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IMRT with Simultaneous Integrated Boost and Concurrent Chemotherapy for Nasopharyngeal Cancer: Plan Evaluation and Treatment Outcome

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Objective: This study evaluated the outcome of intensity-modulated radiation therapy with simultaneous integrated boost and concurrent chemotherapy for nasopharyngeal cancer.
Methods: We analyzed 53 consecutive nasopharyngeal cancer patients who received definitive treatment using intensity-modulated radiation therapy with simultaneous integrated boost and cisplatin-based concurrent chemotherapy. Forty-six patients were treated with concurrent chemoradiation and seven patients with induction chemotherapy plus concurrent chemoradiation. The gross tumor (PTV_{70}) received 69.96 Gy (2.12 Gy/fraction), high-risk subclinical disease (PTV_{60}) received 59.4 Gy (1.8 Gy/fraction) and low-risk subclinical disease (PTV_{56}) received 56.1 Gy (1.7 Gy/fraction) in 33 fractions. Twenty-eight patients were treated with step-and-shoot intensity-modulated radiation therapy and 25 patients with helical tomotherapy. Dosimetric parameters were compared between the two modalities.
Results: The median treatment duration was 49 days (range: 41–65 days). The complete response rate was 92.5%. Three local, two regional, one locoregional and seven distant failures were observed. With the median follow-up of 41 months (range: 8–89 months), the 3- and 5-year local control, locoregional control, disease-free survival and overall survival rates were 91.8 and 91.8%; 87.6 and 87.6%; 77.5 and 70.5%; and 86.4 and 82.1%, respectively. Grade 3 mucositis, dermatitis, leucopenia and grade 4 leucopenia were observed in 10, 1, 2 and 1 patient, respectively. No grade 3 or higher xerostomia occurred. Helical tomotherapy significantly improved dosimetric parameters including the maximum dose, volume receiving $>107\%$ of the prescribed dose and uniformity index (D_5/D_{95}).
Conclusions: Intensity-modulated radiation therapy with simultaneous integrated boost with concurrent chemotherapy is a safe and effective treatment modality for nasopharyngeal cancer. Helical tomotherapy has a dosimetric advantage over step-and-shoot intensity-modulated radiation therapy in a clinical setting.

Key words: nasopharyngeal cancer – IMRT – simultaneous integrated boost – concurrent chemotherapy

INTRODUCTION

Nasopharyngeal carcinoma (NPC) has characteristics distinguishable from other head and neck cancers (HNCs) with respect to epidemiology, clinical features, treatment strategies and response to therapy. NPC is highly endemic in Southeast Asia, with the predominance of the non-keratinizing undifferentiated (WHO type IIb) tumor histology (1). Although NPC is radiosensitive and the addition of chemotherapy added survival advantage in locoregionally advanced NPC (2,3), conventional radiotherapy (RT) still resulted in relatively frequent local failures with a 5-year local control rate among patients with T3/T4 NPC ranging from 69 to 79% (4,5). Local control for NPC is strongly correlated with the radiation dose delivered to the tumor. In a series of 107 patients with NPC, local control was significantly improved when >67 Gy was delivered to the tumor (6). At many centers, intensity-modulated radiation therapy (IMRT) has become the standard RT technique for treating NPC. IMRT provided better tumor coverage, with a greater percentage of the target volume receiving the planned prescription dose than a conventional 3D conformal plan (7,8), and published clinical outcomes demonstrated that IMRT could produce high local and regional control rates in the treatment of NPC (9,10).

Simultaneous integrated boost (SIB) technique delivers various fractional doses to different target volumes in a single phase plan. Incorporating moderate hypofractionation is advantageous in that the reduced overall treatment time can counteract the accelerated tumor repopulation and a larger fractional dose is more effective in eliminating the cancer stem cells, which are intrinsically more radioresistant (11,12). However, hypofractionation and SIB both have a risk of delivering high-dose radiation to adjacent normal organs and these techniques are best incorporated into IMRT, which can deliver highly conformal radiation to the tumor and maximize the therapeutic window. Helical tomotherapy (HT) is a novel and highly accurate apparatus for delivering IMRT with the image-guided support of onboard megavoltage computed tomography (CT). Because of its 360° arrangement of intensity-modulated narrow beams passing through binary multileaf collimators (MLCs), HT plans can provide equal or better dose distribution compared with conventional step-and-shoot IMRT (ssIMRT) plans. It has been reported that HT provides improved dose homogeneity to the target and avoidance of normal structures when compared with ssIMRT in the treatment of many types of cancers including retroperitoneal sarcoma (13), endometrial carcinoma (14), cranio-spinal tumor (15) and HNC (16,17). HT also showed a significant dosimetric gain in the conformity index, homogeneity index and sparing of organs at risk (OARs) when compared with ssIMRT in the treatment of NPC (18).

The current study reports the treatment outcome of 53 NPC patients treated with IMRT-SIB and concurrent chemotherapy and compares dosimetric parameters between ssIMRT and HT in a clinical setting.

PATIENTS AND METHODS

Patients

We analyzed 53 consecutive patients with biopsy proven, previously untreated stages IIB–IVB nasopharyngeal cancer who received a definitive treatment using IMRT with concurrent chemotherapy at the Yonsei Cancer Center, Severance Hospital between January 2002 and December 2008. All patients underwent fiberoptic nasopharyngoscopy and biopsy for pathological diagnosis. The initial staging evaluation included a clinical examination and CT and/or magnetic resonance imaging (MRI) of the head and neck, chest radiography, abdominal sonography or CT, complete blood count with differential count and biochemical profile. Some patients underwent positron emission tomography for systemic assessment. Staging of nasopharyngeal cancer was based on the TNM system of the American Joint Committee on Cancer, 6th edition.

Radiation Therapy

For CT simulation, patients were immobilized in a supine position with custom head and shoulder Aquaplast masks (Aquaplast, Wycoff, NJ), and CT images were obtained every 3 mm extending from the vertex to 5-cm inferior to the clavicular heads. The target volume and normal tissue structures were contoured on each axial CT slice, supplemented with fused diagnostic MRI and/or PET scans. Both ssIMRT and HT plans followed the same target and normal organ delineation protocol and dose prescriptions. SIB technique was used for treatment planning. The gross target volume (PTV_{70}) consisted of the gross primary tumor, the whole nasopharynx and positive lymph nodes, as defined by MRI and/or CT, plus a 0.5-cm margin. The high-risk subclinical disease (PTV_{60}) encompassed PTV_{70} plus a 1.5-cm margin, potential spread of microscopic disease (including the parapharyngeal space, posterior third of nasal cavities and maxillary sinuses, pterygoid processes, base of skull and lower half of sphenoid sinus), and the prophylactic area of the neck (including bilateral retropharyngeal nodes, levels II, III and IV). The low-risk subclinical disease (PTV_{56}) included the remaining levels (IV-VB) of the neck. In cases of induction chemotherapy (IC), disease extents in pre-chemotherapy MRI images were used for target delineation. OARs outlined in three dimensions included the brainstem, spinal cord, lenses, eyes, optic chiasm, optic nerves, cochlea and parotid glands. PTV_{70} received a total dose of 69.96 Gy in daily fractions of 2.12 Gy, PTV_{60} received 59.4 Gy in 1.8 Gy per daily fraction and PTV_{56} received 56.1 Gy in 1.7 Gy per daily fraction. The dose constraints for OARs were as follows: a maximum dose of 54 Gy for the brainstem, optic nerve and optic chiasm; a maximum dose of 45 Gy for the spinal cord; a maximum dose of 70 Gy for the mandible; a mean dose of <26 Gy or dose to 50% of the

parotid volume ($D_{50\%}$) $<$30 Gy for the parotid gland and a mean dose of $<$50 Gy for the inner ear.

For ssIMRT, inverse planning was performed for each patient using CORVUS, version 5.0 (Nomos Corp., Sewickley, PA) and treatment was delivered using PRIMART (Siemens, CA) linear accelerator with 1-cm MLC. A standard coplanar 7- or 9-field gantry arrangement was used for designing all ssIMRT plans. Beam orientation was carefully chosen to achieve optimal parotid sparing. For HT, inverse planning was performed using the Tomotherapy Hi-Art System, version 2.0 (TomoTherapy, Madison, WI). Other parameters for tomotherapy planning included a field width of 2.5 cm, a pitch of 0.3 (distance traveled by the couch during one complete rotation of the gantry divided by the field width), and a modulation factor of 3.0 (a ratio of the maximum and average number of opening of the leaves in active gantry rotations). Both planning systems used least-square minimization as cost functions. Doses to OARs were optimized on an individual basis by a maximum dose constraints set without compromising the PTV coverage, with at least 95% of the PTV receiving the minimum prescribed dose.

Dosimetric Comparison Between ssIMRT and HT Plans

The two planning systems use different algorithms for dose calculation. CORVUS for ssIMRT planning uses finite-sized pencil beam algorithms and the work of Nizin (19), while the Hi-Art system for HT uses superposition convolution algorithm for dose calculation. We used heterogeneity correction options for both planning systems. The following parameters were chosen for PTV_{70} and PTV_{60} to evaluate the efficacy of IMRT planning and compare the treatment plans between ssIMRT and HT: a maximum dose (D_{max}), minimum dose (D_{min}), PTV receiving $>$95% of the prescribed dose ($V_{95\%}$) and PTV receiving $>$107% of the prescribed dose ($V_{107\%}$). In order to assess the uniformity of both plans, we used a uniformity index (UI), defined as the ratio between D_5 and D_{95}, where D_5 and D_{95} are the minimum doses delivered to 5 and 95% of the PTV, respectively.

Chemotherapy

Chemotherapy administered concurrently with external beam radiotherapy included weekly cisplatin 30 mg/m^2 (DDP), weekly cisplatin 20 mg/m^2 plus 5-fluorourcil (FU) 750 mg/m^2 (FP) and 5-FU 750 mg/m^2 plus taxotere 70 mg/m^2 plus cisplatin 75 mg/m^2 every third week (FTP). Radiotherapy with concurrent cisplatin has been the standard treatment for nasopharyngeal cancer in our institution since 2006. Before 2006, chemotherapy regimens were decided according to physicians' discretion, with the preference of FTP or FT regimens for more advanced disease including $\geq$T3 stage or N (+) disease. The IC regimen consisted of cisplatin at a dose of 75 mg/m^2 and 5-FU at 1000 mg/m^2 for 5 days (on days 1–5), repeated every 3 weeks, and followed by the concurrent chemoradiation (CCRT) regimens beginning 3 weeks after the third course of IC. Complete blood counts and blood chemistry were checked at least once a week and before each chemotherapy cycle. Dose modifications were allowed based on blood counts and toxicities from preceding cycles.

Follow-Up

The tumor response was assessed according to the World Health Organization (WHO) criteria, and acute and toxicities according to Radiation Therapy Oncology Group (RTOG) criteria. After completion of treatment, patients were followed up at the first, third and sixth month, and every 6 months thereafter. Physical examination, complete blood count, blood chemistry were performed at each visit, along with head and neck CT or MRI, chest radiography and PET or whole body bone scan every 6 months. Patients were evaluated for treatment response by nasopharyngoscopy and head and neck CT or MRI at the first, third and sixth month after completion of treatment. Biopsy was performed when residual disease or recurrence was suspected.

Statistical Analysis

Local failure-free survival (LFFS), locoregional failure-free survival (LRFFS), disease-free survival (DFS) and overall survival (OS) were measured from the beginning of radiotherapy. Descriptive statistics (mean, median and proportions) were used to characterize the patients, disease and treatment features, as well as toxicity after treatment. The probability of failure due to local disease, distant progression and death were estimated using the Kaplan–Meier method. An independent t-test was used to compare the dosimetric parameters between ssIMRT and HT. P values of $<$0.05 were considered having statistical significance.

RESULTS

Patient Characteristics

The median follow-up periods were 41 months (range: 8–89). Table 1 details patient characteristics. Median age was 45 years (range: 16–67), and the 35 male and 18 female were treated (66 vs. 34%). Two patients were diagnosed with keratinizing squamous cell carcinoma (WHO type I), 11 patients with non-keratinizing differentiated carcinoma (WHO type IIa), and 40 patients with non-keratinizing undifferentiated carcinoma (WHO type IIb). The numbers of patients with stage IIB, III, IVA, and IVB disease were 8, 24, 14 and 7 respectively. Forty-six patients underwent CCRT with weekly DDP in 36 patients, weekly FP in 6 patients, and FTP in 11 patients. Seven patients were treated with IC plus CCRT (IC + CCRT): IC was decided because radiotherapy was delayed due to pre-RT dental care or

Table 1. Patient characteristics ($n = 53$)

Characteristics	No. of patients	%
Age	Median: 45 years	Range: 16–67 years
Sex		
Male	35	66
Female	18	34
Pathology type		
WHO I	2	3.8
WHO IIa	11	20.8
WHO IIb	40	75.5
T stage		
T1	14	26.4
T2a	5	9.4
T2b	10	18.9
T3	9	17.0
T4	15	28.3
N stage		
N0	1	1.9
N1	20	37.7
N2	25	47.2
N3	7	13.2
Stage		
IIB	8	15.1
III	24	45.3
IVA	14	26.4
IVB	7	13.2
Treatment		
CCRT	46	86.8
IC + CCRT	7	13.2
Chemotherapy		
DDP	36	67.9
FP	6	11.3
FTP	11	20.8
Radiotherapy		
ssIMRT	28	52.8
HT	25	47.2

WHO, World Health Organization; CCRT, concurrent chemoradiation; IC + CCRT, induction chemotherapy followed by CCRT; DDP, cisplatin; FP, 5-fluorouracil plus cisplatin; FTP, 5-fluorouracil plus taxotere plus cisplatin; ssIMRT, step-and-shoot intensity modulated radiotherapy; HT, helical tomotherapy.

breakdown of IMRT machine in six patients and because of multiple large lymph node metastases in one patient. After introduction of HT in 2006, all nasopharyngeal cancer patients were treated using HT. Twenty-eight patients were treated with ssIMRT and 25 patients with HT.

Treatment Response and Survival

At the time of analysis, 44 out of 53 patients (83%) remained alive. Forty-nine patients (92.5%) showed a complete clinical and radiographic response (CR) at 3 months after initial treatment. Two patients showed a partial response: one remained with stable disease without further treatment and the other patient, who initially presented with left carotid artery invasion, died of massive bleeding from the treatment site 8 months after treatment. The remaining two patients had progressive disease. The 3- and 5-year Kaplan–Meier estimates for LFFS, LRFFS, DFS and OS were 91.8 and 91.8%; 87.6 and 87.6%; 77.5 and 70.5% and 86.4 and 82.1%, respectively (Fig. 1A–D).

Failure Pattern Analysis

A total of 13 treatment failures occurred: three local, two regional, one locoregional and seven distant failures (Table 2). All local/regional failures were in the regions that received 70 Gy (PTV_{70}). Two patients showed progressive disease after initial treatment: a 60-year-old male, progressed at the primary site (PTV_{70}) after CCRT and received salvage chemoradiation, and a 39-year-old male progressed at a cervical nodal site (PTV_{70}) after IC + CCRT and received salvage chemotherapy. Both patients died of progressive disease despite salvage treatments. The other 11 patients gained CR initially but showed treatment failure during the follow-up. A 37-year-old male with T2bN2 disease failed locally (nasopharynx, in the PTV_{70} region) 13 months after CCRT and died from distant metastasis despite a partial response to salvage chemoradiation. A 62-year-old female, initially staged T3N1, failed locally (skull base, in the PTV_{70} region) 3 months after IC + CRT, progressed after salvage chemotherapy but was still alive at the time of analysis. A 51-year-old male with regional failure (left neck level II, in PTV_{70}) had been staged initially T4N1 and recurred 30 months after treatment. He is alive and free of disease after salvage neck dissection and adjuvant chemoradiation. A 42-year-old male staged T3N2, failed locoregionally (clivus, in PTV_{70}; left neck level II, in PTV_{70}) at 32 months, and is alive with stable disease after salvage chemoradiation. Seven patients showed distant metastases at 4–48 months (median: 21) after treatment: three in the lungs, two in the chest wall, one in the liver and one in multiple sites. A 44-year-old male with a solitary lung metastasis is alive without disease after salvage resection, and other two lung-metastasis patients, a 33-year-old male and 58-year-old female, are alive with stable disease after salvage chemoradiation. The rest of the patients with distant metastasis expired despite various salvage efforts.

Dose–Volume Analysis

Dose–volume histograms (DVH) of the PTVs and critical organs were analyzed. The mean $V_{95\%}$ for PTV_{70} and PTV_{60}

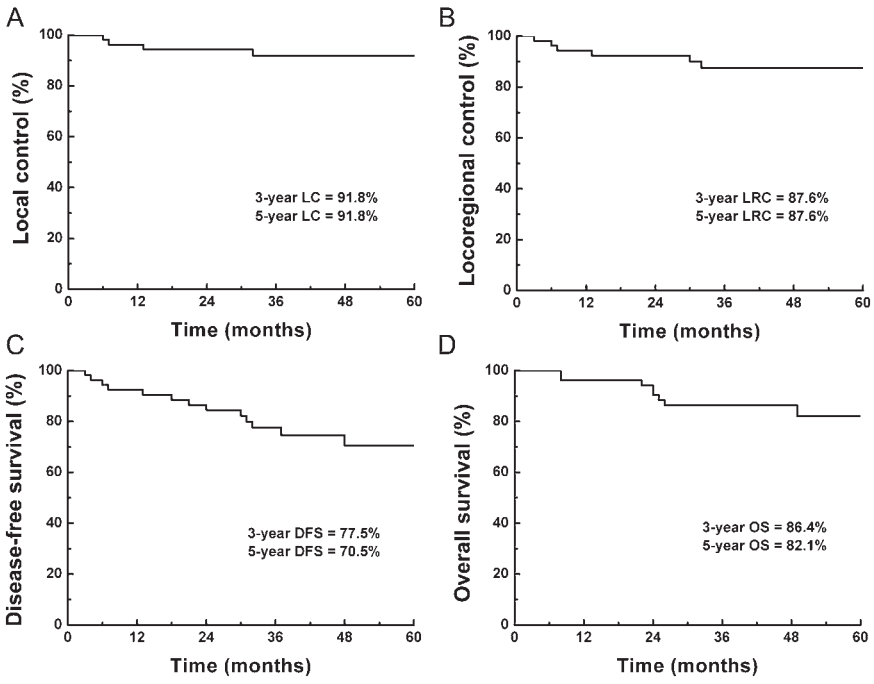

Figure 1. Kaplan–Meier estimated local control with numbers at risk (A), locoregional control with numbers at risk (B), disease-free survival with numbers at risk (C) and overall survival with numbers at risk (D).

Table 2. Treatment failures and results of salvage treatment

Sex/age	Stage	WHO type	Chemo	Initial response	Failure site	Recurrence time (months)	Salvage Tx	Last F/U	OS (months)
M/37	T2bN2	IIa	CCRT	CR	Local (PTV_{70})	13	CRT	DOD	24
M/60	T2aN1	IIb	CCRT	PD	Local (PTV_{70})	7	CRT	DOD	25
F/62	T3N1	IIb	IC + CCRT	CR	Local (PTV_{70})	6	Chemo	AWD	46
M/51	T4N1	IIb	CCRT	CR	Regional (PTV_{70})	30	OP + CRT	NED	42
M/39	T1N3b	IIb	IC + CCRT	PD	Regional (PTV_{70})	3	Chemo	DOD	22
M/42	T3N2	IIb	CCRT	CR	Locoregional (PTV_{70})	32	CRT	AWD	38
M/33	T2aN1	IIb	CCRT	CR	Chest wall	37	OP + CRT	DOD	79
M/44	T2bN2	IIb	CCRT	CR	Lung, single	48	OP	NED	81
F/49	T1N2	IIa	CCRT	CR	Mediastinum, abdomen	21	Chemo	DOD	49
F/33	T2N3a	IIb	CCRT	CR	Chest wall	4	CRT	AWD	47
M/58	T1N1	IIb	IC + CCRT	CR	Liver, LNs	31	Chemo	AWD	47
F/67	T4N1	IIb	CCRT	CR	Lung, multiple	15	Chemo	DOD	24
M/53	T4N1	IIb	CCRT	CR	Lung, multiple	18	Refuse	DOD	26

WHO, World Health Organization; CCRT, concurrent chemoradiation; IC + CCRT, induction chemotherapy followed by CCRT; CR, complete remission; PD, progressive disease; CRT, chemoradiation; DOD, died of disease; AWD, alive with disease; NED, no evidence of disease.

were 98.8 and 96.3%. The mean $V_{107\%}$ for PTV_{70} and PTV_{60} were 35.3 and 57.7%. The average maximum and minimum doses were 80.2 and 56.4 Gy for PTV_{70} and 79.3 and 33.4 Gy for PTV_{60}. The median UI was 1.12 for PTV_{70} and 1.25 for PTV_{60} (Table 3). Table 4 lists dose distribution to normal OARs. The maximum dose was calculated for serial normal organs. The median maximum doses to the spinal cord, brain stem, optic chiasm, right inner ear and left inner ear were 41.1, 50.8, 37.9, 43.8 and 43.9 Gy, respectively. The median mean dose was 21.8 Gy to the right parotid gland and 22.0 Gy to the left parotid gland.

Acute and Late Toxicity

All of the 53 patients completed their full course of radiotherapy. The median treatment duration was 49 days

Table 3. Comparison of dose-volume histogram parameters by radiotherapy modality

DVH parameters	ssIMRT ($n = 28$)	HT ($n = 25$)	Total ($n = 53$)	P value
PTV_{70}				
D_{max} (Gy)	82.0 ± 5.6	78.1 ± 2.7	80.2 ± 4.8	0.002
D_{min} (Gy)	55.9 ± 9.2	56.9 ± 9.7	56.4 ± 9.4	0.706
$V_{95\%}$ (%)	98.4 ± 2.9	99.3 ± 0.8	98.8 ± 2.2	0.111
$V_{107\%}$ (%)	44.9 ± 20.8	24.4 ± 22.3	35.3 ± 23.7	0.001
Median UI (range)	1.13 (1.07–1.25)	1.11 (1.01–1.16)	1.12 (1.01–1.25)	0.003
PTV_{60}				
D_{max} (Gy)	82.0 ± 5.7	76.2 ± 2.4	79.3 ± 5.3	<0.0001
D_{min} (Gy)	33.6 ± 5.6	33.1 ± 9.4	33.4 ± 7.6	0.805
$V_{95\%}$ (%)	96.1 ± 3.7	96.4 ± 5.5	96.3 ± 4.6	0.868
$V_{107\%}$ (%)	71.4 ± 15.3	42.4 ± 22.3	57.7 ± 23.7	<0.0001
Median UI (range)	1.23 (1.07–1.62)	1.20 (1.09–1.63)	1.25 (1.09–1.63)	0.001

DVH, dose-volume histogram; PTV_{70}, planning target volume receiving 70 Gy; D_{max}, maximum dose; D_{min}, minimum dose; $V_{95\%}$, PTV receiving >95% of the prescribed dose; $V_{107\%}$, PTV receiving >107% of the prescribed dose; UI, uniformity index; ssIMRT, step-and-shoot intensity modulated radiotherapy; HT, helical tomotherapy.

Table 4. Dose distribution for organs at risk ($n = 53$)

OARs	ssIMRT ($n = 28$)	HT ($n = 25$)	Total ($n = 53$)	P value
Spinal cord				
D_{max} (Gy)	41.72 ± 7.46	40.39 ± 7.06	41.09 ± 7.24	0.507
Brain stem				
D_{max} (Gy)	49.88 ± 6.98	51.89 ± 11.80	50.83 ± 9.52	0.462
Optic chiasm				
D_{max} (Gy)	37.62 ± 16.40	38.19 ± 17.66	37.91 ± 16.81	0.923
Rt. inner ear				
D_{max} (Gy)	41.44 ± 8.45	45.68 ± 8.45	43.77 ± 9.52	0.124
D_{mean} (Gy)	29.02 ± 8.14	29.70 ± 8.53	29.34 ± 8.25	0.778
Lt. inner ear				
D_{max} (Gy)	41.11 ± 8.02	47.28 ± 11.96	43.87 ± 10.33	0.041
D_{mean} (Gy)	28.90 ± 7.47	30.59 ± 10.72	29.66 ± 9.0	0.530
Rt. parotid gland				
D_{mean} (Gy)	20.75 ± 3.08	23.01 ± 5.39	21.81 ± 4.43	0.072
D_{50} (Gy)	19.16 ± 4.55	20.30 ± 6.04	19.70 ± 5.28	0.439
V_{30} (%)	18.95 ± 12.85	21.36 ± 15.59	20.08 ± 14.12	0.540
Lt. parotid gland				
D_{mean} (Gy)	20.51 ± 3.19	23.56 ± 6.80	21.95 ± 5.39	0.048
D_{50} (Gy)	19.25 ± 3.69	20.80 ± 6.57	19.98 ± 5.25	0.304
V_{30} (%)	17.18 ± 11.82	23.44 ± 20.24	20.13 ± 16.48	0.170

OARs, organs at risk; D_{50}, dose to 50% of parotid volume; V_{30}, parotid volume receiving >30 Gy.

(range: 41–65 days). Five patients experienced a treatment break of 4–7 days due to acute mucositis, two patients experienced 4 and 7 days of a treatment break due to acute dermatitis, and one patient rested for 2 weeks due to neutropenic fever. Acute and late toxicity by site and grade according to the RTOG criteria are listed in Table 5. For acute toxicity, Grade 3 mucositis, dermatitis and leucopenia were observed in 10, 1 and 2 patients, respectively. Only one patient suffered Grade 4 leucopenia due to chemotherapy. No other Grade 4 acute toxicity was observed. For late toxicity, 14 patients suffered Grade 2 xerostomia. One patient died of massive bleeding from the treatment site 8 months after CCRT. He had been initially diagnosed of T4N2 disease with the left carotid artery invasion and bilateral lymph node metastases including the left level II lymph nodes.

ssIMRT Versus HT

Table 3 shows the comparison of DVH parameters between the two groups of patients who were treated with ssIMRT ($n = 28$) and HT ($n = 25$). For both PTV_{70} and PTV_{60}, HT showed a maximum dose to the target (D_{max}) closer to the prescription dose [78.1 ± 2.7 vs. 82.0 ± 5.6 for PTV_{70} ($P = 0.002$); 76.2 ± 2.4 vs. 82.0 ± 5.7 for PTV_{60} ($P < 0.0001$)], lower hot-points ($V_{107\%}$) [24.4 ± 22.3 vs. 44.9 ± 20.8 for PTV_{70} ($P = 0.001$); 42.4 ± 22.3 vs. 71.4 ± 15.3 for PTV_{60} ($P < 0.0001$)] and superior uniform target coverage (UI) [1.11 vs. 1.13 for PTV_{70} ($P = 0.003$); 1.20 vs. 1.23 for PTV_{60} ($P = 0.001$)] compared with ssIMRT. The differences

Table 5. Toxicities by RTOG/WHO criteria

Toxicity	ssIMRT ($n = 28$)		HT ($n = 25$)		Total ($n = 53$)		P value
	No.	%	No.	%	No.	%	
Acute							
Mucositis							0.406
Grade 0	0	0	0	0	0	0	
Grade 1	5	17.9	7	28.0	12	22.6	
Grade 2	16	57.1	15	60.0	31	58.5	
Grade 3	7	25.0	3	12.0	10	18.9	
Grade 4	0	0	0	0	0	0	
Dermatitis							0.054
Grade 0	0	0	0	0	0	0	
Grade 1	15	53.6	21	84.0	36	67.9	
Grade 2	12	42.9	4	16.0	16	30.2	
Grade 3	1	3.6	0	0	1	1.9	
Grade 4	0	0	0	0	0	0	
Leukopenia							0.551
Grade 0	6	21.4	3	12.0	9	17.0	
Grade 1	9	32.1	13	52.0	22	41.5	
Grade 2	11	39.3	8	32.0	19	35.8	
Grade 3	1	3.6	1	4.0	2	3.8	
Grade 4	1	3.6	0	0	1	1.9	
Late							
Xerostomia							0.055
Grade 0	6	21.4	13	52.0	19	35.8	
Grade 1	12	42.9	8	32.0	20	37.7	
Grade 2	10	35.7	4	16.0	14	26.4	
Grade 3	0	0	0	0	0	0	
Grade 4	0	0	0	0	0	0	

RTOG, Radiation Therapy Oncology Group.

were statistically significant. Comparison of the dose distribution for OARs showed no significant differences between the two modalities, except for D_{max} to the left inner ear and D_{mean} to the left parotid gland, for which ssIMRT was superior (Table 4). HT showed a trend for improved dermatitis and xerostomia, although the differences were not significant between ssIMRT and HT (Table 5). Table 6 shows the comparison of clinical parameters and treatment outcomes among patients treated by ssIMRT and HT. N3 stage was more frequently found among the patients treated with HT (2 vs. 11%, $P = 0.028$), and more patients were treated with IC + CCRT in the HT group (2 vs. 11%, $P = 0.028$). The rates of 5-year local control, locoregional control, disease-free survival and overall survival between ssIMRT and HT were 93 vs. 89%, 89 vs. 85%, 77 vs. 66% and 85 vs. 83%. The differences were not statistically significant.

Table 6. Comparison of clinical factors and treatment outcome by radiotherapy modality

Clinical parameters	ssIMRT ($n = 28$)	HT ($n = 25$)	P value
Pathology			0.027
WHO I	2 (3.8%)	0 (0)	
WHO IIa	9 (17.0%)	2 (3.8%)	
WHO IIb	17 (32.1%)	23 (43.4%)	
T stage			0.707
T1–T2	16 (30.2%)	13 (24.5%)	
T3–T4	12 (22.6%)	12 (22.6%)	
N stage			0.028
N0–2	27 (50.9%)	19 (35.8%)	
N3	1 (1.9%)	6 (11.3%)	
Overall stage			0.862
IIB	4 (7.5%)	4 (7.5%)	
III–IVB	24 (45.3%)	21 (39.6%)	
Treatment			0.028
CCRT	27 (50.9%)	19 (35.8%)	
IC + CCRT	1 (1.9%)	6 (11.3%)	
5-year LCR	92.7% (83–100%)	88.6% (73–100%)	0.796
5-year LRCR	89.0% (77–100%)	84.9% (68–100%)	0.711
5-year DFS	76.8% (60–93%)	66.2% (45–88%)	0.196
5-year OS	84.6% (70–99%)	82.8% (67–98%)	0.542

LCR, local control rate; LRCR, locoregional control rate; DFS, disease-free survival; OS, overall survival.

DISCUSSION

NPC is primarily treated by radiation alone or CCRT and locoregional control through optimized radiation treatment remains an important goal. IMRT allows the delivery of increased dose of radiation to the tumor with a high degree of conformity, while sparing adjacent critical normal organs. IMRT is highly effective in delivering SIB for HNC cases. Convenience of a single-phase planning is not the only advantage of IMRT-SIB. The true advantage is in increasing the therapeutic ratio by permitting the differential delivery of escalated daily fraction sizes specifically to the gross disease and standard fraction sizes to the electively treated clinical target volumes, while effectively sparing adjacent critical organs. IMRT-SIB also allows greater conformity compared with other IMRT techniques. In a plan comparison study (20), IMRT-SIB achieved improved normal tissue sparing compared with sequential delivery of IMRT boost after either whole neck IMRT or conventional fields. The potential role of IMRT-SIB in improving local control through a moderate acceleration of the treatment has been identified in several HNC studies including nasopharyngeal cancer (20–23). In the current study, IMRT-SIB was used to treat all patients.

Forty-nine patients (92.5%) showed a complete clinical and radiographic response at 3 months after initial treatment and 2 patients showed a partial response. The 3- and 5-year local control and locoregional control rates were 91.8 and 91.8%, and 87.6 and 87.6%, respectively, showing the durable effect of treatment on disease control. The result of the current study is comparable to 2–4-year local control rates of 88–98% in the other SIB-IMRT studies for nasopharyngeal cancer (10,21,24,25) and significantly higher than 2-year local control of 54–67% from other clinical trials involving delayed concomitant boost for HNC treatment (26,27).

IMRT-SIB is advantageous with respect to counteracting the effects of accelerated tumor repopulation through several mechanisms. It had been demonstrated that the prolongation of the overall treatment time in laryngeal cancer may result in a loss of local control of ~1% per extra day (28). Moderate hypofractionation through SIB shortens the overall treatment time by several days or up to 1 week, and patients will benefit from improved local control without significantly increased toxicity. Early initiation of boost schedule may also improve local control, as IMRT-SIB allows the delivery of the boost dose from the beginning of radiotherapy. Terhaard et al. (29) demonstrated that a concomitant boost in week 3 compared with a boost in week 4 of the treatment schedule improved 3-year local control rate from 59 to 78%, with a notion that the accelerated repopulation had occurred sooner than expected and was counteracted by an early start of the boost schedule. NPC has a higher tendency of cervical lymph node metastasis compared with other HNCs. The early boost to individual metastatic cervical lymph nodes may account for the high control rate of regional disease in the current study. Another mechanism of improving local control is through more effective killing of cancer stem cells with larger fraction sizes. An increasing amount of evidence suggests that failure to eradicate cancer stem cells leads to tumor recurrence. Cancer stem cells, that are tumorigenic and capable of self-renewal, have been isolated from head and neck squamous cell carcinoma (11) and shown to be more radioresistant (12). Recently CD44+ cells with biological characteristics of tumor stem cells have been isolated from human NPC cell line (30).

In the current study, seven patients (13.2%) showed distant metastases at 4–48 months (median: 21) after treatment, while locoregional failure was observed in six patients (11.3%). The distant metastasis free survival (DMFS) rates of 89.7 and 81.9% at 3 and 5 years, respectively (results not shown), are comparable to the results of other studies involving accelerated RT with concurrent chemotherapy for nasopharyngeal cancer, where 3-year DMFS ranged from 79 to 90% (23,25). Although the addition of chemotherapy improves the treatment outcome of locally advanced NPC, toxicities such as hematologic toxicity and oral mucositis increase in the CCRT setting (31). Our study, however, demonstrated that the use of IMRT was highly effective in reducing acute and late toxicities such as Grade 3 or higher mucositis and xerostomia.

HT is an advanced form of IMRT. While ssIMRT delivers 5–9 intensity-modulated radiation beams at fixed gantry angles, HT utilizes a system of 360° rotational gantry and sliding patient couch resulting in the delivery of multiple intensity-modulated beams in a helical motion. Plan comparison studies between conventional IMRT and HT have shown superior dose conformity for PTV and dose sparing of OARs by HT (16,18,32). Lee et al. (18) compared ssIMRT and HT plans for nasopharyngeal cancer patients. SIB technique was used where 72, 64.8 and 54 Gy were prescribed to PTV, elective PTV and clinically negative neck regions, respectively. HT plans significantly improved the conformity index (improvement ratio: 11.9 ± 5.5%), homogeneity index (improvement ratio: 8.8 ± 1.5%) and sparing of OARs compared with ssIMRT plans. In the current study, 28 patients were treated with ssIMRT and 25 patients with HT. In dosimetric comparison, HT showed the maximum dose to target (D_{max}) closer to the prescription dose, lower hot-point ($V_{107\%}$) and superior UI coverage compared with ssIMRT for both PTV_{70} and PTV_{60}. The current study is not to show a direct plan comparison between ssIMRT and HT, since the two treatment plans had not been generated on identical patients. However, a single protocol of targeting and dose prescription was used for both ssIMRT and HT planning, and comparison of dosimetric parameters suggested superiority of HT in the clinical setting. Comparison of treatment outcome between ssIMRT and HT showed no significant difference in terms of local and locoregional control and patient survival. However, it is to be noted that the locoregional control rates of ssIMRT and HT were comparable in spite of the higher incidence of N3 disease among the patients treated with HT. We also noted that patients in the HT group did not report increased rate of mucositis despite the fact that most of the IC + CCRT cases (6/7) belonged to the HT group. We concluded that both ssIMRT and HT are highly effective in tumor control and sparing of normal organs for the treatment of NPC patients. Target volumes of more complicated shapes, stricter dose constraints for normal organs and longer follow-up periods are required to discriminate the two IMRT modalities in terms of clinical outcome.

A weakness of the current study is that a variety of chemotherapy schedule was used including three different CCRT regimens and IC administered in seven patients. However, all patients received concurrent chemotherapy in the current study, and we expect that locoregional control is mostly a result of adequate radiation coverage with concomitant boost through IMRT-SIB. A prospective trial with a uniform protocol of combined modality treatment is required to accurately assess the role of IMRT-SIB in locoregional control of NPC.

Moderately accelerated radiotherapy through IMRT-SIB with concurrent chemotherapy was well tolerated and highly efficacious for the treatment of NPC, resulting in durable locoregional control and minimized toxicity. Further accumulation of clinical data is required to compare treatment outcomes between conventional IMRT and HT.

Conflict of interest statement

None declared.

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