

Comparison of long-term survival and toxicity of simultaneous integrated boost vs conventional fractionation with intensity-modulated radiotherapy for the treatment of nasopharyngeal carcinoma

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Aim: In recent years, the intensity-modulated radiotherapy with simultaneous integrated boost (IMRT-SIB) and intensity-modulated radiotherapy with conventional fractionation (IMRT-CF) have been involved in the treatment of nasopharyngeal carcinoma (NPC). However, the potential clinical effects and toxicities are still controversial.

Methods: Here, 107 patients with biopsy-proven locally advanced NPC between March 2004 and January 2011 were enrolled in the retrospective study. Among them, 54 patients received IMRT-SIB, and 53 patients received IMRT-CF. Subsequently, overall survival (OS), 5-year progression-free survival (PFS), 5-year locoregional recurrence-free survival (LRFS), and relevant toxicities were analyzed.

Results: In the present study, all patients completed the treatment, and the overall median follow-up time was 80 months (range: 8–126 months). The 5-year OS analysis revealed no significant difference between the IMRT-SIB and IMRT-CF groups (80.9% vs 80.5%, $P=0.568$). In addition, there were also no significant between-group differences in 5-year PFS (73.3% vs 74.4%, $P=0.773$) and 5-year LRFS (88.1% vs 90.8%, $P=0.903$). Notably, the dose to critical organs (spinal cord, brainstem, and parotid gland) in patients treated by IMRT-CF was significantly lower than that in patients treated by IMRT-SIB (all $P<0.05$).

Conclusion: Both IMRT-SIB and IMRT-CF techniques are effective in treating locally advanced NPC, with similar OS, PFS, and LRFS. However, IMRT-CF has more advantages than IMRT-SIB in protecting spinal cord, brainstem, and parotid gland from acute and late toxicities, such as xerostomia. Further prospective study is warranted to confirm our findings.

Keywords: intensity-modulated radiotherapy with simultaneous integrated boost, intensity-modulated radiotherapy with conventional fractionation, nasopharyngeal carcinoma, survival, toxicities

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck tumors in the People's Republic of China. The incidence of NPC was $>20/100,000$ in southern China. Most of the patients with NPC are usually diagnosed in locally advanced, nonmetastatic stage III or IV.^{1,2} To date, radiotherapy (RT) has been recommended as the first option for treatment of NPC. Thus, it is essential to investigate multimodal RT to improve survival status of patients with NPC.

With the advent of RT equipment and computer technology, intensity-modulated radiotherapy (IMRT) has been extensively utilized in the treatment of NPC due to its

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benefits in accurately targeting organs, reducing toxicities of organs at risk, and enhancing dose escalation. Importantly, the dosimetric advantage of IMRT has been widely identified and better local control rate.³ On the other hand, simultaneous integrated boost (SIB), also called simultaneous modulated and accelerated RT, can deliver different doses to target regions according to the level of risk, which exploited the “dose-painting” capacity of IMRT.⁴ The safety and efficacy of IMRT-SIB have been confirmed in patients with NPC.^{5–7} Meanwhile, IMRT with conventional fractionation (IMRT-CF) has also been widely used in the treatment of NPC; however, the efficacy of IMRT-CF was little reported, in that CF (2.0 Gy/fraction) was subjected to two-dimensional conventional radiotherapy (2D-RT) or three-dimensional conventional radiotherapy (3D-RT). Besides, few studies compared the efficacy and safety of IMRT-SIB and IMRT-CF in recent decades.

Therefore, in the present study, we enrolled 107 patients with biopsy-proven and locally advanced NPC, and analyzed overall survival (OS), 5-year progression-free survival (PFS), 5-year locoregional recurrence-free survival (LRFS), and relevant toxicities. Our study will contribute to the improvement of clinical IMRT treatment strategies in patients with NPC.

Methods

Patients

The present retrospective cohort was composed of 107 newly diagnosed and previously untreated patients with histopathologically confirmed NPC. All 107 patients were treated with IMRT in Shandong Cancer Hospital and Institute between March 2004 and January 2011. Median age of all patients was 43 years (16–78 years). Human participant approval was obtained from the ethical committee of Shandong Cancer Hospital and Institute. Written informed consent from patients was obtained. Routine workup included a thorough physical examination, hematologic and biochemistry profiles, fiberoptic endoscope examination of the nasopharynx, and magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) of the head and neck, with which the status of the primary tumor and regional lymph nodes could be accurately evaluated. At the same time, the chest X-ray or CT, whole-body bone scan, and abdominal region ultrasonography were used to exclude distant metastasis. Staging of the patients was completed using the American Joint Committee on Cancer/Union for International Cancer Control 2002 system for staging classification of NPC.

Radiotherapy

All patients were immobilized with a thermoplastic mask. The simulation CT images extended from the vertex of

the skull to 5 cm inferior of the clavicular heads, and were obtained at a slice thickness of 3 mm. All patients were treated by IMRT.

In the IMRT-SIB group, the gross tumor volume (GTV) included the primary nasopharyngeal tumor and lymph nodes-involved tumors demonstrated by contrast enhancement CT or MRI. Clinical target volume (CTV) 1, a high-risk region, was defined by appending a 5 mm margin to GTV, which included the inferior sphenoid sinus, clivus, skull base, nasopharynx, ipsilateral parapharyngeal space, posterior third of the nasal cavity, maxillary sinuses, and Level II, III, and Va lymph nodes. CTV2, a low-risk region, was the lower neck below the cricothyroid membrane. A smaller margin (3 mm) was also acceptable in these regions close to the critical structures, such as brainstem, optic nerves, and optic chiasm. CTV intermediate- and low-risk regions were contoured according to Radiation Therapy Oncology Group (RTOG) recommendations. Planning target volume (PTV) was defined by adding a 5 mm margin to the CTV in all dimensions. The prescribed dose was 66 Gy/30 fractions at 2.2 Gy/fraction to the planning gross tumor volume (PGTV), 60 Gy/30 fractions at 2.0 Gy/fraction to the PTV1, and 54 Gy/30 fractions at 1.8 Gy/fraction to the PTV2. Total radiation doses of 66–74, 60, and 54 Gy were delivered to PGTV, PTV1, and PTV2, respectively, with 30–34 fractions at five fractions per week.

In the IMRT-CF group, CTV included the primary nasopharyngeal tumor, lymph nodes-involved tumor, the high-risk regions including the entire nasopharynx, skull base, clivus, inferior sphenoid sinus, retropharyngeal lymph nodal regions, pterygoid fossae, parapharyngeal space, the posterior third of the nasal cavity, maxillary sinuses, and any high- or low-risk nodal regions including bilateral cervical lymph nodes Level II–V. PTV was generated with 5 mm margin. PTV was delivered at 2 Gy/fraction for 25 fractions with total dose of 50 Gy, followed by twice replanning. The first and second replanning were generated, respectively, using a “shrinking-field technique” after 25 fractions and 30 fractions. The accumulated radiation doses were 70–74 Gy to PTV of the GTV for the primary nasopharyngeal tumors and the involved lymph nodes, 60 Gy to high-risk PTV, and 50 Gy to low-risk PTV. All patients were treated with one fraction daily for 5 days per week. The target prescription dose and the critical structures limit dose were planned according to the RTOG trial 0225 criteria. The irradiated doses of both IMRT techniques are summarized in Table 1.

Chemotherapy

In this study, the chemotherapy regimens were cisplatin alone, cisplatin/docetaxel, and cisplatin/5-fluorouracil. These

Table 1 Dosimetric difference of both IMRT strategies

Technique	BED (tumor) (Gy ₁₀)	BED (late) (Gy ₁₀)
IMRT-SIB (2-phase)		
PGTV 2.2×30+2.0×4=74 Gy	90.12	128.27
PTV-HR 2.0×30=60 Gy	72.00	100.00
PTV-LR 1.8×30=54 Gy	63.72	86.40
IMRT-CF (3-phase)		
PGTV 2.0×25+2.0×5+2.0×7=74 Gy	88.80	123.33
PTV-HR 2.0×25+2.0×5=60 Gy	72.00	100.00
PTV-LR 2.0×25=50 Gy	60.00	83.33

Notes: BED calculation is based on the linear-quadratic model for cell kill with an α/β of 10 for tumors and an α/β of 3 for late-responding normal tissue. The BED is calculated by the following equation: $BED = nd[1 + d/(\alpha/\beta)]$.

Abbreviations: IMRT, intensity-modulated radiotherapy; BED, biological effective dose; IMRT-SIB, IMRT with simultaneous integrated boost; PGTV, planning gross tumor volume; PTV-HR, high-risk planning target volume; PTV-LR, low-risk planning target volume; IMRT-CF, IMRT with conventional fractionation.

chemotherapy regimens were known to possess similar activity and effectiveness for treatment of NPC, and were administered as neoadjuvant, concurrent, or adjuvant treatment (Table 2).

Follow-up

The duration of follow-up was calculated from the first day of treatment to either the day of death or day of the last

Table 2 Clinical characteristics and baseline levels between IMRT-SIB and IMRT-CF

Characteristics	IMRT-SIB (n=54)	IMRT-CF (n=53)	P-value
Sex			0.874
Male	39	39	
Female	15	14	
Age (years)			0.147
≤45	31	23	
>45	23	30	
T classification			0.95
T1	3	4	
T2	13	13	
T3	29	26	
T4	9	10	
N classification			0.84
N0	7	5	
N1	7	9	
N2	31	32	
N3	9	7	
Staging			0.917
II	3	2	
III	33	34	
IVA	9	10	
IVB	9	7	
Chemotherapy			0.780
Neoadjuvant	13	14	
DDP + 5-FU	7	6	
Docetaxel + DDP	6	8	
Concurrent	54	53	0.874
DDP	54	53	

(Continued)

Table 2 (Continued)

Characteristics	IMRT-SIB (n=54)	IMRT-CF (n=53)	P-value
Adjuvant	39	38	0.952
DDP + 5-FU	17	19	
Docetaxel + DDP	22	19	
RT duration (days)			
Mean ± SD	45.74±2.21	50.74±2.53	<0.001

Abbreviations: IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation; DDP, cisplatin; 5-FU, 5-fluorouracil; RT, radiotherapy; SD, standard deviation; T, tumor; N, node.

follow-up. Patients were interviewed and examined at least every 3 months during the first 2 years, and subsequent every 6 months. Follow-up information must include clinical examination, and CT or MRI of the head and neck region. When patients had potential locoregional recurrence or distant metastasis, additional examinations or imaging modalities were performed to confirm disease progression at the discretion of the treating physician. Missing data were completed by calling the patient or the treating physician. Acute and late toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0. Besides, the diagnostic criteria for injury of the nervous system involves the following: lesions or necrosis in the nervous system showed contrast enhancement on postcontrast T1-weighted MRI, heterogeneous hyperintense on T2-weighted MRI, and homogeneous peri-necrosis hyperintense on T2-weighted MRI. Furthermore, the recurrence or metastasis of tumor must be excluded when determining the site of radiation encephalopathy.

Last, the time to the first defined event OS, PFS, and LRFS was assessed. OS was measured from the first day of treatment until death or follow-up deadline. PFS was measured from the first day of treatment to the date of the first observation of local or regional recurrence or distant metastasis. LRFS was measured from the date of treatment to the date of the first observation of local and regional recurrence.

Statistical methods

All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., IBM Company, Armonk, NY, USA). The chi-square test was used to calculate statistical group comparisons of categorical variables. Survival analysis was performed using the Kaplan–Meier method, and comparisons were calculated using the log-rank test. The Mann–Whitney test and log-rank method were used to estimate the differences in both groups. Multivariate analyses with the Cox proportional hazards model were used to test independent prognostic factor by backward elimination of insignificant

explanatory variables. The Cox proportional hazards model was used to calculate hazard ratios. $P < 0.05$ was considered statistically significant, and all P -values correspond to two-sided significance tests.

Results

Patient characteristics and baseline level

To figure out the baseline level of all patients, we summarized the characteristics of patients and treatment modality. As shown in Table 2, 78 males and 29 females were included, and the male/female ratio was calculated as ~2.6:1. The most patients presented with stage III (62.6%) and stage IV (32.7%). According to statistics, there were no significant between-group differences in sex, age, T and N classifications, and clinical stage (all $P > 0.05$), indicating that our study was reliable.

Dosimetric comparison

As shown in Table 3, we summarized the maximal doses (D_{\max}) to the critical structures (spinal cord, brainstem, crystalline lens, and optic nerve), and calculated the mean doses (D_{mean}) to the parotid glands. Our results revealed that the doses of spinal cord, brainstem, and parotid gland were significantly lower in patients treated by IMRT-CF than in those patients treated by IMRT-SIB (all $P < 0.05$).

Figure 1A–C illustrates the deformable image registration process in IMRT-SIB group. After recontouring parotids on 30th fraction images, both parotid volumes were mapped to the initial treatment plan with the same beam configurations. These plans were referred to as “simulated plans”, and demonstrated significant migration of the parotids, especially toward the high-dose PTV regions, which would result in increased dose to the parotids. In addition, the dose–volume

histograms showed that estimated delivered doses to both parotids were higher than initial plans during the RT course (Figure 2).

Radiation toxicities

To elucidate the potential toxicities of IMRT-SIB and IMRT-CF, we summarized all types of toxicities in our study, and toxicities after 6 months following RT were defined as late radiation toxicities. No treatment-related deaths were observed in either cohort. Acute and late radiation toxicities are shown in Table 4. Systemic acute toxicities were similar in both groups.

Of 107 patients, the most common late toxicities included xerostomia and hearing loss, which were observed in 40.1% and 30.8% of patients, respectively. Briefly, in the IMRT-SIB group, xerostomia can be found in 26 patients (48.1%), whereas the IMRT-CF group had 17 patients (32.1%) with xerostomia; the difference was significant ($P < 0.001$). Accordingly, the rate of late hearing loss in the IMRT-SIB group was also greater than that in the IMRT-CF group; however, no significant statistic difference was observed ($P = 0.491$).

Subsequently, we summarized late toxicities of the nervous system, and found that in IMRT-SIB group, three patients with NPC (5.5%) suffered from late toxicities of the nervous system, including two patients (1.87%) with temporal lobe injury and one patient (0.93%) with brainstem injury. In addition to that, no injury was observed in temporal lobe, brainstem, and spinal cord.

Patterns of failure and survival outcome

In the present study, the overall median follow-up time was 80 months (range: 8–126 months). Of 107 patients,

Table 3 Adverse event grade according to Common Terminology Criteria for Adverse Events version 3.0

Toxicity	IMRT-SIB					IMRT-CF					P-value
	0	1	2	3	4	0	1	2	3	4	
Acute toxicities											
Dematitis	0	23	27	4	0	0	21	30	2	0	0.636
Mucositis	0	21	14	19	0	0	20	19	14	0	0.465
Xerostomia	10	21	23	0	0	13	21	19	0	0	0.683
Dysphagia	20	26	6	2	0	23	25	4	1	0	0.813
Hearing loss	34	19	1	0	0	36	16	1	0	0	0.859
Late toxicities											
Xerostomia	28	9	15	2	0	36	6	11	0	0	<0.001
Temporal lobe injury	52	1	1	0	0	53	0	0	0	0	0.368
Brainstem injury	53	1	0	0	0	53	0	0	0	0	0.32
Trismus	53	1	0	0	0	53	0	0	0	0	0.375
Hearing loss	33	15	6	0	0	41	9	3	0	0	0.314

Abbreviations: IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation.

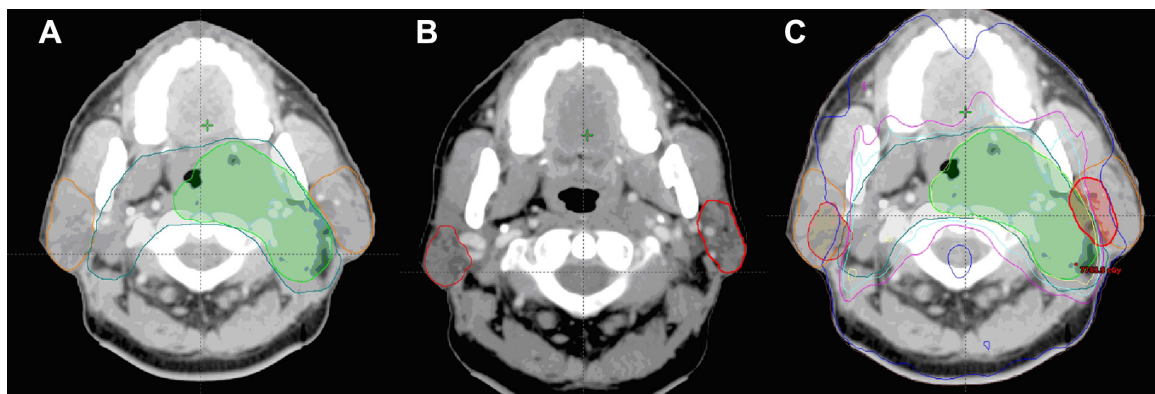


Figure 1 Axial CT images of one patient with target volume and parotid gland contours in IMRT-SIB group.

Notes: (A) Manually drawn target volume (green and blue) and parotid gland (orange) contours on first planning CT. (B) Manually drawn parotid gland contours (red) on second planning CT. (C) The deformable image registration of (A) and (B).

Abbreviations: CT, computed tomography; IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost.

17 patients (15.8%) developed locoregional relapse, 22 patients (20.5%) presented with distant metastasis, and 30 patients (28%) were dead. Seventeen patients with locoregional relapse included eight patients (7.5%) with local relapse, seven patients (6.5%) with regional relapse, and the rest of two patients (1.9%) with both local and regional relapse. Besides, two patients (1.9%) developed both locoregional and distant failure.

Based on follow-up data, the overall 5-year OS, PFS, and LRFS rates were 80.7%, 72.9%, and 89.4%, respectively. According to statistics, we found no significant between-group differences in 5-year OS (80.9% vs 80.5%, $P=0.568$) (Figure 3), PFS (73.3% vs 74.4%, $P=0.773$) (Figure 4), and

LRFS (88.1% vs 90.8%, $P=0.903$) (Figure 5). These results indicated that both IMRT-SIB and IMRT-CF can benefit patients and improve the survival status.

Prognostic factors

To throw light on the independent prognostic factor, we conducted multivariate analysis using variables in this study, including age (>45 years vs ≤ 45 years), T classification (T1–2 vs T3–4), N classification (N0–1 vs N2–3), and RT method (IMRT-CF vs IMRT-SIB). All these variables were summarized and calculated in the Cox proportional hazards model using the backward elimination method. Multivariate analysis revealed that age and N classification act as

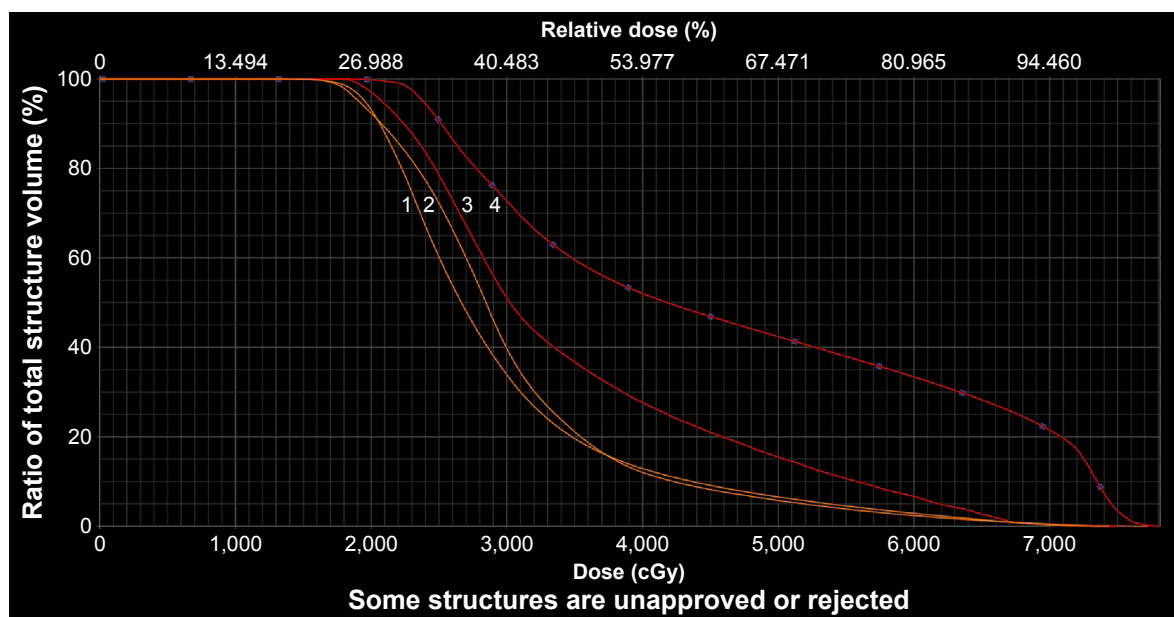


Figure 2 The dose-volume histograms of the parotids.

Notes: 1: the right parotid of first planning CT. 2: the left parotid of first planning CT. 3: the right parotid of second planning CT. 4: the left parotid of second planning CT.

Abbreviation: CT, computed tomography.

Table 4 Comparison of parameters in IMRT-SIB and IMRT-CF groups

OAR	Parameter	IMRT-SIB	IMRT-CF	P-value
Spinal cord	D_{max} (Gy)	45.93±4.20	43.19±2.40	<0.001
Brainstem	D_{max} (Gy)	56.80±3.16	53.91±4.19	<0.001
Left crystalline lens	D_{max} (Gy)	5.65±1.26	5.27±1.25	0.174
Right crystalline lens	D_{max} (Gy)	5.59±1.05	5.44±1.21	0.360
Left optic nerve	D_{max} (Gy)	28.30±16.75	22.80±15.06	0.081
Right optic nerve	D_{max} (Gy)	27.23±16.52	21.99±15.95	0.063
Left parotid	D_{mean} (Gy)	32.99±2.66	30.35±2.25	<0.001
Right parotid	D_{mean} (Gy)	32.76±2.75	30.03±2.36	<0.001

Note: IMRT-SIB and IMRT-CF data presented as mean ± standard deviation.

Abbreviations: IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation; OAR, organs at risk; D_{max} , maximal dose to the volume; D_{mean} , mean dose to the volume.

significant predictive factors for OS ($P<0.001$ and $P=0.039$, respectively), PFS ($P=0.003$ and $P=0.009$, respectively), and LRFS ($P=0.011$ and $P=0.031$, respectively). However, RT method cannot serve as a significant prognostic factor for OS, PFS, and LRFS. At the same time, it should be noted that T classification was another prognostic factor only for PFS ($P=0.037$) (Table 5).

Discussion

In recent decades, IMRT has been widely utilized and benefited most patients with NPC in short-term treatment. It is reported that IMRT has some advantages in improving the local control rate and quality of life.^{8–10} Till now, IMRT has been developed into two models, like IMRT-CF and IMRT-SIB. However, the real effects of IMRT-CF and IMRT-SIB on NPC treatment were not well featured. In the present study, the rate of 2-year OS and PFS in IMRT-CF-treated

patients with NPC was 96.2% and 94.4%, respectively. Consistent with our data, Ng et al included 193 patients in their trial, and concluded that 2-year OS and PFS in IMRT-CF-treated patients with NPC increased up to 92% and 95%, respectively.⁸ As reported, IMRT-SIB has been widely investigated in NPC treatment with a nominal total dose of 64.8–76 Gy to GTV in 2.12–2.4 Gy/fraction over 27–35 fractions.^{8,11,12} Overall, NPC patients with IMRT-SIB treatment achieved a local or locoregional control rate of 88%–96% based on 2–5 years of follow-up, though SIB dose fractionation varied in these studies. Our results showed that the rate of 5-year OS, PFS, and LRFS in patients with IMRT-SIB treatment was 80.9%, 73.3%, and 88.1%, respectively. In accordance to our data, Sun et al⁹ conducted a retrospective analysis on 868 nonmetastatic patients with NPC treated by IMRT-SIB, and found that the rate of 5-year LRFS and PFS for all patients was 91.8% and 77.0%, respectively, and the

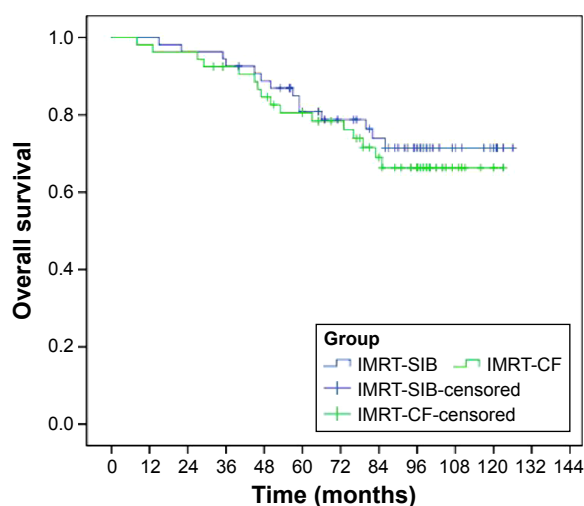


Figure 3 Comparison of overall survival between patients treated with IMRT-SIB and those treated with IMRT-CF ($P=0.568$).

Abbreviations: IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation.

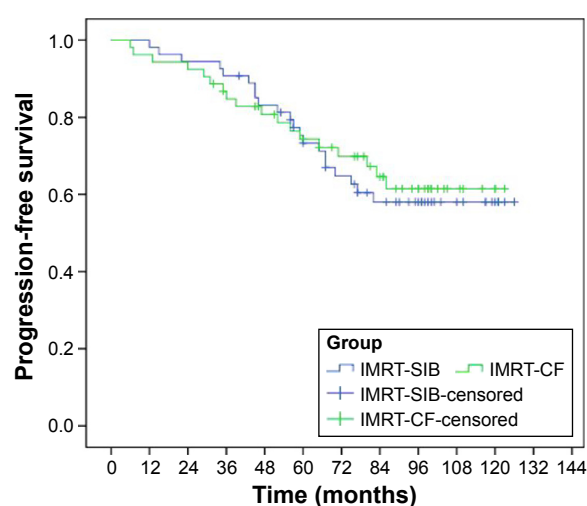


Figure 4 Comparison of progression-free survival between patients treated with IMRT-SIB and those treated with IMRT-CF ($P=0.773$).

Abbreviations: IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation.

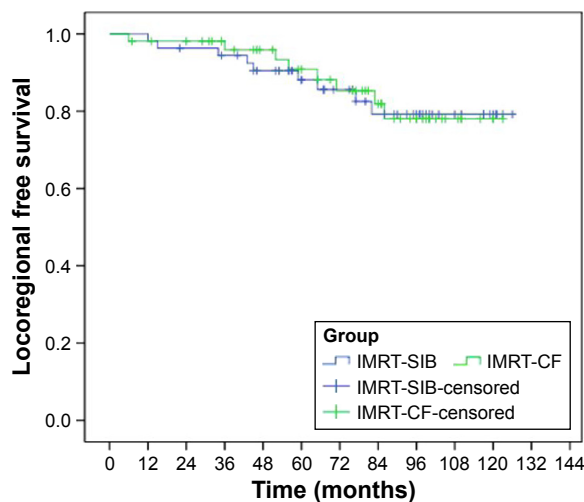


Figure 5 Comparison of locoregional recurrence-free survival between patients treated with IMRT-SIB and those treated with IMRT-CF ($P=0.903$).

Abbreviations: IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation.

5-year OS rate was up to 83.2%. These results indicated that both IMRT-SIB and IMRT-CF can benefit patients and improve the survival status.

Chen et al¹³ and Nesrin et al¹⁴ performed dosimetric studies comparing the target volume coverage and normal tissue sparing of IMRT-SIB vs IMRT-CF for NPC. Both the groups found that the maximal dose to spinal cord and brainstem was lower in IMRT-CF than in IMRT-SIB. They suggested that normal tissues embedded within the target regions may receive higher doses per fraction compared to the doses given by IMRT-CF delivery techniques. Therefore, IMRT-CF may be more appropriate than IMRT-SIB when the dose given to the normal tissues is the major concern. This is the same direction in our study which showed that IMRT-CF provided better sparing of spinal cord and brainstem than did the IMRT-SIB ($P=0.001$ for spinal cord and $P=0.001$ for brainstem). This indicates that a small area of brainstem and spinal cord, especially in T3–T4 patients, was inclined to receive a high dose per fraction (2.2 Gy/fraction) when patients were subjected to IMRT-SIB due to its approach to

the boost volume. Therefore, caution should be taken when applying IMRT-SIB technique when these critical structures are very close to the boost volume.¹³

On the other hand, reports by Chen et al¹³ and Nesrin et al¹⁴ demonstrated that IMRT-SIB could provide better sparing of the parotid glands than IMRT-CF. However, our study identified that IMRT-CF provided better sparing of parotid glands in comparison with IMRT-SIB. This is probably related to the following two reasons: (1) CT scans were performed after the 25th fraction in IMRT-CF, while after 30th in IMRT-SIB group, and then the treatment plans were re-conducted according to these scans. With the shrinking of the primary tumor and nodal masses, the parotids might deviate to the GTV (lymph node involvement) (Figure 1C), which results in higher actual dose in parotid gland than expected (Figure 2). Zhang et al¹⁵ reported that there was a benefit to bilateral parotids through replanning at the fifth week. (2) If the involved lymph nodes in Level II were very large and close to parotids, the calculated total dose to the parotid gland may increase.

Afterward, we analyzed radiation-induced toxicities. Of 107 patients, the most common late toxicities included xerostomia and hearing loss, which were observed in 40.1% and 30.8% of patients, respectively. Consistent with our results, Peng et al¹⁶ showed that 39.5% of patients with NPC had grade I–II xerostomia. Moreover, our results also showed that patients receiving IMRT-CF had a lower incidence of acute and late xerostomia than those who received IMRT-SIB. We think that it may be attributed to the statistical difference in the mean dose to parotid gland.¹⁵ Recently, Marzi et al¹⁷ reported a minor increase of parotid D_{mean} based on the tolerance dose that can result in potential severe xerostomia. Obviously, IMRT-CF significantly decreased the doses to parotids (Table 3) to reduce xerostomia-related symptoms and improve the quality of life. At the same time, an insignificant high incidence of grade 3 dermatitis, oropharyngeal mucositis, dysphagia, and late hearing loss in the IMRT-SIB group was also observed in this work.

Table 5 Multivariate analysis of OS, PFS, and LRFS

Factor	OS hazard ratio (95% CI)	P-value	PFS hazard ratio (95% CI)	P-value	LRFS hazard ratio (95% CI)	P-value
Age >45 years vs ≤45 years	1.055 (1.024–1.087)	<0.001	1.039 (1.013–1.067)	0.003	1.070 (1.016–1.128)	0.011
T classification	0.043 (0.165–1.123)	0.085	0.439 (0.202–0.953)	0.037	0.717 (0.174–2.960)	0.646
N classification	2.568 (1.049–6.286)	0.039	3.000 (1.323–6.802)	0.009	9.342 (1.227–71.126)	0.031
Radiotherapy (IMRT-CF vs IMRT-SIB)	1.378 (0.477–3.981)	0.554	0.685 (0.322–1.456)	0.325	0.697 (0.179–2.714)	0.603

Note: P-values were calculated using an adjusted Cox proportional hazards regression model.

Abbreviations: OS, overall survival; CI, confidence interval; PFS, progress-free survival; LRFS, locoregional recurrence-free survival; IMRT-CF, intensity-modulated radiotherapy with conventional fractionation; IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost; T, tumor; N, node.

Finally, we demonstrated that N staging and age act as a significant predictive factor for OS, PFS, and LRFS. However, T stage was not a significant prognostic factor in this study. In contrast, previous studies showed that both T and N categories act as a significantly independent factor.^{8,9,18} Maybe, our sample size in this study is relatively small. Most importantly, our analysis revealed that RT was not a prognostic factor for OS, PFS, and LRFS, and the difference between IMRT-SIB and IMRT-CF did not affect survival outcome.

In the clinical practice, the overall radiotherapy treatment time of IMRT-CF was significantly longer than IMRT-SIB. In this study, although a lengthening of overall radiotherapy treatment time of 5 days was obtained with the IMRT-CF technique, IMRT-CF only adds three times the cost for the RT. Besides, due to acute IMRT-SIB-related toxicities, the corresponding cost of supportive care and management will increase. Joiner¹⁹ reported that reduction in overall treatment time was assumed to reduce the risk of tumor regrowth during the late phase of radiation treatment, and improve the probability of tumor control. In our study, the biological effective dose to PGTV (90.12 Gy_{10}) was higher in IMRT-SIB than in IMRT-CF (88.80 Gy_{10}). However, the overall 5-year LRFS rates were not significantly different between the two groups (88.1% vs 90.8%, $P=0.903$).

To our knowledge, this is the first single-institution study to investigate the difference between IMRT-CF and IMRT-SIB in patients with NPC. The main limitations in this study exist in retrospective property and relatively small sample size. To draw a definitive conclusion, a randomized Phase II study on IMRT-SIB than IMRT-CF in patients with locally advanced NPC is being conducted in our hospital. This study will allow for the standardization of IMRT technique for patients with NPC.

Conclusion

The IMRT-SIB and IMRT-CF can benefit patients with local advanced-stage NPC, and better the survival status. The IMRT-CF has more advantages than IMRT-SIB in protecting spinal cord, brainstem, and parotid gland from acute and late toxicities, such as xerostomia. Thus, IMRT-CF should be recommended for patients with locally advanced NPC. The results of this study will be further validated in prospective, multicenter controlled trials.

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Disclosure

The authors report no conflicts of interest in this work.

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