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Long-term survival outcomes and adverse effects of nasopharyngeal carcinoma patients treated with IMRT in a non-endemic Region: an experience from northwest China

Running title: A study of IMRT in nonendemic region of China

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Abstract

Objectives: To evaluate the long-term survival outcomes and adverse effects of intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) and to summarize the experiences of IMRT in NPC in the past few decades in non-endemic northwest China.

Design: A population-based retrospective study.

Setting: An experience of using IMRT in nonendemic region of China.

Participants: The study included 792 newly diagnosed and non-metastatic NPC patients who received IMRT from January 2006 to September 2018 in Xijing Hospital.

Outcome measures: The survival outcomes, adverse effects, and failure patterns were evaluated by univariate, multivariate, and subgroup analyses.

Results: With a median follow up time of 46.2 months, the 5-year local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) rates were 90.8%, 97.0%, 82.8%, 69.6%, and 78.0%, respectively. Multivariate analysis showed that age, N stage, clinical stage, pathological type, and primary tumor volume of more than 23cm^3 were the independent prognosis factors for DFS (all p-values < 0.05); age, N stage, pathological type, cervical lymph node necrosis (CNN), and anemia were significantly associated with OS (all p-values < 0.05). The most common acute toxicities of IMRT were dermatitis, mucositis, and dysphagia. Xerostomia and hearing impairment were the top two late toxicities. The main failure patterns were distant metastasis and local and/or regional relapses.

Conclusions: Similar survival, toxicities, and failure patterns have been observed in patients treated with IMRT in a non-endemic area of China when compared with that in endemic areas. Induction chemotherapy (IC) combined with concurrent chemoradiotherapy (CCRT) may benefit locally advanced NPC in non-endemic areas of China.

Keywords

Nasopharyngeal carcinoma (NPC), Nonendemic region, Intensity-modulated radiotherapy (IMRT), Survival, Adverse effects

Strengths and limitations of this study

1. Our study summarizes the experiences of IMRT in NPC in the past few decades in northwest non-endemic area of China.
2. The clinical characteristics, survival outcomes, long-term adverse effects and failure patterns were reported.
3. A large cohort study (n=792) and long-term follow-up (46.2 months).
4. This study is expected to lay the foundation for conducting future prospective study.
5. The limitations of this study are that the patients are derived from a single centre and the study's retrospective design.

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelium malignancy with a characteristic of unbalanced regional distribution. Statistics revealed that more than 70% of newly diagnosed NPCs are in east and southeast Asia. It is prevalent in southern China, with the world age-standardized rate of approximately 3.0 per 100,000 compared with 0.4 per 100,000 in Western countries.[1, 2] In China, the morbidity and mortality of NPC were evidently higher in the southern area than that in the other areas while the northern area ranks the lowest.[3]

Radiotherapy (RT) is the primary treatment modality for NPC due to the high sensitivity of nasopharyngeal tumors to radiation. With the progression of radiation techniques, radiotherapy has changed from conventional two-dimensional radiotherapy (2D-CRT) to three-dimensional conformal radiotherapy (3D-CRT) and to more advanced intensity-modulated radiotherapy (IMRT). Nowadays, IMRT is the most widely used technique in radiotherapy. Local or regional controls and survival have been improved by the parallel advantages of dosimetric properties and reduced toxicity.[4-6] The 5-year loco-regional relapse rate of non-metastatic NPC has been reduced to 7.4%. [7] Furthermore, IMRT was closely related to a better 5-year overall survival (OS) when compared with 2D-CRT or 3D-CRT, along with significantly reduced toxicities such as xerostomia, trismus, and temporal lobe neuropathy.[5] However, these data are mainly acquired from experiences in epidemic regions. To date, the literature related to the long-term survival outcomes and radiation-induced toxicities of a large cohort of patients who underwent IMRT in non-endemic regions are limited. Thus, in the current study, we intend to comprehensively evaluate the survival outcomes and adverse effects of patients treated with IMRT in a non-endemic region of China.

Materials and Methods

Patients

From January 2006 to September 2018, a total of 792 patients were included in the study. The inclusion criteria were as follows: (1) patients from northwest region of China, (2) pathologically confirmed NPC, (3) previously untreated, (4) no evidence of distant metastasis,

(5) no previous malignancies or other concomitant malignant diseases, and (6) received a whole course of IMRT and no molecular targeted therapy.

Radiotherapy

IMRT was delivered within two weeks of completion of the induction chemotherapy (IC). External megavoltage photons were used to treat primary lesions and cervical lymph nodes. The gross tumor volume (GTV) included the entire nasopharygeal tumors (GTVnx) and the positive lymph nodes of the neck (GTVnd). The clinical target volume (CTV) contained the adjacent areas at risk for microscopic disease. The high-risk clinical target volume (CTV1) was the GTV plus the entire nasopharyngeal mucosa, retropharyngeal lymph nodes, skull base, parapharyngeal space, pterygopalatine fossa, sphenoid sinus, posterior third of the nasal cavity, and maxillary sinus. The low-risk clinical target volumes (CTV2) covered the lower neck without lymph node metastasis and supraclavicular fossa. The planning target volumes (PTVs) were delineated by adding 3-mm margins to the GTVs and CTVs. The prescribed radiation doses were 70-74 Gy/30-33 fractions for the PTV of primary tumors (GTVnx-P), 68-74 Gy/30-33 fractions for the PTV of positive lymph nodes (GTVnd-P), 60-64 Gy/30-33 fractions for the PTV of CTV-1, 50-54 Gy/30-33 fractions for the PTV of CTV-2. All patients were treated with 2 Gy/fraction daily for five consecutive days per week. The doses for the normal tissues and organs at risk were confined below tolerance levels.

Chemotherapy

Overall, chemotherapy was administered to 93.9% of patients. The details of the chemotherapy strategy are illustrated in Table 1. The regimens for induction and adjuvant chemotherapy (AC) were TPF, TP, PF, and GP. The TPF regimen consisted of docetaxel (75 mg/m^2) intravenously (IV) on day 1, cisplatin (75 mg/m^2) continuously (IV) on days 1-3, and fluorouracil (500 mg/m^2) continuously (IV) on days 1-5. The TP regimen was administered as docetaxel (75 mg/m^2; IV) on day 1 and cisplatin (75 mg/m^2) continuously (IV) on day 1. The PF regimen comprised of cisplatin (75 mg/m^2; IV) on day 1 and fluorouracil (500 mg/m^2) continuously (IV) on days 1-5. The GP regimen included cisplatin (75 mg/m^2; IV) on day 1 and gemcitabine (1000 mg/m^2; IV) on days 1 and 8. All the regimens were repeated every 3

weeks for 2-3 cycles for IC and every 4 weeks for 2-3 cycles for AC. CCRT consisted of cisplatin-based chemotherapy that was administered as cisplatin (40 mg/m^2; IV) weekly or cisplatin (80-100 mg/m^2) every 3 weeks during radiation.

Table 1. Patient and treatment characteristics.

Patient characteristics	**Number/Mean(range)**
Age (year)	47.3 (9-83)
Tumor volume (mL)	22.5 (2.4-232.0)
Lymph nodes size (cm)	1.7 (0.8-8.9)
Gender (Male/Female)	566/226
Age (＜50 years/≥50 years)	446/346
T stage (T1/T2/T3/T4)	87/277/133/295
N stage (N0/N1/N2/N3a/N3b)	105/186/347/64/90
Clinical stage (Ⅰ/Ⅱ/Ⅲ/Ⅳa/Ⅳb)	22/124/246/246/154
WHO Histology (Ⅰ/Ⅱ/Ⅲ)	3/210/579
Diagnostic imaging technique	
MRI	792
Chemotherapy	
RT/CCRT/IC+CCRT/IC+RT/CCRT+AC/RT+AC/IC+CCRT+AC/IC+RT+AC	48/243/365/51/21/8/55/1
CNN (Yes/No)	401/391

Abbreviations: RT= Radiotherapy; CCRT = concurrent chemo-radiotherapy; IC= Induction chemotherapy; AC=Adjuvant chemotherapy; CNN= cervical nodal necrosis; MRI = Magnetic resonance imaging; WHO = World Health Organization.

Follow-up

The patients were evaluated for treatment response and adverse effect after IMRT as follows: every 2-3 months for the first 2 years, then every 3-4 months for years 3-5, and annually thereafter. The examination items included the following: physical examinations, flexible

nasopharyngoscope, chest X-ray or computerized tomography (CT), abdominal ultrasonography or CT, magnetic resonance imaging (MRI) of the head and neck, and a bone scan when necessary. The acute radiotherapy and chemotherapy related toxicities were assessed by the National Cancer Institute Common Toxicity Criteria (version 4.0). For evaluating the late adverse effects of radiotherapy, the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) were applied.[8]

Statistical analysis

Statistical analyses were performed with SPSS software (version 22.0). Specifically, overall survival (OS) was measured from the end of treatment to the observation of death caused for any reason; disease free survival (DFS) was measured from the end of treatment to the first discovery of tumor recurrence or metastasis or death for any reason; local relapse-free survival (LRFS) and regional recurrence-free survival (RRFS) were measured from the end of treatment to the first observation of local recurrence and regional recurrence, respectively; distant metastasis-free survival (DMFS) was measured from the end of treatment to the observation of distant metastasis. The Kaplan Meier method was used to draw survival curves and the log rank test was applied to compare differences. Multivariable analyses were conducted with a Cox proportional hazard model and the hazard ratio (HR) and the corresponding 95% confidence interval (CI) were calculated. Categorical and continuous variables were compared with a $\chi 2$ test and an independent t-test, respectively. In all cases, a two-sided p-value less than 0.05 was considered to be statistically significant.

Ethical statement

Approval of our study was granted by the Ethics Committee of Xijing Hospital, Air Force Military Medical University, Xian, China. Signed informed consent forms were kindly provided by each patient.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or

dissemination plans of this study.

Results

The characteristics of patients

A total of 792 patients were included. The distribution of the patients is presented in Table 1. Overall, the median age was 47.3 years (with a range of 9-83 years) and the male (n=566)-to-female (n=226) ratio was 2.5:1. The mean volume of primary tumor was 22.5 mL (with a range of 2.4-232 mL). The mean diameter of metastatic cervical lymph nodes was 1.7 cm (with a range of 0.8-8.9cm). The distribution of clinical stage was 22 (2.8%), 124 (15.7%), 246 (31.1%), 246 (31.1%), and 154 (19.4%) for stages I, II, III, IVa, and IVb, respectively. The majority of patients were histologically diagnosed as WHO II (n=210; 26.5%) and WHO III (n=579; 73.1%), except for three patients who were diagnosed as WHO I (n=3; 0.4%). An MRI of the head and neck was selected as the diagnostic imaging technique for all patients. Nearly all patients (93.9%) received chemotherapy, in various patterns, such as CCRT (n=243, 30.7%), IC+CCRT (n=365; 46.1%), IC+RT (n=51; 6.4%), CCRT+AC (n=21; 2.7%), RT+AC (n=8; 1.0%), IC+CCRT+AC (n=55; 6.9%) and IC+RT+AC (n=1; 0.1%). The median follow-up time was 46.2 months (with a range of 1.3-130.2 months).

Survival outcomes

Overall, the 5-year LRFS, RRFS, DMFS, DFS, and OS rates were 93.4%, 97.0%, 82.8%, 69.6%, and 78.0%, respectively (Figure 1). There were significant differences in the DFS and OS rates between the subgroups of age, T-stage, N-stage, clinical stage, histology, and cervical nodal necrosis (CNN). In addition, we found that tumor volume was associated with DFS and anemia, with or without chemotherapy (CCRT, IC, and AC) were related to OS. Significant differences in DMFS rates were observed between subgroups of N-stage, clinical stage, histology, tumor volume, CNN, EBV-DNA copy number, anemia, and with or without chemotherapy. Also, we found CNN and AC were associated with LRFS, and only IC was related to RRFS. Specifically, the patients with T4 disease had a marginally higher risk of local relapse than the patients with T1 disease (χ^2=1.699; p=0.053). After clinical stage stratification by N stage, the RRFS rates were significantly lower in the N3 stage than in the

N1 stage (χ^2=4.916; p=0.027), while the differences were not significant between other subgroups (Table 2).

Table 2. Characteristics of 792 patients and univariate analysis of prognostic factors.

Factor	No	DFS（%）		OS（%）		DMFS（%）		LRFS（%）		RRFS（%）	
		5y	P value	5y	P value	5y	P value	5y	P value	5y	P value
Age											
＜50y	446	85.7	0.013*	86.8	0.001*	88.4	0.766	95.0	0.676	97.5	0.710
≥50y	346	83.3		80.2		87.2		93.1		97.0	
Gender											
Male	566	87.9	0.459	81.7	0.871	89.1	0.598	95.2	0.882	98.5	0.612
Female	226	80.4		83.6		85.2		93.3		98.9	
T											
T1	87	85.9	0.038*	90.7	0.019*	89.2	0.230	94.2	0.358	97.1	0.381
T2	277	83.3		87.6		86.9		93.9		96.9	
T3	133	79.7		81.4		84.8		92.9		96.2	
T4	295	74.9		79.2		82.7		91.8		98.2	
N											
N0	105	84.6	0.004*	89.5	0.005*	89.9	0.005*	94.0	0.558	100.0	0.179
N1	186	76.7		81.6		87.5		90.7		97.1	
N2	347	73.2		79.9		82.6		89.6		97.3	
N3a/3b	154	72.7		74.6		77.4		91.0		93.5	
Clinical stage											
Ⅰ	22	85.7	0.000*	89.3	0.000*	87.3	0.004*	90.7	0.879	97.4	0.512
Ⅱ	124	83.5		83.3		85.9		90.6		98.9	
Ⅲ	246	74.7		79.1		82.8		91.2		97.9	
Ⅳa/b	400	59.6		72.5		76.1		89.3		97.8	
Histology											
WHO	210	76.8	0.046*	79.1	0.006*	81.3	0.034*	90.1	0.267	98.1	0.739

Ⅱ											
WHO	579	83.4		88.1		86.9		91.9		98.5	
Ⅲ											
Tumor volume(ml)											
＜23ml	304	82.6	0.013*	84.6	0.567	85.5	0.042*	92.3	0.178	97.8	0.231
≥23ml	488	73.4		79.5		80.3		89.4		95.3	
CNN (cervical nodal necrosis)											
No	391	81.8	0.000*	83.1	0.015*	86.9	0.032*	96.6	0.097	99.0	0.165
Yes	401	73.1		80.6		76.5		94.3		97.7	
EB-DNA copy number											
＜ 5000 copy /ml	743	80.5	0.564	82.9	0.768	84.9	0.098	91.9	0.452	97.9	0.987
≥5000 copy /ml	49	78.5		79.7		81.3		90.4		98.0	
Anemia											
No	706	80.2	0.124	80.3	0.032*	83.3	0.079	95.4	0.479	99.8	0.546
Yes	86	77.6		71.2		79.5		90.3		95.4	
Concurrent chemotherapy											
No	108	81.2	0.193	79.2	0.064	80.0	0.051	89.5	0.559	97.4	0.635
Yes	684	83.2		82.2		85.3		91.0		98.2	
Induction chemotherapy											
No	320	84.7	0.638	79.9	0.052	81.1	0.104	92.9	0.413	97.1	0.041*
Yes	472	86.2		85.1		77.7		91.0		99.1	
Adjuvant chemotherapy											
No	707	84.7	0.089	83.6	0.039*	87.2	0.525	93.3	0.062	98.9	0.819
Yes	85	79.1		77.6		81.3		90.2		96.6	

Abbreviations: DFS = disease-free survival; OS = overall survival; DMFS = distant metastasis-free survival; LRFS = local relapse free survival; RRFS = regional relapse free survival; WHO = World Health Organization; CNN= cervical nodal necrosis; IC= Induction chemotherapy; AC=Adjuvant chemotherapy.

Multivariate analysis

To do the multivariate analysis, statistically significant factors (p-value less than 0.1) of DFS, OS, DMFS, LRFS and RRFS rates in univariate analyses were enrolled into the Cox regression model. The results showed that age, N-stage, clinical stage, histology, and the volume of primary tumor were independent prognostic factors for DFS. Concerning DMFS, we only identified N-stage and cervical node necrosis (CNN) as the significant prognostic factors. Furthermore, we found that age, N-stage, histology, CNN and anemia were significantly correlated with OS (Table 3).

Table 3. Multivariate Analysis of Variables Correlated with Various Clinical Endpoints.

End-point	Factors	HR	95%CI	P Value
DFS	Age (＜50y versus ≥50y)	1.013	1.002-1.024	**0.018**
	T stage (T1-2 versus T3-4)	1.040	0.882-1.227	0.642
	N stage (N0-1 versus N2-3)	1.490	1.134-1.958	0.004
	Clinical stage (Ⅰ-Ⅱ versus Ⅲ-Ⅳb)	1.031	1.017-1.045	0.000
	Histology (WHO Ⅱ versus WHO Ⅲ)	2.025	1.358-3.020	0.001
	Tumor volume(＜ 23ml versus ≥23ml)	3.025	1.277-7.167	0.012
	CNN (No versus Yes)	1.225	0.967-1.553	0.093
	AC (No versus Yes)	0.870	0.641-1.180	0.370
OS	Age(＜50y versus ≥50y)	1.823	1.328-2.502	0.000
	T stage (T1-2 versus T3-4)	1.117	0.921-1.355	0.260

	N stage (N0-1 versus N2-3)	1.276	1.004-1.618	0.043
	Clinical stage (Ⅰ-Ⅱ versus Ⅲ-Ⅳb)	1.163	0.881-1.534	0.287
	Histology (WHO Ⅱ versus WHOⅢ)	0.690	0.504-0.932	0.016
	CNN (No versus Yes)	2.191	1.038-4.625	0.040
	Anemia (No versus Yes)	0.573	0.378-0.868	0.009
	Concurrent chemotherapy (No versus Yes)	0.810	0.617-1.064	0.130
	IC (No versus Yes)	1.158	0.978-1.371	0.089
	AC (No versus Yes)	1.484	0.990-2.222	0.056
DMFS	N stage (N0-1 versus N2-3)	2.397	1.627-3.531	0.000
	Clinical stage (Ⅰ-Ⅱ versus Ⅲ-Ⅳb)	1.185	0.990-1.419	0.064
	Histology (WHO Ⅱ versus WHOⅢ)	0.654	0.412-1.037	0.071
	Tumor volume(＜23ml versus≥23ml)	1.113	0.931-1.330	0.241
	CNN (No versus Yes)	1.210	1.013-1.444	0.036
	EBV-DNA copy number (<5000copy/ml versus ≥5000copy /ml)	1.183	0.965-1.448	0.105
	Anemia (No versus Yes)	1.116	0.881-1.415	0.362
	Concurrent chemotherapy (No versus Yes)	0.816	0.599-1.111	0.197
LRFS	CNN (No versus Yes)	0.930	0.521-1.660	0.806
	AC (No versus Yes)	1.296	0.773-2.172	0.326
RRFS	IC (No versus Yes)	0.946	0.198-4.519	0.944

Abbreviations: DFS = disease-free survival; OS = overall survival; DMFS = distant

metastasis-free survival; LRFS = local relapse free survival; RRFS = regional relapse free survival; WHO = World Health Organization; CNN= cervical nodal necrosis; IC= Induction chemotherapy; AC=Adjuvant chemotherapy; WHO = World Health Organization.

Adverse effects

There were 792 and 737 patients who were followed up for more than 1 year and were included to assess the acute and late chemo-radiotherapy related toxicities, respectively (Table 4). The most common acute toxicities for radiation were grade I and II dermatitis (534/792; 67.4%), mucositis (520/792; 65.7%), and dysphagia (632/792; 79.8%). The most frequent late toxicity after treatment was xerostomia with occurrence rates of grade I 108 (14.6%), grade II 354 (48.15%) and grade III 108 (14.6%). The incidence rate of xerostomia was significantly increased when combined with synchronous chemotherapy (79.3% vs. 60.2%; p-value=0.002). Grade I hearing impairment (525; 71.2%) was the second most common late toxicity of IMRT. Likewise, combined cisplatin-based chemotherapy increased the incidence rate of hearing impairment caused by radiation (80.6% vs. 15.2%; p-value<0.001). The main grade III acute toxicities of radiotherapy were dermatitis (68/792; 8.6%) and mucositis (64/792; 8.1%). The only detected grade III acute toxicities of chemotherapy was neutropenia (31/792; 3.9%). As for the late toxicities, only 108 patients (14.6%) had grade III xerostomia. Remarkably, no severe grade IV toxicities were observed in our cohort.

Table 4. Treatment-related toxicities.

Toxicities	**No. of patients by toxicity grade (%)**				
	0	**1**	**2**	**3**	**4**
Acute toxicity related to radiotherapy	190（24.0）	320	214	68（8.6）	0（0）
Dermatitis	208（26.3）	（40.4）	（27.0）	64（8.1）	0（0）
Mucositis	160（20.2）	300	220	0（0）	0（0）
Dysphagia		（37.9）	（27.8）		
Acute toxicity related to	724（91.4）	516	116	0（0）	0（0）

chemotherapy	699（88.3）	（65.2）	（14.6）	0（0）	0（0）
Anemia	398（50.3）			31（3.9）	0（0）
Thrombocytopenia	747（94.3）	62（7.8）	6（0.8）	0（0）	0（0）
Neutropenia	238（30.0）	52（6.6）	41（5.2）	0（0）	0（0）
Febrile neutropenia	0（0）	214	149	0（0）	0（0）
Vomiting	669（84.5）	（27.0）	（18.8）	0（0）	0（0）
Hand–foot syndrome	0（0）	40（5.1）	5（0.6）	0（0）	0（0）
Ototoxicity		476	78（9.9）		
Neuropathy	167（22.7）	（60.1）	0（0）	108	0（0）
The late toxicities (737 patients)	716（97.2）	0（0）	0（0）	（14.6）	0（0）
Xerostomia	723（98.1）	123	0（0）	0（0）	0（0）
Neck fibrosis	680（92.3）	（15.5）		0（0）	0（0）
Trismus	200（27.1）	0（0）	354	0（0）	0（0）
Dysphagia	0（0）		（48.1）	0（0）	0（0）
Hearing impairment	731（99.2）	108	0（0）	0（0）	0（0）
Temporal necrosis		（14.6）	0（0）	0（0）	
Cranial nerve palsy		21（2.8）	18（2.4）		
		14（1.9）	12（1.6）		
		39（5.3）	0（0）		
		525	0（0）		
		（71.2）			
		0（0）			
		6（0.8）			

Failure patterns

During the follow-up period, we observed 162 (20.5%) deaths and 196 (24.7%) treatment failures. A shown in Table 5, the major cause of failure was distant metastasis (n=118; 60.2%), followed by local failure (n=60; 30.6%), regional failure (n=18; 9.2%). Concerning the causes of death, distant metastasis ranked the first, while other causes, such as

radiotherapy or chemotherapy-related complications (n=5), other malignant tumors (n=1), no cancer causes (n=3), and unknown causes (n=2), only account for a tiny proportion of the deaths. In our cohort, 87.3% (103/118) of patients developed distant metastasis within 3 years after treatment. The median time for the appearance of distant metastasis was 16.2 months (with a range of 0.8-68.3 months). In patients with distant metastasis, 68 (68/118, 57.6%) had solitary metastasis to the bone, lung, liver, distant lymph nodes, or parotid lymph nodes. Among these patterns, 4 (4/118; 3.4%) had extra regional lymph node metastasis (axillary lymph node metastasis and mediastinal lymph node metastasis), and 2 (2/118; 1.7%) had intraregional parotid lymph node metastasis. There were 45 patients (45/118; 40.7%) developed two sites of metastasis, and the specific metastatic sites and cases are shown in Table 6. In addition, 78 (9.8%) patients developed local or regional failures, with the median recurrence time of 27.0 months (range 4.4-92.3 months). The salvage treatments for these patients were re-irradiation for 62 patients with local failures, surgery for 3 patients with regional failures, and palliative chemotherapy for patients who appropriate.

Table 5. Failure patterns of all patients.

Variable	No. of patients (%)
Pattern of failure	
Distant metastasis	118(14.9%) [a]
Local and/or regional failures	78(9.8%) [a]
Local failures alone	60(7.6%)
Regional failures alone	18(2.3%)
Local and regional failures	9(1.1%)
Distant + local/regional failures	15(1.9%)
Total	196(24.7%)

Cause of death	
Distant metastasis	106(13.4%)
Local or regional failure	45(5.7%)
radiotherapy or chemotherapy-related complications	5(0.6%)
Other malignant tumors	1(0.1%)
No cancer causes	3(0.4%)
Unknown causes	2(0.3%)
Total	162(20.5%)

[a]The number includes the 15 patents with both distant and local/regional failures.

Table 6. Sites of distant metastasis (n=118).

Site of distant metastasis	**No.**
Solitary	
Bone	50
Lung	38
Liver	36
Distant Lymph Nodes	5
Parotid Lymph Nodes	3
Two sites	
Bone & Lung	15
Bone & Liver	12
Lung & Liver	8

Lung & Distant lymph nodes	3
Liver& Distant lymph nodes	1
Parotid Lymph Nodes & Distant Lymph Nodes	2
Epidural & spine	2
Multiple sites	
Bone & Lung & Liver	4
Others	1

The effect of chemotherapy

We further evaluated the effect of combining chemotherapy with IMRT in NPC patients. The most frequently used strategies in our institution were IC plus CCRT (n=365; 46.1%) and CCRT (n=243; 30.7%). During induction chemotherapy, 72.4% (358/472) of patients were treated with docetaxel-based chemotherapy, while 15.0% (71/472) of patients received a gemcitabine-based regimen. The survival analyses demonstrated that there were no significant differences of LRFS, RRFS, DMFS, and OS rates among these regimens of IC or AC. As for IC, specifically, the 5-year DFS and OS rates showed a trend of improving survival in the subgroup of TPF/TP as compared with other regimens, but significant differences were not achieved. In comparison of different AC regimens, these trends were not observed (Table 7).

Table 7. The 5-year estimated survival rates stratified by various regimens of chemotherapy of locally advanced nasopharyngeal carcinoma.

5y	LRFS（%）	RRFS（%）	DMFS（%）	OS（%）
IC regimens				
TPF/TP	95.7	97.8	82.3	90.6
GP	93.1	94.2	73.2	74.2
PF	90.6	93.0	76.3	71.3
others	90.0	93.3	71.2	68.4

χ2	0.156	2.134	2.145	0.313
P value	0.652	0.123	0.276	0.576
AC regimens				
TPF/TP	90.6	92.1	71.8	77.7
GP	89.2	94.3	76.0	79.3
PF	88.1	100	71.4	74.1
others	90.1	88.9	77.7	72.7
χ2	0.117	0.392	0.356	2.242
P value	0.732	0.576	0.516	0.243

Abbreviations: LRFS = local relapse free survival; RRFS = regional relapse free survival; DMFS = distant metastasis-free survival; OS = overall survival; IC= Induction chemotherapy; AC=Adjuvant chemotherapy.

Discussion

IMRT has been generally recognized as the standard radiation technique for NPC patients (NCCN guidelines for head and neck cancer, version 1, 2019). However, studies comparing the survival outcomes and adverse effects of NPC patients treated with IMRT between endemic and non-endemic regions are limited. In the current study, we reported an experience of IMRT for non-metastatic NPC in a non-endemic area of China (northwest China) based on a large cohort (n=792) and long follow-up time (46.2 months).

In recent years, literature has shown that IMRT was significantly associated with improved therapeutic effects of NPC patients. A prospective study enrolled 616 cases of non-metastatic NPCs (306 cases in the IMRT group and 310 cases in the 2D-CRT group) with a median follow-up time of 42 months to compare the survival outcomes. The results confirmed that IMRT was more effective than 2D-CRT. The 5-year LRFS and OS rates increased from 84.7% to 90.5% and 67.1% to 79.6%, respectively. The IMRT related toxicities were significantly lower than that of 2D-CRT.[4] In a retrospective analysis,[9] 527 patients with NPC treated with IMRT achieved excellent survival outcomes; the 5-year LRFS, RRFS,

DMFS, PFS, and OS rates were 91.7%, 96.2%, 83.0%, 75.6%, and 80.9%, respectively. Tian et al.[10] reported the efficacy of IMRT in treating 865 NPC patients. After 10 years of follow-up, the LRFS, RRFS, DMFS, PFS, and OS rates were 92.0%, 96.5%, 83.4%, 75.7%, and 76.6%, respectively.

However, the above results were all obtained from clinical centers in epidemic regions. Compared with the results of IMRT in epidemic regions, the survival outcomes obtained by our clinical center in a non-endemic region of China were similar, except that the DFS and OS rates were slightly lower than that of endemic regions. The discrepancies may be due to several reasons. (1) the early diagnosis of NPC is difficult for its occult onset. Physicians in non-endemic regions particularly lack comprehensive knowledge and high vigilance for NPC. This results in the higher percentage of 81.6% new cases diagnosed as stage III-IV in our center compared to that reported in endemic regions of China.[11, 12] (2) NPCs diagnosed in our center usually have larger primary lesions and more severe cervical lymph node metastases. The average volume of nasopharyngeal tumors was 22.5 mL, and the mean diameter of cervical lymph nodes was 1.7 cm in this cohort. A previous study in our center has reported that the volume of the primary tumor of at least 23 mL was a poor prognostic factor for OS.[13] Similarly, a study of 992 NPC patients treated with IMRT revealed that tumor volume was an independent prognostic factor for OS.[14] In addition, the literature has shown that cervical lymph nodes necrosis was a significant prognostic factor for DMFS and OS.[15] (3) the number of NPC patients with WHO type II histology in our cohort is higher than that in epidemic regions. Studies have confirmed the close relationship of the WHO II pathological type with poor DFS, OS, and DMFS.[16-18]

The tumor, node, and metastasis (TNM) staging system, reflecting the extent of primary tumor invasion and regional lymph node involvement, plays a crucial role in the treatment of tumors and has the clinical value of guiding treatment response and predicting prognosis. With the advancement of radiation technology, the role of T stage on prognosis has been weakened, and only N stage remains a prognostic factor for non-metastatic NPC.[19] Univariate analysis of our cohort demonstrated that T stage was an independent prognostic

factor for DFS and OS, while advanced N stage was an adverse prognostic factor for DFS, OS, and DMFS. In the subgroup analyses, we showed that there was no significant difference in LRFS among T stages (χ^2=0.845; p-value=0.358), except that between T1 and T4 subgroups (χ^2=1.699; p-value=0.053). Similarly, the 5-year local control rates of T1 and T2 were both 94% in a previous study.[20] The other study revealed that the LRFS rates were not significantly varied between patients with stages T1 and T2 and stages T2 and T3.[21] Yang et al.[22] reported that there were no statistical differences in RRFS between stages T2 and T3 and stages T2 and T4 (p-values > 0.05) when using the 7th edition UICC/AJCC staging system. However, a significant difference was observed in RRFS between stages T3 and T4 in the 8th edition staging system (p-value=0.001). These studies suggest that a more optimized TNM staging system is needed to better guide clinical practice and predict prognosis. The negative results of local control achieved by IMRT among various T stages are mainly due to the dosimetric advantages of the IMRT technique, which is sufficient even to treat stage T4 patients. After disease stratification by N stage, the 5-year DMFS of N0, N1, N2, and N3 were 89.9%, 85.7%, 82.6%, and 77.4%, respectively. With the increase in N stage, the DMFS rates declined progressively, and the difference was statistically significant (p-value=0.005). Significant differences were not observed in RRFS among N stages, maybe due to the excellent regional control achieved by IMRT in all N stages (N0-3: 100%, 97.1%, 97.3%, and 93.5%; p-value=0.179). This is similar to the results of previously reported literature.[11, 23]

Apart from the TNM staging system, clinical parameters such as age, gender, histology, and EBV-DNA copy number are also potential prognostic factors for survival outcomes. In our data, age was an independent prognostic factor for DFS and OS. This result is controversial since age was not shown to be a poor prognostic factor in a previous study [24] but has been reported as an independent prognostic factor in another study.[25] In addition, hemoglobin level of less than 110 g/L before treatment was detected to be a poor prognostic factor for OS, which was consistent with previous results reported in our center[16] and a study published by another center.[26] Thus, dynamic monitoring of hemoglobin levels before and during radiotherapy and infusion of red blood cell suspension when necessary are of clinical benefits

in improving the prognosis of NPC patients. The reason may-be that treatment of anemia has the potential to improve tumor hypoxia and further enhances radiation sensitivity. Additionally, the improvement of the nutritional status of patients can enhance their tolerance to chemo-radiotherapy. In our cohort, we detected a proportion of 50.6% of patients with definite cervical lymph node metastasis who simultaneously had lymph node liquefaction necrosis; the necrosis of lymph nodes was significantly associated with DMFS, DFS, and OS. Consistently, Feng et al.[15] reported that necrosis of cervical lymph nodes was a poor prognostic factor for OS and DMFS. Our results indicate that more intensive treatments, such as those combined with induction chemotherapy, adjuvant chemotherapy, and immune or targeted therapy, are needed for patients with stage N3 and with lymph node necrosis.

Regarding failure patterns, our results demonstrated that distant metastasis was the main mode of treatment failure. A majority of distant metastases occur within 3 years after treatment. The most common site of metastasis was bone, followed by lung and liver, which is similar to the data reported by other research centers.[12, 27] In our cohort, 40.7% of patients had multiple organ metastases after treatment, which is consistent with the results in epidemic regions.[28] While in a non-IMRT treatment modality, the most common observed failure mode was local recurrence. [29] The reason could be that IMRT uses more precise immobilization devices to make the error of treatment within a controllable range. Additionally, IMRT can obtain higher biological effects through the simultaneous-integrated boost (SIB) technique.[30] Due to the boosted and uniform doses of IMRT to the primary lesion and metastatic lymph node of NPC, the local and/or regional controls were strikingly enhanced.[31] While the satisfactory local and/or regional controls have been achieved by IMRT, distant metastasis still needs to be further improved. Lai et al.[32] compared 512 NPC patients treated with IMRT and 764 patients treated with 2D-CRT; the DMFS was similar in both groups. This suggests that the role of IMRT in controlling the distant metastasis of NPC is limited. It is reported that[33] the primary tumor cells may spread far away in the early or even pre-cancerous stage of the tumor, forming an occult metastasis. When the body conditions are suitable, for example, in a state of immune deficiency or decline, the disseminated tumor cells will colonize in distant organs and form a pre-metastatic site.

Therefore, how to use more advanced imaging techniques and laboratory examination methods to detect occult lesions may be one of the future directions for reducing the rate of distant metastasis of NPC.

Superior dosimetric advantage of IMRT facilitates the protection of organs at risk, thereby alleviating the adverse effects of patients. We demonstrated that the incidence rates of xerostomia, hearing impairment, cervical fibrosis, and temporal lobe necrosis were similar to those reported in endemic regions. When combined with platinum-based chemotherapy, more severe hearing impairment and xerostomia were observed. Considerations should be made to select appropriate patients to receive appropriate chemotherapy regimens, for the sake of reducing the late oral and ear related toxicities and improving quality of life.

In the era of IMRT, the role of combined chemotherapy with IMRT has been constantly questioned and studied. The risk of death was declined to 0.79 and the 5-year OS rate was increased by 6.3% after CCRT followed by AC.[34] Sun[11] analyzed 868 loco-regionally advanced NPC patients who received various treatment modalities and showed that there were no significant differences among survival outcomes. Our results showed that IC significantly increased RRFS (97.1% vs. 99.1%; p-value=0.041) and OS (79.9% vs. 85.1%; p-value=0.052), while AC had a survival benefit on OS (77.6% vs. 83.6%; p-value=0.039) and increased DFS (84.7% vs. 79.1%; p-value=0.089) and LRFS with marginal significance (93.3% vs. 90.2%; p-value=0.062). In terms of chemotherapy regimens, docetaxel and gemcitabine based IC or AC showed a tendency to improve survival, which was consistent with the results of previous studies in our center.[18] A prospective study also reported that TPF based regimens combined with CCRT significantly reduced the failure rate (3-year FFS: 80% vs. 72%; p-value=0.034) and improved overall survival (3-year OS: 92% vs. 86%; p-value=0.029) for locally advanced NPC.[35]

Conclusions

Based on a large cohort (n=792) and a long follow-up time (46.2 months), we revealed that the survival outcomes of NPC patients achieved by IMRT in the non-endemic region of

China is comparable to that in endemic regions. The most common seen acute and late toxicities were similar to the patients treated in endemic regions. Distant metastasis and local/regional relapses were the top two patterns of failure.

Conflicts of Interest

The authors declared that they have no competing interests to the research.

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None

Author contributions

Man Xu, Jian Zang and Xuqi Li. designed the study, conducted the statistical analysis and interpreted the results. Man Xu Shanquan Luo and Jianhua Wang collected the data. Man Xu drafted the manuscript. All authors have read and approved the final version of the submitted manuscript.

Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to restricting patient privacy regulations by the different countries but are available from the corresponding author on reasonable request.

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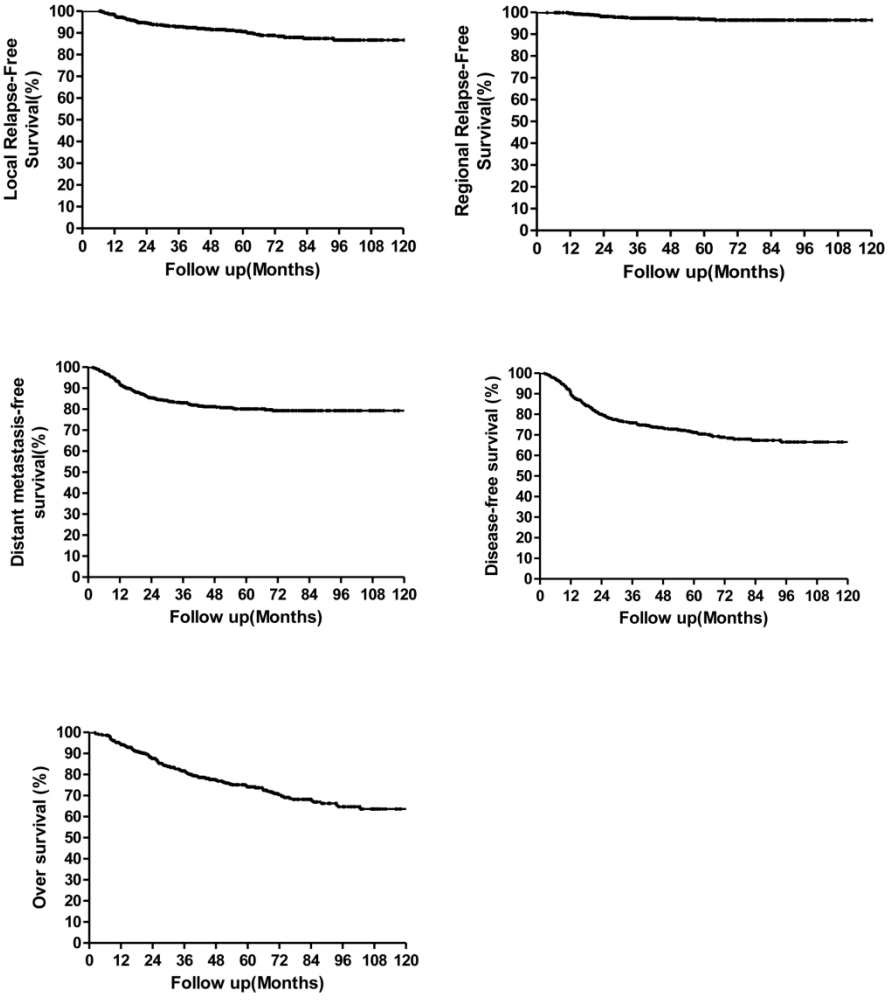
Figure legends

Figure 1. The local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) curves of patients who underwent IMRT.



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	--
		Cross-sectional study—Report numbers of outcome events or summary measures	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Long-term survival outcomes and adverse effects of nasopharyngeal carcinoma patients treated with IMRT in a non-endemic Region: A population-based retrospective study

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Long-term survival outcomes and adverse effects of nasopharyngeal carcinoma patients treated with IMRT in a non-endemic Region: A population-based retrospective study

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Abstract

Objectives: To evaluate the long-term survival outcomes and adverse effects of intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) and to summarize the experiences of IMRT in NPC in the past few decades in non-endemic northwest China.

Design: A population-based retrospective study.

Setting: An experience of using IMRT in nonendemic region of China.

Participants: The study included 792 newly diagnosed and non-metastatic NPC patients who received IMRT from January 2006 to September 2018 in Xijing Hospital.

Outcome measures: The survival outcomes, adverse effects, and failure patterns were evaluated by univariate, multivariate, and subgroup analyses.

Results: With a median follow up time of 46.2 months, the 5-year local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) rates were 90.8%, 97.0%, 82.8%, 69.6%, and 78.0%, respectively. Multivariate analysis showed that age, N stage, clinical stage, pathological type, and primary tumor volume of more than 23cm^3 were the independent prognosis factors for DFS (all p-values < 0.05); age, N stage, pathological type, cervical lymph node necrosis (CNN), and anemia were significantly associated with OS (all p-values < 0.05). The most common acute toxicities of IMRT were dermatitis, mucositis, and dysphagia. Xerostomia and hearing impairment were the top two late toxicities. The main failure patterns were distant metastasis and local and/or regional relapses.

Conclusions: Similar survival, toxicities, and failure patterns have been observed in patients treated with IMRT in a non-endemic area of China when compared with that in endemic areas. Induction chemotherapy (IC) combined with concurrent chemoradiotherapy (CCRT) may benefit locally advanced NPC in non-endemic areas of China.

Keywords

Nasopharyngeal carcinoma (NPC), Nonendemic region, Intensity-modulated radiotherapy (IMRT), Survival, Adverse effects

Strengths and limitations of this study

1. Our study summarizes the experiences of IMRT in NPC in the past few decades in

northwest non-endemic area of China.

2. The clinical characteristics, survival outcomes, long-term adverse effects and failure patterns were reported.
3. A large cohort study (n=792) and long-term follow-up (46.2 months).
4. This study is expected to lay the foundation for conducting future prospective study.
5. The limitations of this study are that the patients are derived from a single centre and the study's retrospective design.

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelium malignancy with a characteristic of unbalanced regional distribution. Statistics revealed that more than 70% of newly diagnosed NPCs are in east and southeast Asia. It is prevalent in southern China, with the world age-standardized rate of approximately 3.0 per 100,000 compared with 0.4 per 100,000 in Western countries.[1, 2] In China, the morbidity and mortality of NPC were evidently higher in the southern area than that in the other areas while the northern area ranks the lowest.[3]

Radiotherapy (RT) is the primary treatment modality for NPC due to the high sensitivity of nasopharyngeal tumors to radiation. With the progression of radiation techniques, radiotherapy has changed from conventional two-dimensional radiotherapy (2D-CRT) to three-dimensional conformal radiotherapy (3D-CRT) and to more advanced intensity-modulated radiotherapy (IMRT). Nowadays, IMRT is the most widely used technique in radiotherapy. Local or regional controls and survival have been improved by the parallel advantages of dosimetric properties and reduced toxicity.[4-6] The 5-year loco-regional relapse rate of non-metastatic NPC has been reduced to 7.4%. [7] Furthermore, IMRT was closely related to a better 5-year overall survival (OS) when compared with 2D-CRT or 3D-CRT, along with significantly reduced toxicities such as xerostomia, trismus, and temporal lobe neuropathy.[5] However, these data are mainly acquired from experiences in epidemic regions. To date, the literature related to the long-term survival outcomes and radiation-induced toxicities of a large cohort of patients who underwent IMRT in non-endemic regions are limited. Thus, in the current study, we intend to comprehensively evaluate the survival outcomes and adverse effects of patients treated with IMRT in a non-endemic region of China.

Materials and Methods

Patients

From January 2006 to September 2018, a total of 792 patients were included in the study. The inclusion criteria were as follows: (1) patients from northwest region of China, (2) pathologically confirmed NPC, (3) previously untreated, (4) no evidence of distant metastasis,

(5) no previous malignancies or other concomitant malignant diseases, and (6) received a whole course of IMRT and no molecular targeted therapy.

Radiotherapy

IMRT was delivered within two weeks of completion of the induction chemotherapy (IC). External megavoltage photons were used to treat primary lesions and cervical lymph nodes. The gross tumor volume (GTV) included the entire nasopharygeal tumors (GTVnx) and the positive lymph nodes of the neck (GTVnd). The clinical target volume (CTV) contained the adjacent areas at risk for microscopic disease. The high-risk clinical target volume (CTV1) was the GTV plus the entire nasopharyngeal mucosa, retropharyngeal lymph nodes, skull base, parapharyngeal space, pterygopalatine fossa, sphenoid sinus, posterior third of the nasal cavity, and maxillary sinus. The low-risk clinical target volumes (CTV2) covered the lower neck without lymph node metastasis and supraclavicular fossa. The planning target volumes (PTVs) were delineated by adding 3-mm margins to the GTVs and CTVs. The prescribed radiation doses to the PTV of primary tumors (GTVnx-P) were 69.96 Gy/33 fractions for T1-2 disease and 72.6-74.25 Gy/33 fractions for T3-4 lesion,-66-73.92 Gy/30-33 fractions for the PTV of positive lymph nodes (GTVnd-P), 60-64 Gy/30-33 fractions for the PTV of CTV-1, 50-54 Gy/28-33 fractions for the PTV of CTV-2. (Figure 1) All patients were treated with 2 Gy/fraction daily for five consecutive days per week. The doses for the normal tissues and organs at risk were confined below tolerance levels.

Chemotherapy

Overall, chemotherapy was administered to 93.9% of patients. The details of the chemotherapy strategy are illustrated in Table 1. The regimens for induction and adjuvant chemotherapy (AC) were TPF, TP, PF, and GP. The TPF regimen consisted of docetaxel (75 mg/m^2) intravenously (IV) on day 1, cisplatin (75 mg/m^2) continuously (IV) on days 1-3, and fluorouracil (500 mg/m^2) continuously (IV) on days 1-5. The TP regimen was administered as docetaxel (75 mg/m^2; IV) on day 1 and cisplatin (75 mg/m^2) continuously (IV) on day 1. The PF regimen comprised of cisplatin (75 mg/m^2; IV) on day 1 and fluorouracil (500 mg/m^2) continuously (IV) on days 1-5. The GP regimen included cisplatin (75 mg/m^2; IV) on day 1

and gemcitabine (1000 mg/m^2; IV) on days 1 and 8. All the regimens were repeated every 3 weeks for 2-3 cycles for IC and every 4 weeks for 2-3 cycles for AC. CCRT consisted of cisplatin-based chemotherapy that was administered as cisplatin (40 mg/m^2; IV) weekly or cisplatin (80-100 mg/m^2) every 3 weeks during radiation.

Table 1. Patient and treatment characteristics.

Patient characteristics	**Number/Mean(range)**
Age (year)	47.3 (9-83)
Tumor volume (mL)	22.5 (2.4-232.0)
Lymph nodes size (cm)	1.7 (0.8-8.9)
Gender (Male/Female)	566/226
Age (＜50 years/≥50 years)	446/346
LDH (≤174 u/L/＞174 u/L)	567/225
T stage (T1/T2/T3/T4)	87/277/133/295
N stage (N0/N1/N2/N3a/N3b)	105/186/347/64/90
Clinical stage (Ⅰ/Ⅱ/Ⅲ/Ⅳa/Ⅳb)	22/124/246/246/154
WHO Histology (Ⅰ/Ⅱ/Ⅲ)	3/210/579
Diagnostic imaging technique	
MRI	792
Chemotherapy	
RT/CCRT/IC+CCRT/IC+RT/CCRT+AC/RT+AC/IC+CCRT+AC/IC+RT+AC	48/243/365/51/21/8/55/1
CNN (Yes/No)	401/391

Abbreviations: RT= Radiotherapy; CCRT = concurrent chemo-radiotherapy; IC= Induction chemotherapy; AC=Adjuvant chemotherapy; CNN= cervical nodal necrosis; MRI = Magnetic resonance imaging; WHO = World Health Organization. LDH= Lactic Dehydrogenase

Follow-up

The patients were evaluated for treatment response and adverse effect after IMRT as follows:

every 2-3 months for the first 2 years, then every 3-4 months for years 3-5, and annually thereafter. The examination items included the following: physical examinations, flexible nasopharyngoscope, chest X-ray or computerized tomography (CT), abdominal ultrasonography or CT, magnetic resonance imaging (MRI) of the head and neck, and a bone scan when necessary. The acute radiotherapy and chemotherapy related toxicities were assessed by the National Cancer Institute Common Toxicity Criteria (version 4.0). For evaluating the late adverse effects of radiotherapy, the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) were applied.[8]

Statistical analysis

Statistical analyses were performed with SPSS software (version 22.0). Specifically, overall survival (OS) was measured from the end of treatment to the observation of death caused for any reason; disease free survival (DFS) was measured from the end of treatment to the first discovery of tumor recurrence or metastasis or death for any reason; local relapse-free survival (LRFS) and regional recurrence-free survival (RRFS) were measured from the end of treatment to the first observation of local recurrence and regional recurrence, respectively; distant metastasis-free survival (DMFS) was measured from the end of treatment to the observation of distant metastasis. The Kaplan Meier method was used to draw survival curves and the log rank test was applied to compare differences. Multivariable analyses were conducted with a Cox proportional hazard model and the hazard ratio (HR) and the corresponding 95% confidence interval (CI) were calculated. Categorical and continuous variables were compared with a $\chi 2$ test and an independent t-test, respectively. In all cases, a two-sided p-value less than 0.05 was considered to be statistically significant.

Ethical statement

Approval of our study was granted by the Ethics Committee of Xijing Hospital, Air Force Military Medical University, Xian, China. Signed informed consent forms were kindly provided by each patient.

Because the patients and/or the public were not involved in the design, or conduct, or

reporting, or dissemination plans of this study. Therefore, the Ethics Committee of Xijing Hospital approved the retrospective study, but did not provide an ethics number/ID.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this study.

Results

The characteristics of patients

A total of 792 patients were included. The distribution of the patients is presented in Table 1. Overall, the median age was 47.3 years (with a range of 9-83 years) and the male (n=566)-to-female (n=226) ratio was 2.5:1. The mean volume of primary tumor was 22.5 mL (with a range of 2.4-232 mL). The mean diameter of metastatic cervical lymph nodes was 1.7 cm (with a range of 0.8-8.9cm). The distribution of clinical stage was 22 (2.8%), 124 (15.7%), 246 (31.1%), 246 (31.1%), and 154 (19.4%) for stages I, II, III, IVa, and IVb, respectively. The majority of patients were histologically diagnosed as WHO II (n=210; 26.5%) and WHO III (n=579; 73.1%), except for three patients who were diagnosed as WHO I (n=3; 0.4%). In this cohort, most patients were Han Chinese (n=772; 97.4%), followed by Hui People (n=15; 1.9%), Tibetan (n=3; 0.4%), and Mongolian (n=2; 0.3%). Only one of the ethnic minorities was histologically diagnosed as WHO type II, and the rest were all WHO type III. An MRI of the head and neck was selected as the diagnostic imaging technique for all patients. Nearly all patients (93.9%) received chemotherapy, in various patterns, such as CCRT (n=243, 30.7%), IC+CCRT (n=365; 46.1%), IC+RT (n=51; 6.4%), CCRT+AC (n=21; 2.7%), RT+AC (n=8; 1.0%), IC+CCRT+AC (n=55; 6.9%) and IC+RT+AC (n=1; 0.1%). The median follow-up time was 46.2 months (with a range of 1.3-130.2 months).

Survival outcomes

Overall, the 5-year LRFS, RRFS, DMFS, DFS, and OS rates were 93.4%, 97.0%, 82.8%, 69.6%, and 78.0%, respectively (Figure 2). There were significant differences in the DFS and

OS rates between the subgroups of age, T-stage, N-stage, clinical stage, histology, LDH and cervical nodal necrosis (CNN). In addition, we found that tumor volume was associated with DFS and anemia, with or without chemotherapy (CCRT, IC, and AC) were related to OS. Significant differences in DMFS rates were observed between subgroups of N-stage, clinical stage, histology, tumor volume, CNN, EBV-DNA copy number, anemia, and with or without chemotherapy. Also, we found CNN and AC were associated with LRFS, and only IC was related to RRFS. Specifically, the patients with T4 disease had a marginally higher risk of local relapse than the patients with T1 disease (χ^2=1.699; p=0.053). After clinical stage stratification by N stage, the RRFS rates were significantly lower in the N3 stage than in the N1 stage (χ^2=4.916; p=0.027), while the differences were not significant between other subgroups (Table 2).

Table 2. Characteristics of 792 patients and univariate analysis of prognostic factors.

Factor	No	DFS（%）		OS（%）		DMFS（%）		LRFS（%）		RRFS（%）	
		5y	P value	5y	P value	5y	P value	5y	P value	5y	P value
Age											
＜50y	446	85.7	0.013*	86.8	0.001*	88.4	0.766	95.0	0.676	97.5	0.710
≥50y	346	83.3		80.2		87.2		93.1		97.0	
Gender											
Male	566	87.9	0.459	81.7	0.871	89.1	0.598	95.2	0.882	98.5	0.612
Female	226	80.4		83.6		85.2		93.3		98.9	
T											
T1	87	85.9	0.038*	90.7	0.019*	89.2	0.230	94.2	0.358	97.1	0.381
T2	277	83.3		87.6		86.9		93.9		96.9	
T3	133	79.7		81.4		84.8		92.9		96.2	
T4	295	74.9		79.2		82.7		91.8		98.2	
N											
N0	105	84.6	0.004*	89.5	0.005*	89.9	0.005*	94.0	0.558	100.0	0.179
N1	186	76.7		81.6		87.5		90.7		97.1	

N2	347	73.2		79.9		82.6		89.6		97.3	
N3a/3b	154	72.7		74.6		77.4		91.0		93.5	
Clinical stage											
Ⅰ	22	85.7	0.000*	89.3	0.000*	87.3	0.004*	90.7	0.879	97.4	0.512
Ⅱ	124	83.5		83.3		85.9		90.6		98.9	
Ⅲ	246	74.7		79.1		82.8		91.2		97.9	
Ⅳa/b	400	59.6		72.5		76.1		89.3		97.8	
Histology											
WHO Ⅱ	210	76.8	0.046*	79.1	0.006*	81.3	0.034*	90.1	0.267	98.1	0.739
WHO Ⅲ	579	83.4		88.1		86.9		91.9		98.5	
Tumor volume(ml)											
＜23ml	304	82.6	0.013*	84.6	0.567	85.5	0.042*	92.3	0.178	97.8	0.231
≥23ml	488	73.4		79.5		80.3		89.4		95.3	
CNN (cervical nodal necrosis)											
No	391	81.8	0.000*	83.1	0.015*	86.9	0.032*	96.6	0.097	99.0	0.165
Yes	401	73.1		80.6		76.5		94.3		97.7	
EB-DNA copy number											
＜ 5000 copy /ml	743	80.5	0.564	82.9	0.768	84.9	0.098	91.9	0.452	97.9	0.987
≥5000 copy /ml	49	78.5		79.7		81.3		90.4		98.0	
LDH											
≤174 u/L	567	82.3	0.032*	82.4	0.041*	88.9	0.645	95.1	0.716	98.7	0.351
＞ 174	225	72.6		78.9		83.2		92.3		97.2	

u/L											
Anemia											
No	706	80.2	0.124	80.3	0.032*	83.3	0.079	95.4	0.479	99.8	0.546
Yes	86	77.6		71.2		79.5		90.3		95.4	
Concurrent chemotherapy											
No	108	81.2	0.193	79.2	0.064	80.0	0.051	89.5	0.559	97.4	0.635
Yes	684	83.2		82.2		85.3		91.0		98.2	
Induction chemotherapy											
No	320	84.7	0.638	79.9	0.052	81.1	0.104	92.9	0.413	97.1	0.041*
Yes	472	86.2		85.1		77.7		91.0		99.1	
Adjuvant chemotherapy											
No	707	84.7	0.089	83.6	0.039*	87.2	0.525	93.3	0.062	98.9	0.819
Yes	85	79.1		77.6		81.3		90.2		96.6	

Abbreviations: DFS = disease-free survival; OS = overall survival; DMFS = distant metastasis-free survival; LRFS = local relapse free survival; RRFS = regional relapse free survival; WHO = World Health Organization; CNN= cervical nodal necrosis; IC= Induction chemotherapy; AC=Adjuvant chemotherapy. LDH= Lactic Dehydrogenase

Multivariate analysis

To do the multivariate analysis, statistically significant factors (p-value less than 0.1) of DFS, OS, DMFS, LRFS and RRFS rates in univariate analyses were enrolled into the Cox regression model. The results showed that age, N-stage, clinical stage, histology, the volume of primary tumor and LDH were independent prognostic factors for DFS. Concerning DMFS, we only identified N-stage and cervical node necrosis (CNN) as the significant prognostic factors. Furthermore, we found that age, N-stage, histology, CNN and anemia were significantly correlated with OS (Table 3).

Table 3. Multivariate Analysis of Variables Correlated with Various Clinical Endpoints.

End-poi	Factors	HR	95%CI	P Value

nt				
DFS	Age (＜50y versus ≥50y)	1.013	1.002-1.024	**0.018**
	T stage (T1-2 versus T3-4)	1.040	0.882-1.227	0.642
	N stage (N0-1 versus N2-3)	1.490	1.134-1.958	0.004
	Clinical stage (Ⅰ-Ⅱ versus Ⅲ-Ⅳb)	1.031	1.017-1.045	0.000
	Histology (WHO Ⅱ versus WHO Ⅲ)	2.025	1.358-3.020	0.001
	Tumor volume(＜ 23ml versus ≥23ml)	3.025	1.277-7.167	0.012
	CNN (No versus Yes)	1.225	0.967-1.553	0.093
	LDH(≤174IU/L versus ＞ 174 IU/L)	1.669	1.110-2.921	0.014
	AC (No versus Yes)	0.870	0.641-1.180	0.370
OS	Age(＜50y versus ≥50y)	1.823	1.328-2.502	0.000
	T stage (T1-2 versus T3-4)	1.117	0.921-1.355	0.260
	N stage (N0-1 versus N2-3)	1.276	1.004-1.618	0.043
	Clinical stage (Ⅰ-Ⅱ versus Ⅲ-Ⅳb)	1.163	0.881-1.534	0.287
	Histology (WHO Ⅱ versus WHO Ⅲ)	0.690	0.504-0.932	0.016
	CNN (No versus Yes)	2.191	1.038-4.625	0.040
	Anemia (No versus Yes)	0.573	0.378-0.868	0.009
	Concurrent chemotherapy (No versus Yes)	0.810	0.617-1.064	0.130
	IC (No versus Yes)	1.158	0.978-1.371	0.089
	AC (No versus Yes)	1.484	0.990-2.222	0.056
DMFS	N stage (N0-1 versus N2-3)	2.397	1.627-3.531	0.000
	Clinical stage (Ⅰ-Ⅱ versus	1.185	0.990-1.419	0.064

	Ⅲ-Ⅳb)			
	Histology (WHO Ⅱ versus WHOⅢ)	0.654	0.412-1.037	0.071
	Tumor volume(< 23ml versus≥23ml)	1.113	0.931-1.330	0.241
	CNN (No versus Yes)	1.210	1.013-1.444	0.036
	EBV-DNA copy number (<5000copy/ml versus ≥5000copy /ml)	1.183	0.965-1.448	0.105
	Anemia (No versus Yes)	1.116	0.881-1.415	0.362
	Concurrent chemotherapy (No versus Yes)	0.816	0.599-1.111	0.197
LRFS	CNN (No versus Yes)	0.930	0.521-1.660	0.806
	AC (No versus Yes)	1.296	0.773-2.172	0.326
RRFS	IC (No versus Yes)	0.946	0.198-4.519	0.944

Abbreviations: DFS = disease-free survival; OS = overall survival; DMFS = distant metastasis-free survival; LRFS = local relapse free survival; RRFS = regional relapse free survival; WHO = World Health Organization; CNN= cervical nodal necrosis; IC= Induction chemotherapy; AC=Adjuvant chemotherapy; WHO = World Health Organization.
LDH= Lactic Dehydrogenase

Adverse effects

There were 792 and 737 patients who were followed up for more than 1 year and were included to assess the acute and late chemo-radiotherapy related toxicities, respectively (Table 4). The most common acute toxicities for radiation were grade I and II dermatitis (534/792; 67.4%), mucositis (520/792; 65.7%), and dysphagia (632/792; 79.8%). The most frequent late toxicity after treatment was xerostomia with occurrence rates of grade I 108 (14.6%), grade II 354 (48.15%) and grade III 108 (14.6%). The incidence rate of xerostomia was significantly increased when combined with synchronous chemotherapy (79.3% vs.

60.2%; p-value=0.002). Grade I hearing impairment (525; 71.2%) was the second most common late toxicity of IMRT. Likewise, combined cisplatin-based chemotherapy increased the incidence rate of hearing impairment caused by radiation (80.6% vs. 15.2%; p-value<0.001). The main grade III acute toxicities of radiotherapy were dermatitis (68/792; 8.6%) and mucositis (64/792; 8.1%). The only detected grade III acute toxicities of chemotherapy was neutropenia (31/792; 3.9%). As for the late toxicities, only 108 patients (14.6%) had grade III xerostomia. Remarkably, no severe grade IV toxicities were observed in our cohort.

Table 4. Treatment-related toxicities.

Toxicities	No. of patients by toxicity grade (%)				
	0	1	2	3	4
Acute toxicity related to radiotherapy	190（24.0）	320	214	68（8.6）	0（0）
Dermatitis	208（26.3）	（40.4）	（27.0）	64（8.1）	0（0）
Mucositis	160（20.2）	300	220	0（0）	0（0）
Dysphagia		（37.9）	（27.8）		
Acute toxicity related to chemotherapy	724（91.4）	516	116	0（0）	0（0）
Anemia	699（88.3）	（65.2）	（14.6）	0（0）	0（0）
Thrombocytopenia	398（50.3）			31（3.9）	0（0）
Neutropenia	747（94.3）	62（7.8）	6（0.8）	0（0）	0（0）
Febrile neutropenia	238（30.0）	52（6.6）	41（5.2）	0（0）	0（0）
Vomiting	0（0）	214	149	0（0）	0（0）
Hand–foot syndrome	669（84.5）	（27.0）	（18.8）	0（0）	0（0）
Ototoxicity	0（0）	40（5.1）	5（0.6）	0（0）	0（0）
Neuropathy		476	78（9.9）		
The late toxicities (737 patients)	167（22.7）	（60.1）	0（0）	108	0（0）
Xerostomia	716（97.2）	0（0）	0（0）	（14.6）	0（0）
Neck fibrosis	723（98.1）	123	0（0）	0（0）	0（0）
	680（92.3）	（15.5）		0（0）	0（0）

Trismus	200（27.1）	0（0）	354	0（0）	0（0）
Dysphagia	0（0）		（48.1）	0（0）	0（0）
Hearing impairment	731（99.2）	108	0（0）	0（0）	0（0）
Temporal necrosis		（14.6）	0（0）	0（0）	
Cranial nerve palsy		21（2.8）	18（2.4）		
		14（1.9）	12（1.6）		
		39（5.3）	0（0）		
		525	0（0）		
		（71.2）			
		0（0）			
		6（0.8）			

Failure patterns

During the follow-up period, we observed 162 (20.5%) deaths and 196 (24.7%) treatment failures. A shown in Table 5, the major cause of failure was distant metastasis (n=118; 60.2%), followed by local failure (n=60; 30.6%), regional failure (n=18; 9.2%). Concerning the causes of death, distant metastasis ranked the first, while other causes, such as radiotherapy or chemotherapy-related complications (n=5), other malignant tumors (n=1), no cancer causes (n=3), and unknown causes (n=2), only account for a tiny proportion of the deaths. In our cohort, 87.3% (103/118) of patients developed distant metastasis within 3 years after treatment. The median time for the appearance of distant metastasis was 16.2 months (with a range of 0.8-68.3 months). In patients with distant metastasis, 68 (68/118, 57.6%) had solitary metastasis to the bone, lung, liver, distant lymph nodes, or parotid lymph nodes. Among these patterns, 4 (4/118; 3.4%) had extra regional lymph node metastasis (axillary lymph node metastasis and mediastinal lymph node metastasis), and 2 (2/118; 1.7%) had intraregional parotid lymph node metastasis. There were 45 patients (45/118; 40.7%) developed two sites of metastasis, and the specific metastatic sites and cases are shown in Table 6. In addition, 78 (9.8%) patients developed local or regional failures, with the median recurrence time of 27.0 months (range 4.4-92.3 months). The salvage treatments for these

patients were re-irradiation for 62 patients with local failures, surgery for 3 patients with regional failures, and palliative chemotherapy for patients who appropriate.

Table 5. Failure patterns of all patients.

Variable	No. of patients (%)
Pattern of failure	
Distant metastasis	118(14.9%) [a]
Local and/or regional failures	78(9.8%) [a]
Local failures alone	60(7.6%)
Regional failures alone	18(2.3%)
Local and regional failures	9(1.1%)
Distant + local/regional failures	15(1.9%)
Total	196(24.7%)
Cause of death	
Distant metastasis	106(13.4%)
Local or regional failure	45(5.7%)
radiotherapy or chemotherapy-related complications	5(0.6%)
Other malignant tumors	1(0.1%)
No cancer causes	3(0.4%)
Unknown causes	2(0.3%)
Total	162(20.5%)

[a]The number includes the 15 patents with both distant and local/regional failures.

Table 6. Sites of distant metastasis (n=118).

Site of distant metastasis	No.
Solitary	
Bone	50
Lung	38
Liver	36
Distant Lymph Nodes	5
Parotid Lymph Nodes	3
Two sites	
Bone & Lung	15
Bone & Liver	12
Lung & Liver	8
Lung & Distant lymph nodes	3
Liver& Distant lymph nodes	1
Parotid Lymph Nodes & Distant Lymph Nodes	2
Epidural & spine	2
Multiple sites	
Bone & Lung & Liver	4
Others	1

The effect of chemotherapy

We further evaluated the effect of combining chemotherapy with IMRT in NPC patients. The most frequently used strategies in our institution were IC plus CCRT (n=365; 46.1%) and

CCRT (n=243; 30.7%). During induction chemotherapy, 72.4% (358/472) of patients were treated with docetaxel-based chemotherapy, while 15.0% (71/472) of patients received a gemcitabine-based regimen. The survival analyses demonstrated that there were no significant differences of LRFS, RRFS, DMFS, and OS rates among these regimens of IC or AC. As for IC, specifically, the 5-year DFS and OS rates showed a trend of improving survival in the subgroup of TPF/TP as compared with other regimens, but significant differences were not achieved. In comparison of different AC regimens, these trends were not observed (Table 7).

Table 7. The 5-year estimated survival rates stratified by various regimens of chemotherapy of locally advanced nasopharyngeal carcinoma.

5y(No./%)	LRFS（%）	RRFS（%）	DMFS（%）	OS（%）
IC regimens (472)				
TPF/TP (67/291/27.4)	95.7	97.8	82.3	90.6
GP (71/5.4)	93.1	94.2	73.2	74.2
PF (29/2.2)	90.6	93.0	76.3	71.3
Others (14/1.1)	90.0	93.3	71.2	68.4
$\chi 2$	0.156	2.134	2.145	0.313
P value	0.652	0.123	0.276	0.576
AC regimens (85)				
TPF/TP (11/22/38.8)	90.6	92.1	71.8	77.7
GP (6/7.1)	89.2	94.3	76.0	79.3
PF (30/35.3)	88.1	100	71.4	74.1
Others (16/18.8)	90.1	88.9	77.7	72.7
$\chi 2$	0.117	0.392	0.356	2.242
P value	0.732	0.576	0.516	0.243

Abbreviations: LRFS = local relapse free survival; RRFS = regional relapse free survival; DMFS = distant metastasis-free survival; OS = overall survival; IC= Induction chemotherapy;

AC=Adjuvant chemotherapy.

Discussion

IMRT has been generally recognized as the standard radiation technique for NPC patients (NCCN guidelines for head and neck cancer, version 1, 2019). However, studies comparing the survival outcomes and adverse effects of NPC patients treated with IMRT between endemic and non-endemic regions are limited. In the current study, we reported an experience of IMRT for non-metastatic NPC in a non-endemic area of China (northwest China) based on a large cohort (n=792) and long follow-up time (46.2 months).

In recent years, literature has shown that IMRT was significantly associated with improved therapeutic effects of NPC patients. A prospective study enrolled 616 cases of non-metastatic NPCs (306 cases in the IMRT group and 310 cases in the 2D-CRT group) with a median follow-up time of 42 months to compare the survival outcomes. The results confirmed that IMRT was more effective than 2D-CRT. The 5-year LRFS and OS rates increased from 84.7% to 90.5% and 67.1% to 79.6%, respectively. The IMRT related toxicities were significantly lower than that of 2D-CRT.[4] In a retrospective analysis,[9] 527 patients with NPC treated with IMRT achieved excellent survival outcomes; the 5-year LRFS, RRFS, DMFS, PFS, and OS rates were 91.7%, 96.2%, 83.0%, 75.6%, and 80.9%, respectively. Tian et al.[10] reported the efficacy of IMRT in treating 865 NPC patients. After 10 years of follow-up, the LRFS, RRFS, DMFS, PFS, and OS rates were 92.0%, 96.5%, 83.4%, 75.7%, and 76.6%, respectively.

However, the above results were all obtained from clinical centers in epidemic regions. Compared with the results of IMRT in epidemic regions, the survival outcomes obtained by our clinical center in a non-endemic region of China were similar, except that the DFS and OS rates were slightly lower than that of endemic regions. The discrepancies may be due to several reasons. (1) the early diagnosis of NPC is difficult for its occult onset. Physicians in non-endemic regions particularly lack comprehensive knowledge and high vigilance for NPC. This results in the higher percentage of 81.6% new cases diagnosed as stage III-IV in our

center compared to that reported in endemic regions of China.[11, 12] (2) NPCs diagnosed in our center usually have larger primary lesions and more severe cervical lymph node metastases. The average volume of nasopharyngeal tumors was 22.5 mL, and the mean diameter of cervical lymph nodes was 1.7 cm in this cohort. A previous study in our center has reported that the volume of the primary tumor of at least 23 mL was a poor prognostic factor for OS.[13] Similarly, a study of 992 NPC patients treated with IMRT revealed that tumor volume was an independent prognostic factor for OS.[14] In addition, the literature has shown that cervical lymph nodes necrosis was a significant prognostic factor for DMFS and OS.[15] (3) the number of NPC patients with WHO type II histology in our cohort is higher than that in epidemic regions. Studies have confirmed the close relationship of the WHO II pathological type with poor DFS, OS, and DMFS.[16-18]

The tumor, node, and metastasis (TNM) staging system, reflecting the extent of primary tumor invasion and regional lymph node involvement, plays a crucial role in the treatment of tumors and has the clinical value of guiding treatment response and predicting prognosis. With the advancement of radiation technology, the role of T stage on prognosis has been weakened, and only N stage remains a prognostic factor for non-metastatic NPC.[19] Univariate analysis of our cohort demonstrated that T stage was an independent prognostic factor for DFS and OS, while advanced N stage was an adverse prognostic factor for DFS, OS, and DMFS. In the subgroup analyses, we showed that there was no significant difference in LRFS among T stages (χ^2=0.845; p-value=0.358), except that between T1 and T4 subgroups (χ^2=1.699; p-value=0.053). Similarly, the 5-year local control rates of T1 and T2 were both 94% in a previous study.[20] The other study revealed that the LRFS rates were not significantly varied between patients with stages T1 and T2 and stages T2 and T3.[21] Yang et al.[22] reported that there were no statistical differences in RRFS between stages T2 and T3 and stages T2 and T4 (p-values > 0.05) when using the 7th edition UICC/AJCC staging system. However, a significant difference was observed in RRFS between stages T3 and T4 in the 8th edition staging system (p-value=0.001). These studies suggest that a more optimized TNM staging system is needed to better guide clinical practice and predict prognosis. The negative results of local control achieved by IMRT among various T stages

are mainly due to the dosimetric advantages of the IMRT technique, which is sufficient even to treat stage T4 patients. After disease stratification by N stage, the 5-year DMFS of N0, N1, N2, and N3 were 89.9%, 85.7%, 82.6%, and 77.4%, respectively. With the increase in N stage, the DMFS rates declined progressively, and the difference was statistically significant (p-value=0.005). Significant differences were not observed in RRFS among N stages, maybe due to the excellent regional control achieved by IMRT in all N stages (N0-3: 100%, 97.1%, 97.3%, and 93.5%; p-value=0.179). This is similar to the results of previously reported literature.[11, 23]

Apart from the TNM staging system, clinical parameters such as age, gender, histology, and EBV-DNA copy number, LDH are also potential prognostic factors for survival outcomes. In our data, age was an independent prognostic factor for DFS and OS. This result is controversial since age was not shown to be a poor prognostic factor in a previous study [24] but has been reported as an independent prognostic factor in another study.[25] In addition, hemoglobin level of less than 110 g/L before treatment was detected to be a poor prognostic factor for OS, which was consistent with previous results reported in our center[16] and a study published by another center.[26] Thus, dynamic monitoring of hemoglobin levels before and during radiotherapy and infusion of red blood cell suspension when necessary are of clinical benefits in improving the prognosis of NPC patients. The reason may-be that treatment of anemia has the potential to improve tumor hypoxia and further enhances radiation sensitivity. Additionally, the improvement of the nutritional status of patients can enhance their tolerance to chemo-radiotherapy. In our cohort, we detected a proportion of 50.6% of patients with definite cervical lymph node metastasis who simultaneously had lymph node liquefaction necrosis; the necrosis of lymph nodes was significantly associated with DMFS, DFS, and OS. Consistently, Feng et al.[15] reported that necrosis of cervical lymph nodes was a poor prognostic factor for OS and DMFS. Our results indicate that more intensive treatments, such as those combined with induction chemotherapy, adjuvant chemotherapy, and immune or targeted therapy, are needed for patients with stage N3 and with lymph node necrosis. High level of LDH(＞174IU/L) was found to be associated with poor disease control in this study, which was consistent with the findings of previous studies.

[27, 28] However, multivariate analysis failed to select the LDH level as an independent prognostic factor in patients with WHO type Ⅱ, which warrants further prospective and large cohort studies to confirm the results in the future.

Regarding failure patterns, our results demonstrated that distant metastasis was the main mode of treatment failure. A majority of distant metastases occur within 3 years after treatment. The most common site of metastasis was bone, followed by lung and liver, which is similar to the data reported by other research centers.[12, 29] In our cohort, 40.7% of patients had multiple organ metastases after treatment, which is consistent with the results in epidemic regions.[30] While in a non-IMRT treatment modality, the most common observed failure mode was local recurrence. [31] The reason could be that IMRT uses more precise immobilization devices to make the error of treatment within a controllable range. Additionally, IMRT can obtain higher biological effects through the simultaneous-integrated boost (SIB) technique.[32] Due to the boosted and uniform doses of IMRT to the primary lesion and metastatic lymph node of NPC, the local and/or regional controls were strikingly enhanced.[33] While the satisfactory local and/or regional controls have been achieved by IMRT, distant metastasis still needs to be further improved. Lai et al.[34] compared 512 NPC patients treated with IMRT and 764 patients treated with 2D-CRT; the DMFS was similar in both groups. This suggests that the role of IMRT in controlling the distant metastasis of NPC is limited. It is reported that[35] the primary tumor cells may spread far away in the early or even pre-cancerous stage of the tumor, forming an occult metastasis. When the body conditions are suitable, for example, in a state of immune deficiency or decline, the disseminated tumor cells will colonize in distant organs and form a pre-metastatic site. Therefore, how to use more advanced imaging techniques and laboratory examination methods to detect occult lesions may be one of the future directions for reducing the rate of distant metastasis of NPC.

Superior dosimetric advantage of IMRT facilitates the protection of organs at risk, thereby alleviating the adverse effects of patients. We demonstrated that the incidence rates of xerostomia, hearing impairment, cervical fibrosis, and temporal lobe necrosis were similar to

those reported in endemic regions. When combined with platinum-based chemotherapy, more severe hearing impairment and xerostomia were observed. Considerations should be made to select appropriate patients to receive appropriate chemotherapy regimens, for the sake of reducing the late oral and ear related toxicities and improving quality of life.

In the era of IMRT, the role of combined chemotherapy with IMRT has been constantly questioned and studied. The risk of death was declined to 0.79 and the 5-year OS rate was increased by 6.3% after CCRT followed by AC.[36] Sun[11] analyzed 868 loco-regionally advanced NPC patients who received various treatment modalities and showed that there were no significant differences among survival outcomes. Our results showed that IC significantly increased RRFS (97.1% vs. 99.1%; p-value=0.041) and OS (79.9% vs. 85.1%; p-value=0.052), while AC had a survival benefit on OS (77.6% vs. 83.6%; p-value=0.039) and increased DFS (84.7% vs. 79.1%; p-value=0.089) and LRFS with marginal significance (93.3% vs. 90.2%; p-value=0.062). In terms of chemotherapy regimens, docetaxel and gemcitabine based IC or AC showed a tendency to improve survival, which was consistent with the results of previous studies in our center.[18] A prospective study also reported that TPF based regimens combined with CCRT significantly reduced the failure rate (3-year FFS: 80% vs. 72%; p-value=0.034) and improved overall survival (3-year OS: 92% vs. 86%; p-value=0.029) for locally advanced NPC.[37]

Limitations

Our study has several limitations. First, based on the characteristics of retrospective studies, we were unable to manually control the confounding variables, such as different induction or adjuvant chemotherapy regimens. Hence, we conducted multivariate analyses to adjust for these confounding factors. Second, this was a single-center study from a non-endemic region in China. A well-designed multicenter randomized controlled study is necessary to further explore the best treatment modality for newly diagnosed non-metastatic NPC in non-endemic region.

Conclusions

Based on a large cohort (n=792) and a long follow-up time (46.2 months), we revealed that the survival outcomes of NPC patients achieved by IMRT in the non-endemic region of China is comparable to that in endemic regions. The most common seen acute and late toxicities were similar to the patients treated in endemic regions. Distant metastasis and local/regional relapses were the top two patterns of failure.

Conflicts of Interest

The authors declared that they have no competing interests to the research.

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None

Author contributions

Man Xu, Jian Zang and Xuqi Li. designed the study, conducted the statistical analysis and interpreted the results. Man Xu Shanquan Luo and Jianhua Wang collected the data. Man Xu drafted the manuscript. All authors have read and approved the final version of the submitted manuscript.

Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to restricting patient privacy regulations by the different countries but are available from the corresponding author on reasonable request.

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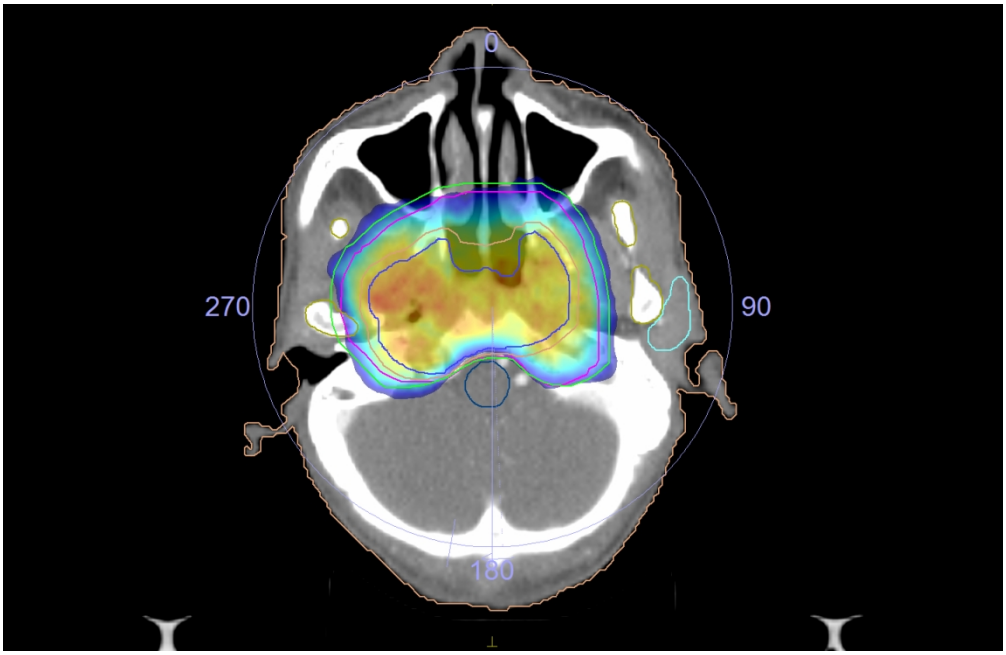
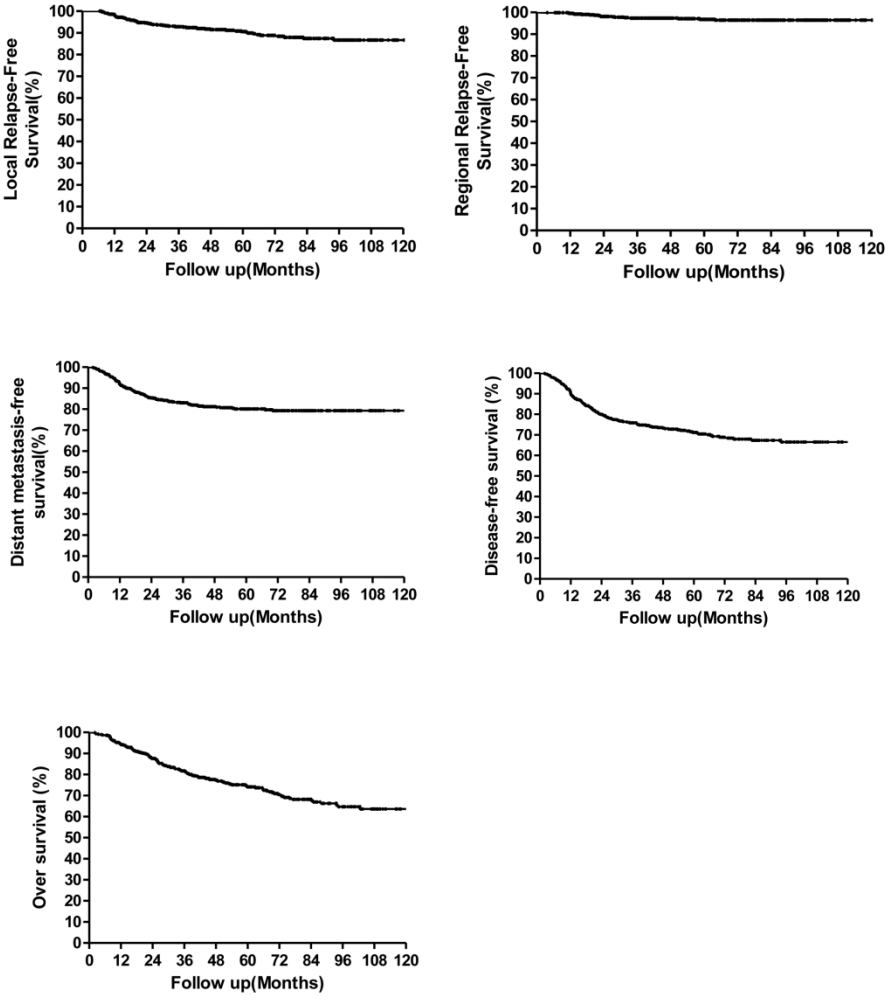
Figure legends

Figure 1. Target paint example.

Figure 2. The local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) curves of patients who underwent IMRT.





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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	--
		Cross-sectional study—Report numbers of outcome events or summary measures	8-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.