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High-Dose Static and Dynamic Intensity-Modulated Radiotherapy Combined with Chemotherapy for Patients with Locally Advanced Nasopharyngeal Carcinoma Improves Survival and Reduces Brainstem Toxicity

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Statistical Analysis C
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Background: Intensity-modulated radiotherapy (IMRT) is the standard treatment for patients with nasopharyngeal cancer (NPC). However, the dose-volume criteria for adjacent anatomically normal organs at risk (OARs) remain controversial. The aim of this study was to evaluate the effects of higher than conventional doses of static and dynamic IMRT on the locoregional control of NPC, patient survival, and brainstem radiation toxicity.

Material/Methods: Patients (n=186) with stage III and stage IVa NPC underwent high-dose static and dynamic IMRT treatment (68–76.96 Gy) with or without chemotherapy for 34–57 days. Overall survival (OS), the presence of distant metastases, and brainstem toxicity were assessed. One-year, three-year, and five-year follow-up was performed.

Results: High-dose IMRT alone or in combination with chemotherapy resulted in a 100% objective response rate and significantly improved OS rates, with one-year, three-year, and five-year OS rates of 94.1%, 89.8%, and 88.2%, respectively. The local recurrence rate (17.6%), and distant metastasis to the lung, liver, and bone (17.2%), and mortality (n=22) were reduced. Chemotherapy was the only factor that was significantly correlated with patient survival. Brainstem toxicity was reduced in patients treated with static IMRT (0.07%) and dynamic IMRT (0.08%). There were 26 additional factors that were not found to significantly affect brainstem toxicity.

Conclusions: High-dose static or dynamic IMRT combined with chemotherapy improved survival and reduces distal metastasis with a very low occurrence of brainstem toxicity in patients with locally advanced NPC. These findings might provide therapeutic guidance for clinicians when planning optimal dose-volume IMRT parameters.

MeSH Keywords: Chemoradiotherapy • Nasopharyngeal Neoplasms • Radiotherapy

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Background

Nasopharyngeal carcinoma (NPC) is a malignancy of nasopharyngeal epithelium and is diagnosed in approximately half a million people per year worldwide and leads to 34.1 million deaths annually [1,2]. NPC is endemic in East and Southeast Asia, occurring in 15–50 per 100,000 people, while it occurs less commonly (1 per 100,000 people) in other regions in the world [3]. Histologically, NPC can be subclassified into three subtypes, keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma, and undifferentiated carcinoma [4,5].

Radiotherapy has been recommended for early-stage NPC due to the complex anatomic location and high radiosensitivity of the tumors and is commonly used in combination with other treatments, typically induction or concurrent chemotherapy for locally-advanced stage NPC, which is when the majority of cases are diagnosed [2,6]. Advances in radiotherapy technology and the application of chemotherapy, together with accurate diagnosis and staging have improved the prognosis of NPC [7].

Traditional two-dimensional radiation therapy (2D-RT) employing 4–6 MV X-ray or cobalt-c 60 γ irradiation has been curative for early-stage NPC, with a locoregional control rate of 76.7–93% [8]. However, the efficacy of 2D-RT is significantly reduced, with a locoregional control rate of 58–79%, and for advanced-stage NPC, due to the limitation of the radiation dose affecting adjacent normal organs [8]. Three-dimensional conformal radiotherapy (3D-CRT) uses computed tomography (CT) or magnetic resonance imaging (MRI) to generate three-dimensional images of individual tumors as well as the adjacent organs at risk (OARs), to ensure conformal dose distribution within the target regions, while sparing the nearby normal organs and tissues.

The current standard radiotherapy for NPC, intensity-modulated radiotherapy (IMRT), is an advanced 3D-CRT technique that allows balanced target coverage and minimizes local radiation damage [9]. Several studies have demonstrated the advantages of IMRT over conventional radiotherapy in reducing radiation-associated toxicities and improving the quality of life for the patient [9–16]. With the development of computation, multileaf collimators (MLCs), these are now widely applied in static IMRT and dynamic IMRT. The MLCs in static IMRT separates each radiation beam into a set of smaller segments of differing MLC shape, and the radiation beam is turned off between the sections. Whereas each radiation beam in dynamic IMRT remains switched on by continuously moving the MLCs [17,18]. Therefore, an improved clinical outcome has been achieved in the treatment of NPC by using both static and dynamic methods [19,20]. However, it remains unclear which treatment approach is for patients with locally advanced NPC.

Although IMRT is now well developed and regularly used, there is still the potential risk of radiation damage to the brainstem, especially in patients with Stage T3–T4 NPC when the tumor is adjacent to the brainstem. Commonly, during IMRT planning, the radiation dose is prescribed based on the dose constraints for critical organs at risk (OARs), and the maximal IMRT dose for tumors near the brainstem is lower than the conventional radiation dose. According to the findings from the Radiation Therapy Oncology Group (RTOG) trial (0225), the recommended maximal dose for IMRT should not exceed 54 Gy or 60 Gy for locally advanced NPC [21]. These thresholds were established based on dosimetry data from conventional two-dimensional and three-dimensional radiotherapy [9,22].

However, when the planned target volume (PTV) is similar to or overlaps with the planned organ at risk volume (PRV), the maximal PRV dose delivered often exceeds the conventional radiation dose recommended by RTOG [21]. Therefore, it is questionable whether such dose constraints are most effective in clinical practice, in terms of patient clinical outcome. Also, sometimes it is difficult for clinicians to achieve a satisfactory outcome under the restriction of an IMRT dose for stage T3–T4 NPC [7,10,22–26]. Currently, there are few reports regarding the study of brainstem radiation toxicity in patients treated for NPC [22]. Apart from radiation dose, the distance between the planned target volume (PTV) and the planned organ at risk volume (PRV) needs to be taken into account to adjust the amount of radiation to the brainstem [9]. These requirements necessitate further characterization of the tolerance of OARs in patients undergoing IMRT.

The questions that remain are what is the optimum effective IMRT dose that spares radiation damage to the brainstem and whether the use of static IMRT or dynamic IMRT make any difference to the effects on the brainstem and to clinical outcome. Therefore, this study aimed to evaluate the effects of high-dose static and dynamic IMRT on the locoregional control of NPC, patient survival, and brainstem radiation toxicity, using static or dynamic IMRT, with or without cisplatin. The short-term and long-term patient survival and the effect of radiation on the brainstem were assessed to provide guidance for future radiation planning.

Material and Methods

Patient recruitment

Between October 2009 and October 2012, a total of 186 patients with locally advanced nasopharyngeal carcinoma (NPC) were recruited from The First Affiliated Hospital of Guangxi Medical University, China. All patients provided with written informed consent to participate in the study. The study was

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approved by the Human Research Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (No: TF-ECN-2010ES091008).

All patients had previously untreated, histologically confirmed locally advanced NPC without distant metastases other concomitant malignancies or brain disorders. The patients were treated with radical intensity-modulated radiation therapy (IMRT) at doses higher than the findings from the Radiation Therapy Oncology Group (RTOG) trial (0225) [21], that is 1% of the brainstem received a dosage higher than 60 Gy and followed up for at least 60 months or until deaths. Patients with previous brainstem hemorrhage or a history of head and neck irradiation were excluded. All patients underwent tumor restaging according to the 7th edition of The American Joint Committee on Cancer (AJCC) Cancer Staging Manual [27].

Radiotherapy protocols and measurements

Patients were treated with radiation for 34–57 days (median, 44 days). During the treatment, the head and neck and shoulders of the patient were immobilized with a thermoplastic mask lying in a supine position. Radiation was performed by intravenous contrast-enhanced computed tomography (CT) using a Siemens Somatom Emotion16 (Siemens, Munich, Germany) with 3 mm of slice thickness and the target region delineating from the vertex to 3 mm inferior to the clavicle.

The target volumes were defined according to the International Commission on Radiation Units and Measurements Reports (*https://icru.org*). Treatment planning volume (TPV), gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were determined according to the tumor location, size, invasion, and involvement of adjacent lymph nodes, which were determined by imaging, clinical, and endoscopic observations. GTV described the range of tumors estimated by imaging examination, including the primary nasopharynx (GTVnx) and nodal gross tumor volumes (GTVnd). Clinical target volume, including GTV and immediately neighboring microscopic tumor or lymph node extension, was determined by defining a high-risk region, CTV1, and a low-risk lymph nodal region, CTV2. Planning target volume (PTV) included the CTV plus 3–5 mm margins to account for uncertainties associated with patient positioning and internal movement during the radiation treatment.

Clinical target volume 1 (CTV1) generally includes GTV with a 5–10 mm margin as well as the entire nasopharynx, the parapharyngeal space, skull base, sphenoid sinus, ethmoid sinus, pterygopalatine fossae, the posterior third of the nasal cavity and maxillary sinuses, and bilateral upper deep jugular nodes. CTV2 was defined as regions outside CTV1 with 5–10 mm margins and low-risk lymph nodal regions. When the CTVs were near critical organs, such as the brainstem or spinal cord, the margins were limited to 1–3 mm.

Clinical target volume 2 (CTV2) was defined as lymph node regions at low risk, including the lymph node regions of the neck which were not included in the CTV1. The PTV_C was defined as including the CTV with a 3 mm margin in all directions. However, when the CTV was near critical organs, such as the brainstem and spinal cord, the PTV generated was as low as 1 mm.

Organs at risk (OARs) were also mapped out on CT, including the brainstem, spinal cord, pituitary glands, temporal lobes, eyeballs, optic lens, optic nerves, optic chiasm, middle ear, inner ear, parotid glands, throat, tongue, temporomandibular joints, and lower jaw. Radiation to OARs was conventionally limited according to the findings from the RTOG trial (0225) [21], and determined by the distance from the primary tumor and the tolerance of the organs. However, these doses were insufficient to achieve radical removal of tumors in patients with skull base and cerebral invasion, compromising the local disease control and increasing the risk of tumor recurrence. All patients received, with written consent, relatively higher doses than those recommended from the RTOG 0225 trial [21], after being informed of the risks associated with radiotherapy, particularly the adverse effects on the brainstem.

Static IMRT

Radiation planning was performed using a Pinnacle Treatment Planning System, version 7.6 (Philips, Amsterdam, The Netherlands) with 7–9 radiation fields. Individual plans were designed to minimize radiation to OARs, particularly the brainstem, and dose volume histograms (DVHs) were applied for quantitative evaluation. The isocenter was positioned at the GTV geometrical center and the radiation plan evaluated by a physicist. IMRT was performed using a Primus Linear Accelerator (Siemens, Munich, Germany) at 2.2–2.4 Gy/fraction per day for five days a week, up to a prescription total of 68.6–76.4 Gy (mean, 72.8 Gy). Dose volume histograms (DVHs) of the target areas, and OARs were recorded and analyzed.

Dynamic IMRT

Dynamic IMRT was planned and conducted using an Eclipse Treatment Planning System (Varian, Palo Alto, CA, USA) and included 7–9 radiation fields, which were designed to minimize the impacts on the OARs, including the brainstem. The radiation plan was quantitatively evaluated with the use of the DVH. The isocentre was placed at the GTV geometrical center, and the collimator angle was zero degrees. Dynamic IMRT was performed using a Varian Clinac iX 4948 Accelerator with 120 multileaf collimators, at 2.2–2.4 Gy/fraction per day and for five

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days a week up to a total of 68.0–76.96 Gy (mean, 70.89 Gy). DVHs of the target areas and OARs were recorded and analyzed.

Chemotherapy

All patients with stage III and IVa NPC in this study were recommended to have a combined treatment of radiotherapy and chemotherapy. There were 164 out of 186 patient who received cisplatin-based chemotherapy (80 mg cisplatin/m^2) at three weeks per cycle, with 2–4 cycles in total; 22 patients refused chemotherapy treatment. As shown in Table 1, there were 52 patients who were treated with concurrent chemotherapy, 50 patients with induction plus concurrent chemotherapy, 52 patients with concurrent and adjuvant chemotherapy, and ten patients with induction, concurrent, and adjuvant chemotherapy.

Patient follow-up

Patient follow-up commenced from the end of radiotherapy by examining re-hospitalized patients, reviewing treatment plans, and outpatient assessments. Blood tests and imaging were performed every three months for the first two years, every six months for the next three years, and every 12 months after five years. The effect of treatment on the brainstem and the short-term and long-term efficacy of treatment were evaluated based on routine blood tests and biochemistry, chest X-ray, abdominal ultrasound, head and neck magnetic resonance imaging (MRI), the presence of distant metastases, chest and abdominal computed tomography (CT), and whole-body bone scintigraphy.

Assessment and analysis of treatment efficacy and adverse effects

MRI was performed on all patients before the radiation treatment to confirm the absence of any abnormality in the brain and spinal cord. Damage to OARs, with the primary focus on the brainstem, were examined and new-onset of neurological symptoms after radiotherapy were compared with known reported effects of radiation-induced brainstem injury [8,23]. The clinical effects resulting from cancer progression, metastases, traumatic brain injury, or neurodegenerative disorders were excluded.

Short-term efficacy was evaluated following the World Health Organization criteria for tumor-response assessment [28,29], and categorized into the complete response (CR) and partial response (PR). The objective response rate (ORR) was calculated as a total of CR and PR. Long-term efficacy was assessed by Kaplan–Meier analysis of the patient overall survival (OS), local tumor control, and the distant metastasis-free survival. Data analysis was performed using the chi-squared (χ^2) test and using Statistical Product and Service Solutions (SPSS) version 22.0. Adverse effects on the brainstem were assessed using a Cox's stepwise regression model. A P-value <0.05 was considered as statistically significant.

Results

Patient characteristics

Among the 186 patients with locally advanced nasopharyngeal carcinoma (NPC) recruited into the study, there were 131 men and 55 women, aged between 19–76 years (median, 44 years). The baseline clinicopathological characteristics of the patients are summarized in Table 1. The staging classification of the tumor, node, and metastasis (TNM) was based on the American Joint Committee on Cancer (AJCC) 2010 staging system [27]. There were 60 patients with stage III NPC and 126 patients with stage IVa NPC identified, including 57 patients with T3 tumors and 129 patients with T4 tumors. Regional lymph node assessment identified 12 cases of N1, 106 cases of N2 and 68 cases of N3 NPC. The majority of patients presented with non-keratinizing squamous carcinoma. All 186 patients received radiotherapy, and 164 out of 186 patients underwent chemotherapy. Of these patients, 32 also had hypertension and 17 had diabetes mellitus.

Complete response (CR), partial response (PR), objective response rate (ORR) locoregional control, overall survival (OS), and objective response rate (ORR)

Dosimetric parameters of intensity-modulated radiotherapy (IMRT) for all patients are summarized in Table 2. A median dose of 72 Gy (range, 68.00–76.96 Gy) was determined and delivered in 31–33 fractions. Twenty-two patients in this study accepted IMRT only, while the others were also treated with cisplatin, for 2–4 cycles at 80 mg/m^2, as induction, concurrent, and/or adjuvant therapy (Table 1). At the three-month follow-up, all groups showed a 100% objective response rate (ORR) (Table 3). IMRT treatment alone led to complete response (CR) in 20 patients and partial response (PR) in the other two patients. The inclusion of chemotherapy into the treatment plan improved the short-term outcome (Table 3), with all patients demonstrating CR when cisplatin was used concurrently with and after IMRT, but no statistically significant difference was observed, based on the chi-squared test.

By November 2017, all patients had been followed-up for 13–81 months (median, 61 months). The one-year overall (OS), local recurrence-free (LRFS), and distant metastasis-free survival (DMFS) rates were 94.1%, 91.4%, and 87.1%, respectively (Figure 1). The three-year OS, LRFS, and DMFS were 89.8%, 85.0%, and 83.3%, respectively; and the five-year OS, LRFS, and DMFS were 88.2%, 82.3%, and 82.8%, respectively.

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Table 1. Demographic and clinico-pathological characteristics of the patients.

Characteristics		Value
Age (years)	Median	44
	Range	19–76
Gender	Male	131
	Female	55
Smoking	Yes	98
	No	88
Alcohol drinking	Yes	91
	No	95
Complications	Hypertension	32
	Diabetes	17
histopathological types	Keratinizing squamous cell carcinoma	13
	Differentiated non-keratinizing carcinoma	170
	Undifferentiated non-keratinizing carcinoma	3
TNM classification		
Primary tumor	T3	57
	T4	129
Regional lymph nodes	N1	12
	N2	106
	N3	68
Stage	III	60
	IVa	126
Chemotherapy	Concurrent chemotherapy	52
	Induction plus concurrent chemotherapies	50
	Concurrent and adjuvant chemotherapies	52
	Induction, concurrent, and adjuvant chemotherapies	10
	Refuse chemotherapy	22

Table 2. Dosimetric parameters of IMRT for all 186 patients and the radiation to the brainstems.

Evaluation indicator	Prescribed dose	GTV dose	Radiation to the brainstem													
			Volume	Dose	Dmax	D2	D5	Dmean	D98	Dmin	V55		V60		V65	
	(Gy)	(Gy)	(cm^3)	(Gy)	(Gy)	(Gy)	(Gy)	(Gy)	(Gy)	(Gy)	R(%)	A(cm^3)	R(%)	A(cm^3)	R(%)	A(cm^3)
Mean	72.36	74.55	29.59	45.08	67.31	59.79	56.54	35.92	14.76	11.29	9.06	3.11	3.52	1.25	0.64	0.24
Median	72.00	74.37	26.60	48.15	62.71	59.60	56.06	36.33	14.35	9.55	8.21	3.07	3.03	0.98	0.29	0.11
Minimum	68.00	70.14	12.48	41.53	61.77	53.58	48.06	18.59	1.65	1.14	4.62	1.23	1.13	0.23	0.00	0.00
Maximum	76.96	78.48	61.46	69.01	73.28	68.04	65.53	49.01	38.03	34.03	33.88	16.10	21.18	10.31	6.38	3.42
STDEV	1.49	1.36	9.51	3.23	2.78	3.52	3.868	7.51	9.62	8.09	4.17	1.88	2.43	1.09	0.90	0.45

R – relative volume to the brainstem; A – absolute volume; STDEV – standard deviation; GTV – gross tumour volume; Dmax – the maximum dose; Dmean – the mean dose; Dmin – The minimum dose; D2 – maximal dose to 2% of the volume; D5 – maximal dose to 5% of the volume; D98 – maximal dose to 98% of the volume; V55 – dose received is more than 55 Gy of the volume, including relative and absolute volume; V60 – dose received is more than 60 Gy of the volume, including relative and absolute volume; V65 – dose received is more than 65 Gy of the volume, including relative and absolute volume.

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Table 3. Response of patients at the 3-month follow-up.

Treatments	Cases	Short-term response	
		CR	PR
IMRT	22	20 (91.9%)	2 (9.1%)
IMRT-concurrent cisplatin	52	50 (96.2%)	2 (3.8%)
IMRT-induction+concurrent cisplatin	50	49 (98.0%)	1 (2.0%)
IMRT-concurrent+adjuvant cisplatin	52	52 (100.0%)	0
IMRT-induction+concurrent+adjuvant cisplatin	10	10 (100.0%)	0

CR – complete remission; PR – partial remission.

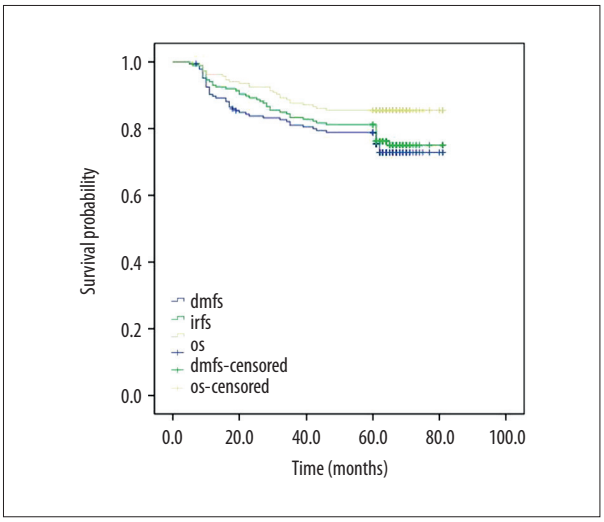

Figure 1. Overall survival (OS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) of patients in the study with nasopharyngeal carcinoma (NPC) treated with high-dose intensity-modulated radiotherapy (IMRT).

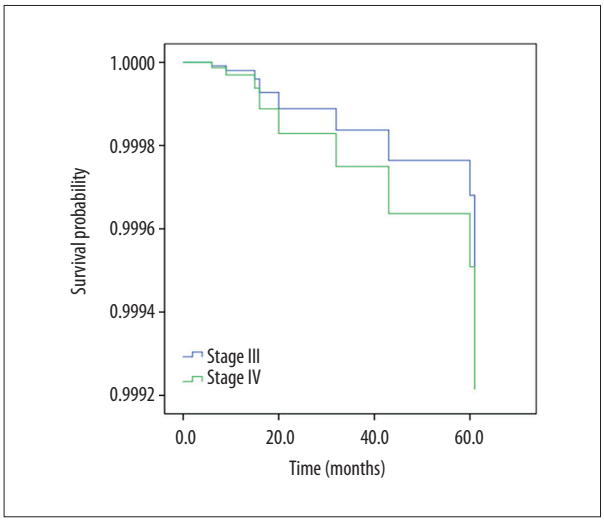

Figure 2. Overall survival (OS) of patients with stage III and stage IV nasopharyngeal carcinoma (NPC).

No statistically significant difference was found between the OS of stages III and IVa patients (P=0.15) (Figure 2).

Multivariate analysis showed that and chemotherapy was identified as the only factor that significantly correlated with patient survival (P=0.012) (Table 4). Other clinical factors included in the analysis were age, gender, radiation doses, radiation treatment time, tumor classification and histopathological types, cigarette and alcohol use, and concomitant disease, and were found to have no significant effect on the patient outcome (Table 4). Comparison of patients treated with combined IMRT and chemotherapy with those by IMRT alone showed that inclusion of chemotherapy in the treatment plan delayed the occurrence of distant metastasis and local recurrence of NPC (Table 5). Both static and dynamic IMRT were used in the study, as monotherapy or used in combination with chemotherapy, but no statistically significant difference was found between the two types of IMRTs in short-term response, disease progression, and patient survival.

Overall disease progression was found in 50 patients. Thirty-three patients showed local recurrence within the radiation fields, accounting for 17.6% of the total patients. Distant metastasis was found in 32 patients (17.2%), including 15 patients with contemporaneous local recurrence. Metastases were most frequently seen in the lung (14 patients), liver (nine patients), and bone (seven patients). During the study, 22 patients died, including seven treated with IMRT only, five with IMRT and concurrent cisplatin, six with IMRT and induction and concurrent cisplatin, and two from each of the other two treatment groups (Table 6). Concurrent and adjuvant cisplatin infusion significantly reduced the NPC-associated mortality.

Radiation to the brainstem and adverse effects

Patients underwent high-dose IMRT for 34–57 days in combination with different types of chemotherapy. The adverse effect on OARs was monitored, with specific attention to the brainstem considering this previously reported association with IMRT [17,25]. As summarized in Table 2, the brainstem received a median dose of 48.15 Gy (range, 41.53–69.01 Gy).

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Table 4. Multivariate analysis of factors affecting survival.

Variables	Significance
Age (years)	0.732
Prescribed dose	0.234
Radiation treatment time	0.191
Maximum dose	0.430
Minimum dose	0.695
Average dose	0.780
Classification	0.694
Histopathological types	0.801
Chemotherapy	0.012
Gender	0.429
Smoking	0.089
Alcohol drinking	0.807
Concomitant disease	0.991

In this study, 15 patients demonstrated radiation toxicity to the brainstem. Static and dynamic IMRTs exhibited no significant difference in their effects on the brainstem. Eight of 94 patients (0.08%) who underwent dynamic IMRT showed brainstem damage, including two cases of Grade I, three cases of Grade II, and two cases of Grade III damage, which were scored according to the Subjective, Objective, Management, Analytic (SOMA) Late Effects of Normal Tissue (LENT) system. Among 92 patients who received static IMRT, seven patients (0.07%) including one case of Grade I, four cases of Grade II, and two cases of Grade III radiation damage were found.

At a mean gross tumor volume (GTV) dose of 74.55 Gy (range, 70.14–78.48 Gy), the maximum dose (Dmax) delivered to the brainstem was 61.77–73.28 Gy, with a median of 62.71 Gy, while the mean dose (Dmean) was 18.59–49.01 Gy (Table 2, Figure 3). The highest radiation exposure of 2% (D2) of the brainstem was 53.58–68.04 Gy, and the minimum radiation to the remaining 98% of the brainstem was1.65–38.03 Gy. The median level of radiation received by 5% (D5) of the brainstem was 56.07 Gy. A radiation dose >55 Gy was delivered to 4.62–33.88% of the brainstem (corresponding with 1.23–16.1 cm^3 in volume);

Table 5. Overall, local recurrence-free, and distant metastasis-free survival rates in patients*.

Treatments	Cases (n)	1-year			3-year			5-year		
		OS	LRFS	DMFS	OS	LRFS	DMFS	OS	LRFS	DMFS
IMRT	22	19 (86.4%)	18 (81.8%)	15 (68.2%)	16 (72.7%)	15 (68.2%)	13 (59.1%)	15 (68.2%)	13 (59.1%)	13 (59.1%)
IMRT-concurrent cisplatin	52	50 (96.2%)	49 (94.2%)	**47 (90.4%)**	48 (92.3%)	44 (84.6%)	**44 (84.6%)**	**47 (90.4%)**	**43 (82.7%)**	**44 (84.6%)**
IMRT-induction+concurrent cisplatin	50	46 (92.0%)	45 (90.0%)	43 (86.0%)	44 (88.0%)	43 (86.0%)	**42 (84.0%)**	44 (88.0%)	**43 (86.0%)**	**42 (84.0%)**
IMRT-concurrent+adjuvant cisplatin	52	51 (98.1%)	49 (94.2%)	**49 (94.2%)**	**51 (98.1%)**	**48 (92.3%)**	**49 (94.2%)**	**50 (96.2%)**	**47 (90.4%)**	**48 (92.3%)**
IMRT-induction+concurrent+ adjuvant cisplatin	10	9 (90.0%)	9 (90.0%)	8 (80.0%)	8 (80.0%)	8 (80.0%)	7 (70.0%)	8 (80.0%)	7 (70.0%)	7 (70.0%)

* Statistically significant values in comparison with IMRT were calculated by Fisher's exact test and are shown in bold.

Table 6. Mortality of patients under different treatments.

Treatments	Cases	Mortality (n)			
		LR	DM	Unknown	*P**
IMRT	22	2	5	0	
IMRT-concurrent cisplatin	52	1	3	1	0.03
IMRT-induction+concurrent cisplatin	50	2	2	2	0.09
IMRT-concurrent+adjuvant cisplatin	52	0	1	1	0.002
IMRT-induction+concurrent+adjuvant cisplatin	10	0	1	1	0.38

* Significance was calculated by a Fisher's exact test, and deaths of patients with local recurrence and distant metastases within each treatment were added up prior to comparison. LR – local recurrence; DM – distal metastasis.

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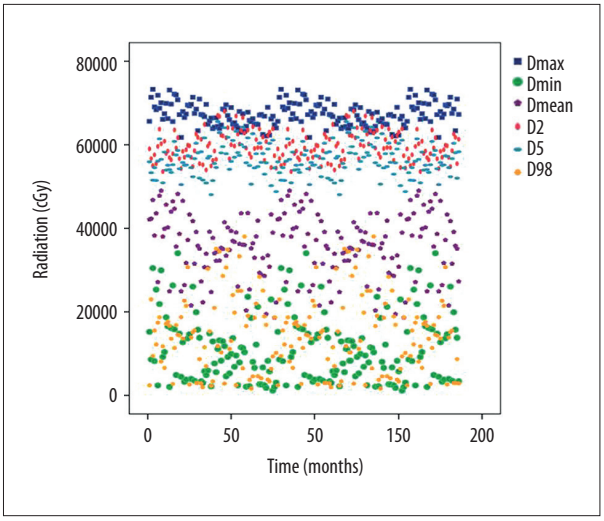

Figure 3. Dot plots of the radiation dose to the brainstem in 186 cases of nasopharyngeal carcinoma (NPC) treated with high-dose intensity-modulated radiotherapy (IMRT).

>60 Gy to 1.13–21.18% of the brainstem (corresponding with 0.23–10.31 cm^3); and >65 Gy to 0–6.38% of the brainstem (corresponding with 0–3.42 cm^3).

Multivariate analysis was performed to identify factors that might affect brainstem response. Twenty-six factors including age, gender, smoking and alcohol drinking, TNM classification, histopathological tumor type, brainstem volume, chemotherapy, concomitant diseases, and a range of radiation dosimetric parameters were assessed, but none was found to affect brainstem response to radiation (Table 7).

Discussion

Intensity-modulated radiotherapy (IMRT) permits highly conformal radiation delivery to the tumor while minimizing the dose to the healthy tissues. IMRT allows accurate shaping of the radiation field and adjustment of the dose-intensity of individual radiation beams and is currently a standard treatment approach in the management of patients with nasopharyngeal carcinoma (NPC) [7,12]. The advantage of IMRT over conventional two-dimensional radiotherapy (2D-RT) and three-dimensional chemoradiotherapy (3D-CRT) have been commonly recognized, particularly for the treatment of early-stage NPC [12]. However, radiotherapy of locally advanced NPC remains technically challenging due to the proximity of the tumor to organs at risk (OARs), including the brainstem, which limits the dose and field coverage, contributing to the poor prognosis for patients with NPC [30,31].

Previously reported escalation of radiation dose has been attempted successfully for advanced NPC [31]. However, the associated radiation toxicity has yet to be characterized in a large

Table 7. Multivariate analysis of factors affecting the response of the brainstem to radiation.

Variable	Significance	Variable	Significance
Age (years)	0.91	Highest dose – Brainstem	0.191
Prescribed dose	0.559	Lowest dose – Brainstem	0.140
Radiation treatment time	0.389	Average dose – Brainstem	0.372
Maximum dose	0.490	D2	0.706
Minimum dose	0.480	D5	0.720
Average dose	0.759	D98	0.416
Classification	0.580	V55 relative value	0.183
Histopathological type	0.567	V55 absolute value	0.243
Chemotherapy	0.328	V60 relative value	0.390
Gender	0.587	V60 absolute value	0.300
Smoking	0.844	V65 relative value	0.697
Alcohol drinking	0.217	V65 absolute value	0.921
Concomitant disease	0.164	Volume of brainstem	0.900

D2 – maximal dose to 2% of the volume; D5 – maximal dose to 5% of the volume; D98 – maximal dose to 98% of the volume; V55 – dose received is more than 55 Gy of the volume, including relative and absolute volume; V60 – dose received is more than 60 Gy of the volume, including relative and absolute volume; V65 – dose received is more than 65 Gy of the volume, including relative and absolute volume.

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cohort of patients. Therefore, in this study, a group of 186 patients with stage III and stage IVa NPC were treated IMRT with radiation doses higher than the limit recommended by the findings from the Radiation Therapy Oncology Group (RTOG) trial (0225) [21], in the presence or absence of cisplatin, and the effect on the brainstem was examined.

Static or dynamic IMRT at a prescribed dose of 68–76.96 Gy was undertaken in this study in all 186 patients, with the aim of improving locoregional control. The doses were comparable with the previously reported escalation dose, according to the gross tumor volume (GTV), of 76 Gy, which was used in combination with chemotherapy for patients with T3 and T4 NPC, and proved to be feasible and beneficial to patient outcome [31]. The results of the present study showed a 100% objective response rate (ORR) in all patients at the three-month follow-up. IMRT treatment alone achieved a complete response (CR) in 20 out of 22 patients, and a partial response (PR) in the other two cases. The combination of cisplatin infusion showed no significant further improvement in short-term disease control. These data indicate that it is feasible to apply the dose conformity of IMRT to boost the dose for NPC treatment and improve locoregional control.

The one-year, three-year, and five-year overall survival (OS) rates of all patients were 94.1%, 89.8%, and 88.2%, respectively, which compared favorably with the findings of a previous phase 2 trial of simultaneous modulated accelerated radiotherapy combined with concurrent cisplatin treatment on stage III–IVa NPC [32] and with a more recent study of IMTR with cisplatin-based chemotherapy on T4 NPC [33].

In the present study, the advantage of combining chemotherapy with high-dose IMRT, in 164 patients, became gradually more apparent with time, with a three-year OS rate of 92.1%, compared with an OS rate of 72.7% for patients treated with IMRT alone (P=0.013). The five-year OS rate was 90.9% compared with an OS rate of 68.2% for patients treated with IMRT monotherapy (P=0.006). This finding correlated with significantly prolonged local recurrence-free survival (LRFS) rates and distant metastasis-free survival (DMFS) rates for patients treated with chemotherapy (Table 3). Patients treated with IMRT and induction, concurrent, and adjuvant chemotherapy also showed a trend of an increased five-year OS, LRFS, and DMFS rates, despite the lack of statistical significance, due to the limited number of patients in this group. The results of this study highlight the importance of combining chemotherapy with high-dose IMRT in the management of locally advanced NPC. These findings are consistent with those of recently published studies showing that improvements in tumor control were attributed to improved IMRT and increasing use of more effective chemotherapy [34,35].

The dose-volume criteria for the brainstem during radiotherapy to protect this critical organ has yet been established and remains controversial [23,25,26,36-38]. A maximum dose (Dmax) ranging from 50–56 Gy has been recommended [10,31,32,34–40], and the dose >60 Gy has previously been recommended to be less than 1% [10,35,37,40–45]. In this study, radiation dose to the brainstem exceeded these thresholds. As a result, 15 of 186 patients demonstrated damage to the brainstem, whereas the other 171 patients exhibited no apparent effects, suggesting a possibly wider window of tolerance for this critical organ when receiving IMRT. Also, none of other 26 factors examined in this study were associated with brainstem toxicity, which is inconsistent with a previous study showing skull-based surgery, diabetes, and hypertension [25], younger patient age, and the use of hyperfractionated radiotherapy [38] were related to brainstem radiation toxicity. Also, there was no significant difference in brainstem damage in patients receiving dynamic IMRT (0.08%) and static IMRT (0.07%).

The findings of the present study showed that for patients with advanced NPC and large tumor size, increasing the dose of IMRT rarely adversely affected the brainstem. This finding is consistent with the findings of recent studies showing that brainstem necrosis is rare in NPC after long-term follow-up of a large cohort of NPC patients receiving a higher dose of IMRT [46]. It has also been previously reported that a Dmin ≥54.0 Gy to the gross tumor volume (GTV) demonstrated excellent local control with few late toxicities for stage T3–T4 NPC treated with IMRT plus docetaxel, cisplatin and fluorouracil chemotherapy [35]. Also, the findings of the present study showed that there were no statistically significant differences in brainstem damage between static and dynamic IMRT treatment. These findings indicated that more flexible criteria with strict restrictions in the high-dose range of IMRT regardless of static or dynamic IMRT could be a choice for advanced NPC. The study findings also support that reconsideration of the radiation tolerance of the brainstem should be made, with the prerequisites of optimal target region delineation, dose prescription, beam angle selection, and reverse planning, to improve the locoregional lesion control and prolong the patient survival of locally advanced NPC.

Conclusions

An increased dose of intensity-modulated radiotherapy (IMRT), at doses exceeding the currently used upper limit, was performed in a group of 186 patients with locally advanced nasopharyngeal carcinoma (NPC), in the presence or absence of chemotherapy. A 100% objective response rate (ORR) was achieved in the short-term. The one-year, three-year, and five-year overall survival (OS) rates were 94.1%, 89.8%, and 88.2%, respectively.

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There was no radiation-associated toxicity to the brainstem in the majority of patients. The findings of this study suggest that for patients with locally advanced NPC, with a large tumor size who may have limited available therapeutic options, high-dose IMRT might improve patient survival. Further large-scale controlled studies are recommended to support the findings from this study, with the aim of providing further guidance for clinicians and radiotherapists when planning radiation treatment and the choice of optimal IMRT dose.

Competing interests

None.

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