

Ten-Year Outcomes Of Intensity-Modulated Radiotherapy (IMRT) Combine With Chemotherapy Versus IMRT Alone For Stage II Nasopharyngeal Carcinoma In The Real-World Study (RWD)

This article was published in the following Dove Press journal:
Cancer Management and Research

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Objectives: The aim was to define the role of chemotherapy in stage II nasopharyngeal carcinoma (NPC) and to identify the toxicity of chemotherapy for these patients in the era of intensity-modulated radiotherapy (IMRT).

Methods: Between January 2002 and December 2013, 169 patients with stage II NPC were analyzed. Of these patients, 149 patients treated with chemotherapy were divided into three groups as follows: neoadjuvant chemotherapy followed by IMRT (NCT) group, concurrent chemotherapy with IMRT (CCRT) group, and neoadjuvant chemotherapy followed by CCRT (NC+CCRT) group. In addition, 20 patients received IMRT alone. We retrospectively assessed the 10-year survival and acute adverse effects in the patients using SPSS software.

Results: The median follow-up time was 93 months (2–160 months). The 10-year OS of the NCT, CCRT, NC+CCRT groups vs the IMRT alone group was 69.8%, 63.4%, 69.7% vs 72.4%, respectively ($P=0.664$, 0.940 , and 0.998 , respectively). Both univariable and multivariable analyses showed that the addition of chemotherapy to IMRT did not significantly improve the 10-year survival outcomes. The hematotoxicity and mucous reaction of patients with chemotherapy were more serious than those with IMRT alone ($P=0.007$ and 0.049). Distant metastasis for stage II NPC patients mostly occurred within 3 years, which is very different from patients with advanced NPC.

Conclusion: Patients with stage II NPC who are treated with IMRT may obtain satisfactory long-term survival outcomes. The additional chemotherapy cannot significantly increase survival; however, it may remarkably increase treatment-associated acute toxic reactions.

Keywords: stage II nasopharyngeal carcinoma, NPC, intensity-modulated radiotherapy, IMRT, chemotherapy

Introduction

Nasopharyngeal carcinoma (NPC), characterized by its unique geographic distribution, is endemic in the eastern and southeastern regions of Asia. Approximately 80% of NPC cases occur in People's Republic of China.¹ NPC is more sensitive to radiotherapy (RT) than other head and neck carcinomas due to its specific biological characteristics. As a consequence, RT has been the basic curative treatment of NPC. Although NPC is also highly chemosensitive, the benefit of RT varies in different stages. For stage I NPC, it has been reported that RT as a single modality achieves an excellent outcome with a >95% overall survival (OS) at 10 years.² For

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patients with stage III–IVB, combined chemotherapy and RT has become a standard treatment due to sufficient evidence showing improved OS from 50% to 70% compared to RT alone.^{3–6} To date, it is still controversial if chemotherapy is beneficial for patients with stage II NPC.

In the traditional RT era, several studies demonstrated that the addition of chemotherapy to RT improves the clinical outcomes for stage II NPC.^{2,7–9} As the RT technique advances rapidly, intensity-modulated radiotherapy (IMRT) has replaced traditional RT to become the standard treatment technique for NPC. Previous studies have reported that IMRT alone has acquired superb outcomes for stage II NPC.^{10–16} Currently, the necessity of IMRT combined with chemotherapy for stage II NPC is questioned. The National Comprehensive Cancer Network and European Society for Medical Oncology recommend concurrent chemoradiotherapy with or without adjuvant chemotherapy as the standard basic treatment for stage II–IVB patients. However, AC is mainly used in patients with residual disease or those with advanced disease due to the lower compliance rate, especially after concurrent chemoradiotherapy.^{17,18} Evidence from a Phase III trial supports that concurrent chemoradiotherapy is recommended for some early stages of NPC,¹⁹ which comprises the level 2B evidence in the latest version of guidelines.²⁰ Interestingly, neoadjuvant chemotherapy plus concurrent chemoradiotherapy has been commonly used in stage II–IVB NPC patients in many hospitals in People's Republic of China because the considerable response rate is superb. Nevertheless, this combined treatment was recommended as level 3 evidence in the latest version of guidelines.²⁰ A pooled data analysis of two Phase III studies has shown that the addition of neoadjuvant chemotherapy to RT significantly improves the disease-specific survival of stage II–IVB NPC patients but that no improvement in OS is observed.²¹ The efficacy of neoadjuvant chemotherapy remains unclear, and data for stage II NPC patients are limited in the IMRT era. Until recently, almost all previous studies have demonstrated that IMRT combined with chemotherapy (IMRT+CT) does not improve survival for stage II NPC patients but instead increases the acute toxicity reaction.^{22–25} In these studies, however, the median reported follow-up was 2–5 years, which is relatively short for early-stage patients with NPC.

In our practice, the majority of patients with NPC received IMRT after 2002. Therefore, we retrospectively reviewed the long survival outcome of patients with stage II NPC who were treated with IMRT with or without

chemotherapy. The aim of the study was to investigate the roles of chemotherapy for stage II NPC patients and to further evaluate the efficacy of different chemotherapy patterns in treatments during the IMRT era.

Patients And Methods

Patients And Workup

This study was approved by the Institutional Review Board of Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences (no SDTHEC201806036). All procedures were in accordance with the principles of the Declaration of Helsinki and its later amendments or comparable ethical standards. Due to the retrospective nature of the study, informed consent was waived by the Ethics Committee. Between January 2002 and December 2013, 2647 patients were histologically diagnosed with NPC at the Shandong Cancer Hospital. Pretreatment evaluation included complete blood chemistry, fiberoptic endoscopic examination of the nasopharynx, contrast-enhanced computed tomography and/or magnetic resonance imaging (MRI) of the head-and-neck region to evaluate the primary tumor and regional lymph nodes. Chest computed tomography, bone scintigraphy, ultrasonography of the abdominal region and/or fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG PET/CT) were used to diagnosis distant metastases. All patients were reviewed and restaged according to the 8th edition AJCC classification system. Two hundred forty-four patients were classified as having stage II NPC. Of the stage II patients, 75 were excluded due to the following reasons: inadequate dose of RT (<66 Gy); age <18 or >80 years old; second primary tumor; previous chemotherapy history and RT of neck region history; or traditional RT. Finally, the remaining 169 patients were analyzed in the study. All patients were divided into the T₂N₀M₀ and T₁₋₂N₁M₀ subgroups.

Radiotherapy

All patients received computed tomography simulation with intravenous injection contrast to delineate the target volume, and the head, neck, and shoulder of all patients were immobilized by a thermoplastic mask. Target volumes include gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). GTV₆₆₋₇₂ (the subscript 66–72 denotes the radiation dose delivered) includes primary tumor and metastatic lymph nodes. Different regions need accurate selection and

delineation of the CTV. The high-risk region (CTV_{54–60}) was defined as the entire nasopharynx, ensuring inferior coverage of soft palate, clivus, skull base, pterygoid fossae, parapharyngeal space, sphenoid sinus, posterior 1/3 of the maxillary sinuses, posterior 1/3 of the nasal cavity, posterior ethmoid sinuses, and retropharyngeal nodal regions in levels II–V. When the lymph nodes in level II were larger than 3 cm or had extranodal extension, level IB nodal region was included. The low-risk region (CTV_{44–50}) was the cervical lymph node prevention area. PTV was delineated by adding 3 mm margins around CTVs to setup the variability and internal motion. If CTVs were adjacent to critical organs, such as brain stem and spinal cord, the margin was reduced to 1 mm. The organs at risk, including the brainstem, spinal cord, optic nerves, optic chiasm, pituitary gland, lens, temporal lobes, parotid glands, temporomandibular joints, and mandible, were also delineated. All patients were administered 1.8–2 Gy/d for 5 days a week.

Chemotherapy

Chemotherapy was used in neoadjuvant and concurrent settings. Accordingly, there were four treatment groups as follows: IMRT alone in 20 patients; neoadjuvant chemotherapy followed by IMRT (NCT) in 25 patients; concurrent chemotherapy with IMRT (CCRT) in 55 patients; and neoadjuvant chemotherapy followed by CCRT (NC+CCRT) in 69 patients. Among the patients treated with chemotherapy, 96 patients used the PF regimen as follows: cisplatin (75–100 mg/m² intravenously in three daily doses) plus 5-fluorouracil (500–1000 mg/m² intravenously in five daily doses). In addition, 27 patients received the TP regimen as follows: cisplatin (75–100 mg/m² intravenously in three daily doses) plus paclitaxel (135 mg/m² intravenously on day 1). Of patients who underwent concurrent chemotherapy, 34 received cisplatin only (75–100 mg/m² intravenously in three daily doses), 16 received the TP regimen, and 40 received the PF regimen. The reason that patients received chemotherapy mainly for patients with advanced N, larger tumor volume, or at the physician's discretion and so on (the record was incomplete due to retrospective nature).

Management Of Acute Toxicity Reactions

Treatment-related toxicity was scored according to the Radiation Therapy Oncology Group radiation morbidity scoring criteria. The acute toxicity mainly included skin reaction, mucous reaction, and hematotoxicity. Hematotoxicity mainly included leucopenia, neutropenia, thrombopenia, and

oligocythemia. Routine blood work was performed at least once a week, and biochemical analysis was performed at least once every 2 weeks during the course of treatment. The acute RT reactions were evaluated once a week from the start of RT to 3 months after the end of RT.

Follow-Up

After completing treatment, patients were subsequently followed up every 3 months during the first 2 years and every 6 months during the second year to the fifth year, and patients were then followed up every year until death. Basic blood chemistry, computed tomography and/or MRI (including base of skull, nasopharynx, and neck to clavicles) as well as chest radiography, computed tomography and abdomen ultrasonography were performed. For patients with evidence of local-regional recurrence or distant metastasis, biopsy, pathological diagnosis, and/or FDG PET-CT were required to confirm disease progression.

The OS was defined as the period from the start of treatment to the date of death from any cause or the censoring of patients at the last follow-up. Progression-free survival (PFS) was defined as the period from the start of treatment to the first progression or final follow-up. Local-regional relapse-free survival (LRFS) was defined as the period from the start of treatment to first local-regional recurrence or final follow-up. Distant metastasis-free survival (DMFS) was defined as the interval from the start of treatment to first distant metastasis or final follow-up.

Statistical Analysis

SPSS for Windows (version 20.0; IBM Corporation, NY, USA) was used to perform all statistical analyses. Chi-square test or Fisher exact test was performed to compare the difference of basic characteristics (age, sex, N stage, T stage, pathology (WHO), and clinical stage) among patients treated by NCT, CCRT, NC+CCRT, and IMRT alone. Nonparametric tests were used to compare acute toxicity reactions among treatment arms. Survival curves were calculated using the Kaplan–Meier method and were analyzed by the log-rank test. The Cox proportional hazard model using backward stepwise elimination procedure to remove variables with a p-value of ≥ 0.10 was used in multivariate analysis to determine the prognostic significance of variables. Considering the imbalance date between different groups, a bootstrap validator was used during the analyses to revise the statistical bias.²⁶ All

statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient And Tumor Characteristics

The study population consisted of 126 males and 43 females, and the median age was 46 years old (range from 18 to 78 years). The patients received the following treatments: 149 patients received IMRT+CT; 63.1% of patients (94/149) received neoadjuvant chemotherapy; and 88.6% of patients (124/140) received concurrent chemotherapy. In a subgroup, there were 47 patients staged in $T_2N_0M_0$, and the other 122 were staged in $T_{1-2}N_1M_0$. The clinical characteristics of patients were compared according to IMRT with or without chemotherapy (Table 1). The characteristics of patients in the different groups were in good balance, except for N stage and clinical stage. There were significantly more patients with N1 stage and $T_2N_1M_0$ stage in the IMRT+CT groups compared to the IMRT alone group (NCT, CCRT, and NC+CCRT vs IMRT alone; N stage: 12.4%, 20.1%, and 34.4% vs 5.3%,

respectively, $P = 0.001$; and $T_2N_1M_0$ stage: 11.8%, 18.3%, and 33.8% vs 5.3%, respectively, $P = 0.001$).

Survival

By the end of December 2017, the median follow-up was 93 months (2–160 months) with the following stats: 43 patients died, 7 patients experienced loco-regional recurrence, and 5 patients developed distant metastases. The total 10-year OS, PFS, LRFS, and DMFS were 70.8%, 87.4%, 87.4%, and 87.4%, respectively. The survival curves are shown in Figure 1. No statistically significant differences in the 10-year OS, PFS, and LRFS were found in the NCT, CCRT, and NC+CCRT groups compared to the IMRT alone group (OS: 69.8%, 63.4%, and 69.7% vs 72.4%, $P = 0.664$, 0.940, and 0.998, respectively; PFS: 74.1%, 93.8%, and 89.3% vs 75.5%, $P = 0.620$, 0.169, and 0.156, respectively; LRFS: 74.1%, 93.8%, and 89.3% vs 75.5%, $P = 0.620$, 0.169, and 0.156, respectively; DMFS: 74.1%, 98%, and 96.5% vs 100%, $P = 0.170$, 0.552, and 0.452, respectively) as shown in Table 2.

Table 3 shows the results of univariate and multivariate analyses of prognostic factors. In the univariate analyses,

Table 1 Baseline Characteristics Of The 169 Patients With Stage II NPC

Characteristics	Total (n=169, 100%)	IMRT Alone (n=20, 11.8%)	NCT (n=25, 14.8%)	CCRT (n=55, 32.5%)	NC+CCRT (n=69, 40.9%)	P
Age (median age 46-year)						0.131
≤ 46	80 (47.3%)	7 (4.1%)	13 (7.7%)	21 (12.4%)	39 (23.1%)	
>46	89 (52.7%)	13 (7.7%)	12 (7.1%)	34 (20.1%)	30 (17.8%)	
Sex						0.279
Male	126 (74.6%)	17 (10.1%)	15 (8.9%)	42 (24.9%)	52 (30.8%)	
Female	43 (25.5%)	3 (1.7%)	10 (5.9%)	13 (7.6%)	17 (10.1%)	
Pathology (WHO)						0.062
II type	81 (47.9%)	7 (4.1%)	14 (8.3%)	33 (19.5%)	27 (16.0%)	
III type	88 (52.1%)	13 (7.7%)	11 (6.5%)	22 (13.0%)	42 (24.9%)	
T stage ^a						0.485
T1	5 (3%)	0 (0.0%)	1 (0.6%)	3 (1.8%)	1 (0.6%)	
T2	164 (97%)	20 (11.8%)	24 (14.2%)	52 (30.8%)	68 (40.3%)	
N stage ^a						0.001*
N0	47 (27.8%)	11 (6.5%)	4 (2.4%)	21 (12.4%)	11 (6.5%)	
N1	122 (72.2%)	9 (5.3%)	21 (12.4%)	34 (20.1%)	58 (34.4%)	
Clinical stage ^a						0.001*
T1N1M0	5 (3%)	0 (0.0%)	1 (0.6%)	3 (1.8%)	1 (0.6%)	
T2N0M0	47 (27.8%)	11 (6.5%)	4 (2.4%)	21 (12.4%)	11 (6.5%)	
T2N1M0	117 (69.2%)	9 (5.3%)	20 (11.8%)	31 (18.3%)	57 (33.8%)	

Notes: ^aAccording to the eighth edition AJCC/UICC staging system. *Means $P \leq 0.05$.

Abbreviation: IMRT, intensity-modulated radiotherapy; NCT, neoadjuvant chemotherapy followed by RT alone; CCRT, concurrent chemoradiotherapy; NC+CCRT, neoadjuvant chemotherapy followed by CCRT; T, primary tumor; N, lymph node; n, number.

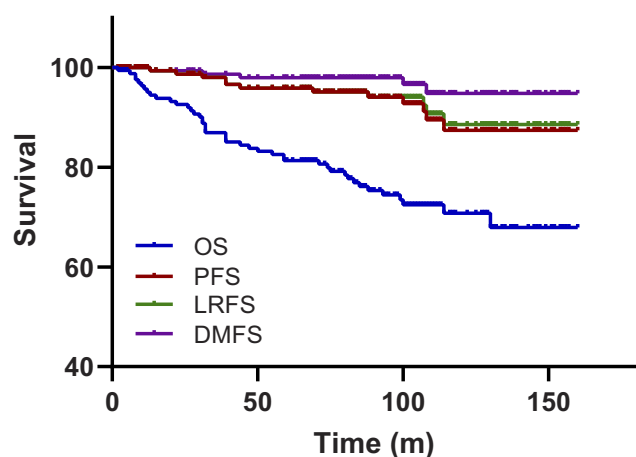


Figure 1 Overall survival (OS), progression-free survival (PFS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) rates for all patients.

age and N stage were significant prognostic factors for OS of stage II patients ($P=0.007$ and $P=0.035$, respectively). No significant prognostic factor was identified for PSF, LRFS, or DMFS. Moreover, the results of the multivariable analyses were in line with the outcome of the univariable analyses. The OS tended to decrease with N1 stage (Figure 2A) and older age (Figure 2B) (age: HR 2.686, 95% CI 1.347–5.353, $P=0.005$; and N stage: HR 3.065, 95% CI 1.238–7.588, $P=0.015$).

Upon subgroup analysis, we further analyzed whether adding chemotherapy to IMRT can improve survival benefits in the $T_{1-2}N_1M_0$ group. In the $T_{1-2}N_1M_0$ group, neoadjuvant chemotherapy with concurrent chemoradiotherapy significantly improved PFS (86.4% vs 60%, $P=0.037$) (Figure 3A and Table 2). Adding neoadjuvant chemotherapy, concurrent chemoradiotherapy or both to IMRT significantly improved the LRFS (NCT, CCRT, and NC+CCRT vs IMRT alone: 100%, 92.6%, and 90.3% vs 60%, $P=0.02$, 0.034, and 0.007, respectively) (Figure 3B and Table 2). However, no statistically significant difference in OS and DMFS was found between the IMRT+CT groups and the IMRT group. The results of the multivariate analyses for the $T_{1-2}N_1M_0$ subgroup are shown in Table 3. The results of the multivariate analyses for the $T_{1-2}N_1M_0$ subgroup are shown in Table 3. Older age was associated with poor OS (HR 2.589, 95% CI 1.243–5.392, $P=0.011$). Neoadjuvant chemotherapy and concurrent chemotherapy were dependent prognostic factors for PFS (NCT: HR 0.320, 95% CI 0.102–1.002, $P=0.05$; CCRT: HR 0.207, 95% CI 0.055–0.775, $P=0.019$) and LRFS (NCT: HR 0.121, 95% CI 0.023–0.628, $P=0.012$; CCRT: HR 0.093, 95% CI 0.011–0.780,

$P=0.029$). None of the tested factors was found to be prognostic for DMFS.

Toxicity Reaction

No fatal toxicity reaction occurred in the patients. Fifty-nine patients suffered $\geq$ grade 3 hematotoxicity with 98.3% (58/59) occurring in the IMRT+CT groups. Seventeen patients suffered $\geq$ grade 3 skin reaction with 94.1% (16/17) occurring in the IMRT+CT groups. Sixty patients suffered $\geq$ grade 3 mucous reaction with 91.7% (55/60) occurring in the IMRT+CT groups (Table 4). The hematotoxicity and mucous reaction of patients in the IMRT+CT groups were much more serious than those patients treated with IMRT alone ($P=0.007$ and 0.049, respectively) (Table 4). Table 4 shows the higher incidence of skin reaction in the IMRT+CT groups than the IMRT alone group, but there were no statistical differences between the groups ($P=0.173$). In the $T_{1-2}N_1M_0$ subgroup, the same results were obtained. The incidence of $\geq$ grade 3 hematotoxicity and mucositis was significantly higher in patients treated with IMRT+CT than in those treated with IMRT alone ($P=0.033$ and 0.022, respectively), but there was no difference in skin reaction.

Discussion

The present study showed that combining neoadjuvant chemotherapy, concurrent chemotherapy or both with IMRT did not improve survival outcomes in stage II NPC patients, but the combination treatments increased the incidences of acute treatment-associated toxicities compared to treatment with IMRT alone. Furthermore, subgroup analysis showed that IMRT combined with chemotherapy had more effective loco-regional control than IMRT alone in patients in the $T_{1-2}N_1M_0$ subgroup.

Although many studies have documented the survival outcomes in early-stage NPC, there have been few studies reporting the outcomes with 10-year follow-up, especially for NPC patients with stage II. To the best of our knowledge, the present study was the first to report the longest follow-up time in stage II NPC patients treated by IMRT. With a median follow-up of 93 months, 169 patients with stage II had excellent survival outcome. Using traditional RT in a retrospective study with long-term follow-up, the 5-year and 10-year disease-specific survival rates were 77% and 60%, the LRFS values were 83% and 78%, and the DMFS values were 72% and 64%, respectively,²⁷ which were lower than in patients treated with IMRT. The worse OS and loco-regional control of traditional RT may be due to the underdosing of tumor with the goal of normal tissue

Table 2 Survival Of Patients With II Stage NPC

Variable	Overall Survival			P	Progression-Free Survival			P	Locoregional Relapse-Free Survival			P	Distant Metastasis-Free Survival			P
	3-	5-	10-		3-	5-	10-		3-	5-	10-		3-	5-	10-	
Total	85.1%	81.3%	70.8%	0.664	96.6%	95.1%	87.4%	0.620	96.6%	95.1%	87.4%	0.620	98.7%	97.9%	94.8%	0.170
	78.9%	72.4%	72.4%		88.5%	88.5%	75.5%		88.5%	88.5%	75.5%		100%	100%	100%	
	87.3%	78.6%	69.8%		100%	100%	74.1%		100%	100%	74.1%		100%	100%	74.1%	
	88.7%	85.0%	63.4%		96.0%	93.8%	93.8%		96.1%	93.9%	93.9%		98.0%	98.0%	98.0%	
T ₂ N ₀ M ₀	83.1%	76.9%	69.7%	0.998	98.3%	94.0%	89.3%	0.156	98.3%	96.5%	89.3%	0.156	98.3%	96.5%	96.5%	0.452
	97.7%	95.5%	83.6%		100%	100%	100%		100%	100%	100%		100%	100%	100%	
	90.0%	77.1%	77.1%		100%	100%	100%		100%	100%	100%		100%	100%	100%	
	100%	100%	100%		100%	100%	100%		100%	100%	100%		100%	100%	100%	
T ₁₋₂ N ₁ M ₀	100%	94.1%	81.4%	0.569	100%	100%	100%	-	100%	100%	100%	-	100%	100%	100%	-
	100%	90.0%	90.0%		100%	100%	100%		100%	100%	100%		100%	100%	100%	
	100%	90.0%	90.0%		100%	100%	100%		100%	100%	100%		100%	100%	100%	
	100%	90.0%	90.0%		100%	100%	100%		100%	100%	100%		100%	100%	100%	
T ₁₋₂ N ₁ M ₀	80.3%	75.9%	62.8%	0.726	95.1%	93.0%	82.7%	0.177	97.0%	95.8%	89.2%	0.02*	98.1%	97.0%	92.7%	0.268
	66.7%	66.7%	66.7%		75.0%	75.0%	60.0%		75.0%	75.0%	60%		100%	100%	100%	
	85.4%	76.0%	66.5%		100%	100%	70%		100%	100%	100%		100%	100%	70%	
	81.9%	75.8%	56.2%		93.3%	89.6%	89.6%		96.4%	92.6%	92.6%		96.8%	96.8%	96.8%	
NC+CCRT	79.6%	74.1%	65.2%	0.824	98.0%	95.6%	86.4%	0.037*	100%	96.8%	90.3%	0.007*	97.9%	95.6%	95.6%	0.593

Notes: P means the difference in 10-year survivals of NCT, CCRT, and NC+CCRT groups compared with IMRT alone group. *Means P≤0.05. Data are percentages unless especially indicated.

Abbreviations: IMRT, intensity-modulated radiotherapy; NCT, neoadjuvant chemotherapy followed by IMRT; CCRT, concurrent chemotherapy with IMRT; NC+CCRT, neoadjuvant chemotherapy followed by CCRT; T, primary tumor; N, lymph node; M, metastasis.

Table 3 Univariate Analysis And Multivariable Analysis

	OS			PFS			LRFS			DMFS		
	Uni	Multi		Uni	Multi		Uni	Multi		Uni	Multi	
	P	P	HR (95% CI)	P	P	HR (95% CI)	P	P	HR (95% CI)	P	P	HR (95% CI)
All patients												
Age (≤ 46 -yr vs >46 years)	0.007*	0.005*	2.686 1.347–5.353	0.962	–	–	0.292	–	–	0.209	–	–
Gender (male vs female)	0.745	–	–	0.544	–	–	0.858	–	–	0.472	–	–
Histology (II vs III)	0.706	–	–	0.614	–	–	0.755	–	–	0.681	–	–
T stage ^a (T1 vs T2)	0.453	–	–	0.668	–	–	0.749	–	–	0.775	–	–
N stage ^a (N ₀ vs N ₁)	0.035*	0.015*	3.065 1.238–7.588	0.184	–	–	0.313	–	–	0.388	–	–
NC (no vs yes)	0.630	–	–	0.742	–	–	0.503	–	–	0.106	–	–
CC (no vs yes)	0.895	–	–	0.513	–	–	0.760	–	–	0.519	–	–
NC+CC (no vs yes)	0.880	–	–	0.569	–	–	0.495	–	–	0.945	–	–
T₁₋₂N₁M₀ patients												
Age (≤ 46 years vs >46 years)	0.006*	0.011*	2.589 1.243–5.392	0.909	–	–	0.249	–	–	0.247	–	–
Gender (male vs female)	0.531	–	–	0.600	–	–	0.912	–	–	0.500	–	–
Histology (II vs III)	0.770	–	–	0.638	–	–	0.779	–	–	0.692	–	–
T stage (T1 vs T2)	0.412	–	–	0.608	–	–	0.703	–	–	0.732	–	–
NCT (no vs yes)	0.232	–	–	0.107	0.005*	0.320 0.102–1.002	0.027*	0.012*	0.121 0.023–0.628	0.681	–	–
CCRT (no vs yes)	0.111	0.702	0.854 0.380–1.920	0.034*	0.019*	0.207 0.055–0.775	0.052	0.029*	0.093 0.011–0.780	0.426	–	–
NC+CC (no vs yes)	0.064	0.338	0.619 0.232–1.650	0.144	–	–	0.218	–	–	0.417	–	–

Notes: *Means $P \leq 0.05$. ^aDate between two comparison groups were imbalance, bootstrap validator was used during the analyses to revise the statistics bias.

Abbreviations: OS, overall survival; PFS, progression-free survival; LRFS, progression-free survival; DMFS, distant metastasis-free survival; CC, concurrent chemotherapy; NC, neoadjuvant chemotherapy; NC+CC, neoadjuvant and concurrent chemotherapy; Uni, univariate analysis; Multi, multivariable analysis.

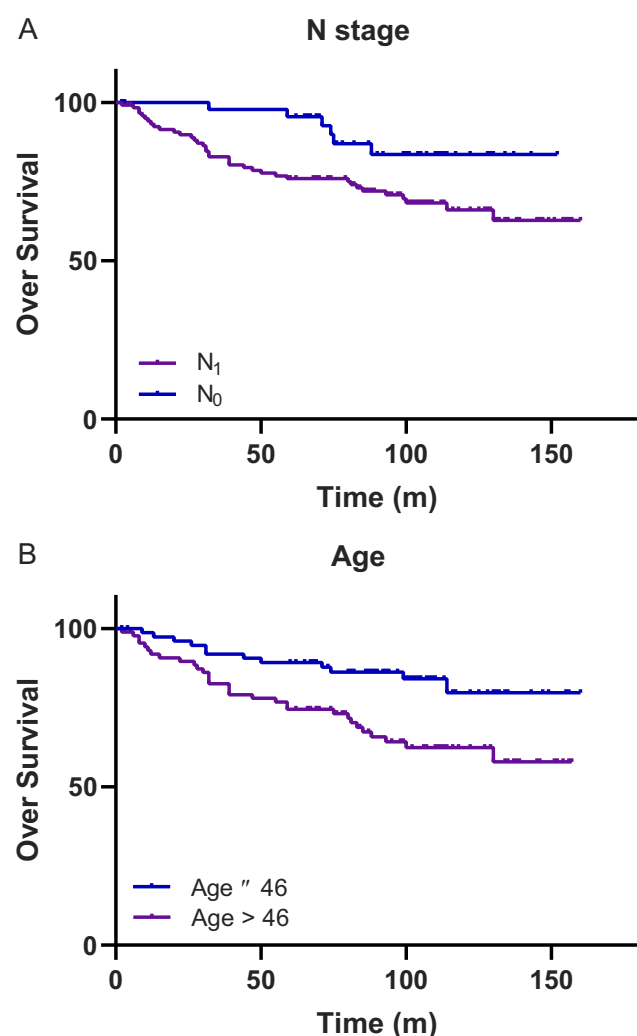


Figure 2 N stage and age were the independent prognostic factors for over survival (OS) of stage II NPC patients. **(A)** OS tended to decrease with N₁ stage ($P=0.005$); **(B)** OS tended to decrease with older age (>46 years old) ($P=0.015$).

protection. In other words, IMRT can improve tumor delineation and target coverage, resulting in excellent outcomes for stage II NPC. Meta-analyses of randomized studies have indicated that combining chemotherapy and RT increases 5-year survival by 4% to 6% and reduces the risk of mortality by 18%.²⁸ Nevertheless, the value of chemotherapy for stage II NPC is still unknown in the IMRT era. The main advantage of neoadjuvant chemotherapy is early eradication of micro-metastasis, which consequently enhances OS by reducing the distant metastasis rate. Due to both loco-regional control and survival benefit, concurrent chemoradiotherapy is better than RT alone, which has been a standard treatment for locally advanced NPC.^{29,30} For early-stage treatment, Cheng et al³¹ reported that RT alone achieves a loco-regional control rate of 91.7% in patients (12) with stage I or II NPC and that concurrent

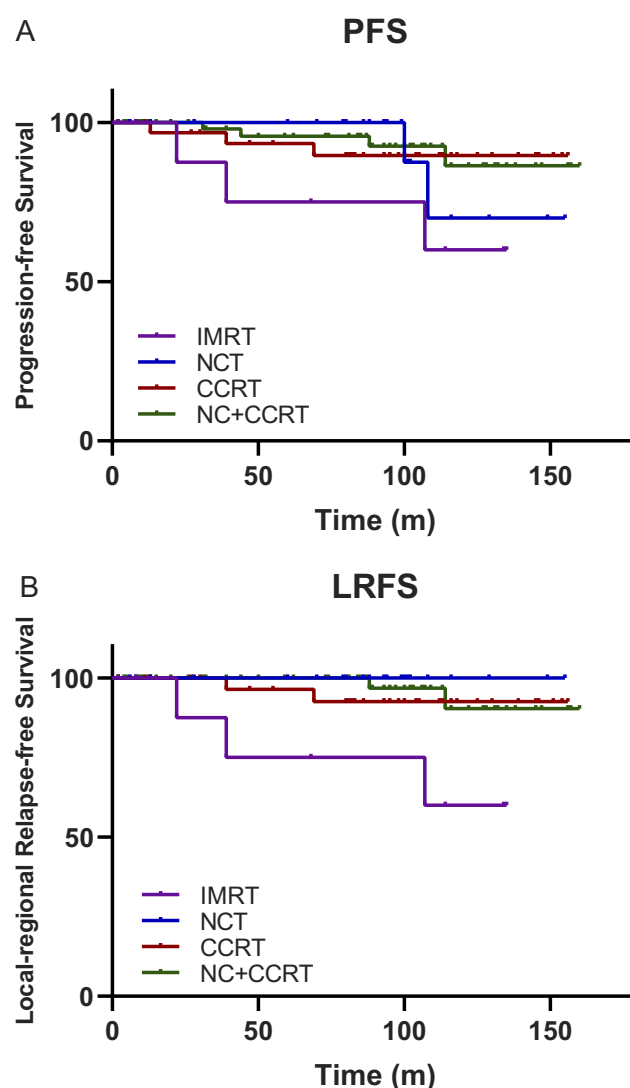


Figure 3 In T₁₋₂N₁M₀ group, intensity-modulated radiotherapy (IMRT) combined with chemotherapy had more loco-regional control effective. **(A)** Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy (NC+CCRT) can improve progression-free survival significantly ($P=0.037$); **(B)** the addition of chemotherapy to IMRT can improve the local-regional relapse-free survival significantly (neoadjuvant chemotherapy with radiotherapy (NCT) vs IMRT, $P=0.02$, concurrent chemoradiotherapy (CCRT) vs IMRT, $P=0.034$; NC+CCRT vs IMRT, $P=0.007$).

chemotherapy achieves 100% at 3 years in patients (32) with AJCC 1997 stage II NPC. Other clinical trials have produced similar results.^{9,25} However, the expected advantageous effect of neoadjuvant chemotherapy or concurrent chemotherapy was not found in the present study. The 3-year OS, 5-year OS, 10-year OS, PFS, LRFS, and DMFS all had no significant differences between IMRT+CT groups and IMRT alone group, but they increased the acute toxicity reactions. Similar results were obtained in another recently reported retrospective study,³² 242 stage II NPC patients in the study received IMRT combining with neoadjuvant chemotherapy and/or concurrent chemotherapy, the result

Table 4 Acute Toxicity Reactions Between IMRT Alone, NCT, CCRT, NC+CCRT Groups

	Number	<Grade 3	≥Grade 3	P
		Number (%)	Number (%)	
All patients	169			
Hematotoxicity				0.007*
IMRT alone	20	19 (95)	1 (5)	
NCT	25	18 (72)	7 (28)	
CCRT	56	34 (60.7)	22 (39.3)	
NCT+CCRT	68	39 (57.4)	29 (42.6)	
Skin reaction				0.173
IMRT alone	20	19 (95)	1 (5)	
NCT	25	25 (100)	0 (0)	
CCRT	56	50 (89.3)	6 (10.7)	
NCT+CCRT	68	58 (85.3)	10 (14.7)	
Mucous reaction				0.049*
IMRT alone	20	15 (75)	5 (25)	
NCT	25	21 (84)	4 (16)	
CCRT	56	35 (62.5)	21 (37.5)	
NCT+CCRT	68	38 (55.9)	30 (44.1)	
T ₁₋₂ N ₁ M ₀ patients	122			
Hematotoxicity				0.033*
IMRT alone	9	8 (88.9)	1 (11.1)	
NCT	21	18 (85.7)	3 (14.3)	
CCRT	35	21 (60)	14 (40)	
NCT+CCRT	57	34 (59.6)	23 (40.4)	
Skin reaction				0.435
IMRT alone	9	8 (88.9)	1 (11.1)	
NCT	21	21 (100)	0 (0)	
CCRT	35	31 (88.6)	4 (11.4)	
NCT+CCRT	57	48 (84.2)	9 (15.8)	
Mucous reaction				0.022*
IMRT alone	9	7 (77.8)	2 (22.2)	
NCT	21	17 (81)	4 (19)	
CCRT	35	21 (60)	14 (40)	
NCT+CCRT	57	25 (43.9)	32 (56.1)	

Note: *Means $P \leq 0.05$.

Abbreviations: IMRT, intensity-modulated radiotherapy; NCT, neoadjuvant chemotherapy with intensity-modulated radiotherapy; CCRT, concurrent chemotherapy with intensity-modulated radiotherapy; NC+CCRT, neoadjuvant and concurrent chemotherapy with intensity-modulated radiotherapy.

showed that combined regimens did not improve 5-year OS, PFS, LRFS, and DMFS, but were associated with higher incidences of acute toxicity reactions than IMRT alone.

The disappointing results of chemotherapy for stage II NPC patients may have several explanations. First, distant metastasis was the most common pattern of treatment failure. Significantly more patients with N₁ stage and

T₂N₁M₀ stage were in the IMRT+CT groups compared to the IMRT alone group (both $P=0.001$), which may explain the inferior prognosis in the IMRT+CT groups. For patients with stage II, several studies have demonstrated that stage N₁ is the greatest risk factor in predicting DMFS and OS. Luo et al²³ reported that patients with stage T₁₋₂N₁M₀ have greater 5-year accumulated distant metastasis rates than those with stage T₁₋₂N₀M₀, and they also showed that OS is significantly higher in the T₂N₀M₀ group than the T₁₋₂N₁M₀ group ($P = 0.028$). Similarly, all 5 (6.5%) patients who developed distant metastasis belonged to stage T₁₋₂N₁M₀ in the present study. Additionally, N stage was an independent prognosis of increasing risk of OS ($P = 0.015$). Together, these conclusions suggest that T₁₋₂N₁M₀ is a unique subgroup with treatment outcomes far from satisfactory. Therefore, it is reasonable to presume that stage T₁₋₂N₁M₀ NPC may need a more intensive treatment modality than stage T₂N₀M₀ NPC. For T₁₋₂N₁M₀ NPC patients in the subgroup analysis, adding chemotherapy to IMRT favored loco-regional control, but it did not improve OS or prevent distant failure. Based on these findings, neoadjuvant chemotherapy and concurrent chemotherapy can both be expected to improve local-regional control in T₁₋₂N₁M₀ NPC patients, but this expectation was not reflected by an OS improvement.

Second, the potential effect of chemotherapy on eliminating distant metastasis could be diluted by an uncontrolled loco-regional tumor. In the present study, four patients (4/5) developed metastasis synchronously or after loco-regional recurrence. DMFS was still stable in the third year (98.7%), fifth year (97.9%), and tenth year (94.8%), indicating that distant metastasis mostly occurred in the first 3 years. The important finding for stage II NPC was different from advanced NPC, in which distant metastasis mainly occurred after 3 years.³ Because IMRT provides a sufficient dose to the tumor target and kills micro-foci in early-stage NPC, chemotherapy probably reaches the highest efficacy with the combined modality of IMRT in stage II NPC. However, there was no room for improving local tumor control or to decrease distant metastases. With gradually decreasing PFS, LRFS and DMFS rates, the OS rate greatly decreased (14.3%) from the third year to tenth year in the study. These results also suggested that death was mainly caused by cancer indirectly early on, while the reasons of death later on were mainly related to noncancer effects, including treatment-related toxicities, second primary tumor, natural deaths or other diseases, which agreed with

the opinions of others.^{3,33} Therefore, longer follow-up periods of early-stage NPC patients resulted in lower potential effects of chemotherapy.

Finally, using neoadjuvant or concurrent chemotherapy can enhance radio-sensitivity in the treatment of NPC. However, delayed administration of RT may cause accelerated repopulation of tumor clones, which may contribute to lower LRFS in the neoadjuvant chemotherapy group. Acute toxicities associated with chemotherapy may decrease the survival benefit, which agreed with the conclusions of Guo et al²⁴ and Xu et al³⁴. Similar to previous studies, leucopenia, neutropenia, thrombocytopenia, skin reaction, and mucous reaction were mainly observed in patients. Compared to the IMRT alone group, the degrees of acute treatment-associated toxicities were notably higher in the IMRT+CT groups in the present study. There were more patients who suffered $\geq$ grade 3 acute hematologic toxicities and mucous reaction in the chemotherapy (including NCT, CCRT, NT+CCRT) groups, which was consistent with previous studies.^{23,35} Because the chemotherapy was untargeted, the combination of chemotherapy and IMRT not only attacked tumor cells but also normal cells, indicating that the balance between disease and human body was disturbed. This disadvantage may compromise the advantage of killing micrometastasis in the early phase. Therefore, further studies on combining high efficiency and low toxicity medicines, target therapy or immunotherapy with IMRT should be conducted to improve the OS of patients with stage II NPC.

The present study has several limitations. First, the number of IMRT alone patients was limited. Second, late toxicity reactions could not be completely collected for analysis. Third, during the long follow-up period, the chemotherapy regimens were not unified, which may influence the results. Therefore, well-designed randomized trials with long-term follow-up are important in the future.

Conclusion

In conclusion, patients with stage II NPC treated with IMRT obtained satisfactory survival outcomes. Moreover, the addition of chemotherapy did not further improve the survival of stage II NPC patients treated with IMRT. Almost all disease progress developed within 3 years after treatment, which differs from advanced NPC. Chemotherapy can improve local-regional control in T₁₋₂N₁M₀ NPC patients, but it does not improve OS. Furthermore, the addition of chemotherapy increased the acute toxicity reactions, especially hematotoxicity and mucous reaction. In the future, additional

data from randomized trials are still urgently needed to guide the management of stage II NPC patients.

Acknowledgments

This work was supported by the Key Research and Development Plan of Shandong, China (grant no. 2019GGX101057), National key research and development program of China (grant no. 2018YFC1313200), and Science Technology Program of Jinan (grant no. 201821011).

Disclosure

The authors report no conflicts of interest in this work.

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