of the isodose curve was much more

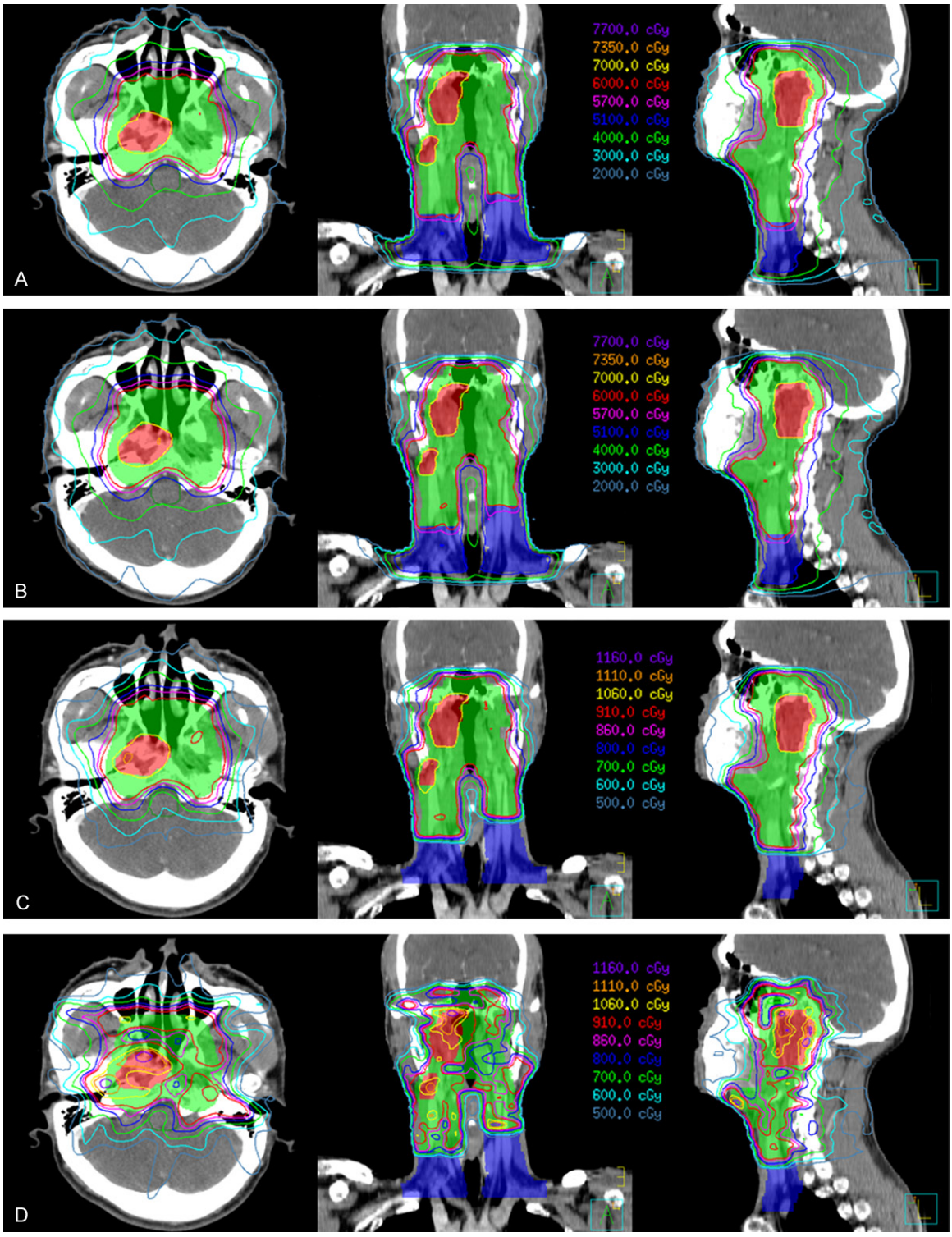

Figure 1. Isodose curve distributions for a representative patient with nasopharyngeal carcinoma. A. The summed plan in the entire course designed by composite planning approach. B. The summed plan in the entire course designed by synchronous planning approach. C. The boost plan in the second phase designed by composite planning approach. D. The boost plan in the second phase designed by synchronous planning approach. Color-wash areas: PTVg: red; PTV1: green; PTV2: blue.

uniform. In the DVH (**Figure 2B**), the dashed lines indicate the dose of PTVg, PTV1 and PTV' in the synchronous plan were much more oblique than those of the solid lines which indi-

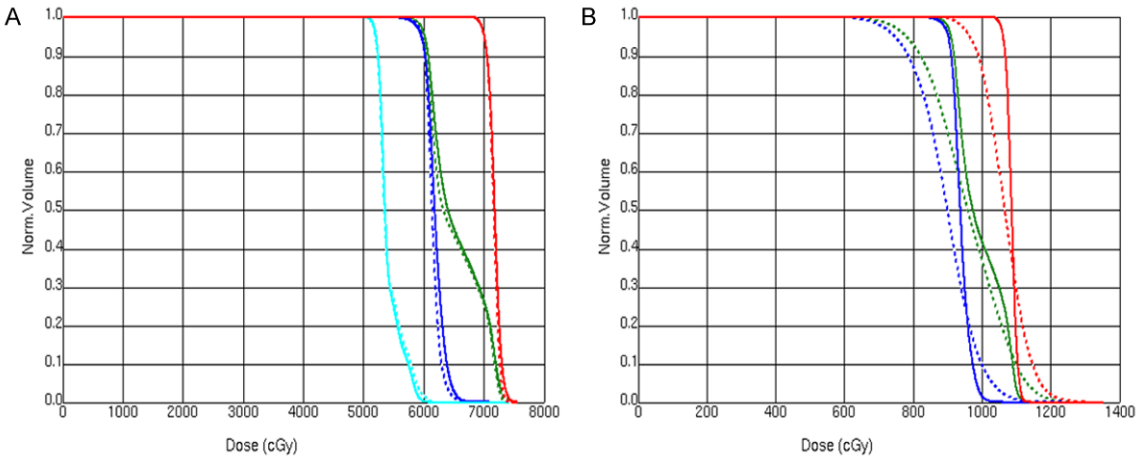

Figure 2. The cumulative dose volume histograms for a representative patient with nasopharyngeal carcinoma. A. The summed plans in the entire course. B. The boost plans in the second phase. The solid lines are to the composite plan and the dashed lines to the synchronous plan. The red lines indicate the dose of PTVg, the green lines indicate the dose of PTV1, the blue lines indicate the dose of PTV', and the sky-blue lines indicate the dose of PTV2.

Table 5. The differences of OARs receiving dose in the summed IMRT plans between synchronous and composite planning approaches in the entire treatment course

	Composite planning	Synchronous planning	t-value	*p*-alue
Brain stem				
D_{Max} (Gy)	53.9 ± 1.1	53.7 ± 0.7	1.691	0.105
$D_{Max\ 1\%}$ (Gy)	50.4 ± 1.1	49.8 ± 1.1	1.400	0.175
Spinal cord				
D_{Max} (Gy)	42.7 ± 1.4	42.2 ± 1.5	0.896	0.380
$D_{Max\ 1\%}$ (Gy)	40.1 ± 1.2	39.5 ± 1.3	1.081	0.291
Parotid-L				
V_{30Gy} (%)	49.8 ± 2.4	49.8 ± 2.0	-0.001	0.999
Parotid-R				
V_{30Gy} (%)	49.2 ± 2.9	49.1 ± 3.1	0.130	0.898

Abbreviations: D_{Max} = maximum point dose; $D_{Max\ 1\%}$ = maximum dose covering 1% of the OAR volume; V_{30} = volume of the parotids receiving 30 Gy.

Table 6. The differences of segments and MUs in the boost IMRT plans between synchronous and composite planning approaches in the second phase

	Composite planning	Synchronous planning	t-value	*p*-value
Segments	79.8 ± 4.6	79.2 ± 4.3	0.371	0.716
MUs	852.5 ± 85.0	1264.1 ± 146.1	-11.400	0.000

cate the dose in the composite plan. The dose coverage of the former target area was significantly lower than the latter.

The differences of OARs receiving dose in the summed IMRT plans between synchronous and composite planning approaches

The OARs receiving dose in the summed IMRT plans of synchronous and composite planning approaches in the entire treatment course was listed in (**Table 5**). With regard to sparing brain stem, spinal cord and parotid glands, there was no significant difference in the summed IMRT plans between these two different planning approaches.

The differences of segments and MUs in the boost IMRT plans between synchronous and composite planning approaches

The segments and MUs in the boost IMRT plans between synchronous and composite planning approaches in the second phase were listed in (**Table 6**). Compared to the boost IMRT plan by synchronous planning approach, the boost plan by composite planning approach reduced the MUs significantly (P = 0.000). No significant difference existed in segments between two different planning approaches.

Discussion

Sequential IMRT scheme has been clinically applied in radiotherapy for nasopharyngeal carcinoma in many institutes [8, 9]. For some patients in our institute, the sequential two-phase IMRT plan was also used to treat naso-

pharyngeal carcinoma. In the initial plan, the PTVg, PTV1 and PTV2 were planned for 59.4, 50.9 and 50.9 Gy in 28 fractions. Then the PTVg and PTV1 were planned for 10.6 and 9.1 Gy in 5 fractions further in the boost plan. However, the design for the planning of sequential IMRT is relatively difficult to implement because the normal tissue constrains typically apply to the entire treatment course rather than the individual phase. The challenge in planning design and optimization is determining the appropriate distribution of the normal tissue tolerance dose between the treatment phases [10]. The composite and synchronous planning approaches are available for the development of sequential IMRT plans.

The present study has shown that the DVHs of the summed IMRT plans between composite and synchronous planning approaches were similar. Both of the two summed IMRT plans were achieved according to the original planning goals (**Figure 2A**; **Tables 3**, **5**). However, the DVHs of the boost IMRT plans between composite and synchronous planning approaches in the second phase existed significant differences (**Figure 2B**; **Table 4**). The $V_{100\%}$ of PTVg and PTV1 in the boost plans by synchronous planning approach is much lower than that of composite approach (51.26 ± 11.96 vs. 95.34 ± 1.15; 66.70 ± 8.27 vs. 94.90 ± 0.20). The CI of PTVg and PTV1 in the boost plans by synchronous planning approach is also much lower than that of composite approach (0.28 ± 0.12 vs. 0.78 ± 0.07; 0.44 ± 0.09 vs. 0.78 ± 0.03). The HI of PTVg and PTV' in the boost plans by synchronous planning approach is higher than that of composite approach (0.22 ± 0.04 vs. 0.07 ± 0.02; 0.38 ± 0.07 vs. 0.13 ± 0.02). At the same time, the boost plan by synchronous planning approach increases the MUs significantly compared to the plan by composite approach (1264.1 ± 146.1 vs. 852.5 ± 85.0). The results suggest that the boost IMRI plan by synchronous planning approach is inferior to the plan by composite approach. Because the optimization of the boost plans is the only considering the summed plan rather than the boost plan [10]. The optimizer has taken the dose already planned in the initial course into account. If there were hotspots in the initial plan, the optimizer will not need to put as much dose in that region for the boost. This can produce coldspots in the boost. When including the initial plan as the base dose in the optimization of the boost plan in the synchronous planning approach, the dose heterogeneities in the initial plan may result in much inhomogeneous dose distribution in the boost plan. This may be clinically significant. Furthermore, the poor dose distribution of the boost plan by synchronous planning approach may lead to an unfavorable impact on the biological effects [11-14]. At the same time, to achieve the adjustment for the heterogeneous dose distribution extremely in the boost plan by synchronous planning approach, more MUs is needed in the same constrains for beam numbers in the second course.

However, with the composite planning approach, the initial and boost plans were both designed with the fractions of entire treatment course. After completing optimization of each plan, the initial and boost plans were summed directly according to the predetermined dose and fractions of each plan. This method made it more convenient and feasible to restriction doses to the OARs. Moreover, with optimizing the boost IMRT plans independently, the conformity and homogeneity of each target volume would be able to meet the original requirements of clinic.

In conclusion, the results indicated that the radiotherapeutic plan by composite planning approach may be more preferable compared to the plan by synchronous planning approach in sequential IMRT for nasopharyngeal carcinoma.

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Disclosure of conflict of interest

None.

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References

[1] Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. Int J Radiat Oncol Biol Phys 2009; 75: 1071-1078.

[2] Tham IW, Hee SW, Yeo RM, Salleh PB, Lee J, Tan TW, Fong KW, Chua ET, Wee JT. Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy-the national cancer centre Singapore experience. Int J Radiat Oncol Biol Phys 2009; 75: 1481-1486.

[3] Su SF, Han F, Zhao C, Chen CY, Xiao WW, Li JX, Lu TX. Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. Int J Radiat Oncol Biol Phys 2012; 82: 327-333.

[4] Wang TJC, Riaz N, Cheng SK, Lu JJ, Lee NY. Intensity-modulated radiation therapy for nasopharyngeal carcinoma: a review. J Radiat Oncol 2012; 1: 129-146.

[5] Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, Akazawa P, Weinberg V, Fu KK. Intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma: aFn update of the UCSF experience. Int J Radiat Oncol Biol Phys 2002; 53: 12-21.

[6] Chen SW, Yang SN, Liang JA, Shiau AC, Lin FJ. Comparative dosimetric study of two strategies of intensity-modulated radiotherapy in nasopharyngeal cancer. Med Dosim 2005; 30: 219-227.

[7] Lauve A, Morris M, Schmidt-Ullrich R, Wu Q, Mohan R, Abayomi O, Buck D, Holdford D, Dawson K, Dinardol L, Reiter E. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head and neck squamous cell carcinomas: II clinical results. Int J Radiat Oncol Biol Phys 2004; 60: 374-387.

[8] Wang J, Shi M, Hsia Y, Luo S, Zhao L, Xu M, Xiao F, Fu X, Li J, Zhou B, Long X. Failure patterns and survival in patients with nasopharyngeal carcinoma treated with intensity modulated radiation in Northwest China: a pilot study. Radiat Oncol 2012; 7: 2-8.

[9] Wang J, Bai S, Chen N, Xu F, Jiang X, Li Y, Xu Q, Shen Y, Zhang H, Gong Y, Zhong R, Jiang Q. The clinical feasibility and effect of online cone beam computer tomography-guided intensity-modulated radiotherapy for nasopharyngeal cancer. Radiother Oncol 2009; 90: 221-227.

[10] Popple RA, Prellop PB, Spencer SA, De Los Santos JF, Duan J, Fiveash JB, Brezovich IA. Simultaneous optimization of sequential IMRT plans. Med Phys 2005; 32: 3257-3266.

[11] Dogan N, King S, Emami B, Mohideen N, Mirkovic N, Leybovich LB, Sethi A. Assessment of different IMRT boost delivery methods on target coverage and normal tissue sparing. Int J Radiat Oncol Biol Phys 2003; 57: 1480-1491.

[12] Mohan R, Wu Q, Manning M, Schmidt-Ullrich R. Radiobiological considerations in the design of fractionation strategies for intensity-modulated radiation therapy for head and neck cancers. Int J Radiat Oncol Biol Phys 2000; 46: 619-630.

[13] Jones B, Dale RG, Deehan C, Hopkins KI, Morgan DAL. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol 2001; 13: 71-81.

[14] Mavroidis P, Ferreira BC, Papanikolaou N, Lopes Mdo C. Analysis of fractionation correction methodologies for multiple phase treatment plans in radiation therapy. Med Phys 2013; 40: 31-715.