Translational Oncology
www.transonc.com

Volume 13 Number 1 January 2020 pp. 25–31 25

Concurrent Chemoradiotherapy With or Without Induction Chemotherapy for Patients with Stage II Nasopharyngeal Carcinoma: An Update

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Abstract

PURPOSE: In contrast to other studies, our previous study showed that adding induction chemotherapy (IC) to concurrent chemoradiotherapy (CCRT) significantly worsened the prognosis of patients with stage II nasopharyngeal carcinoma (NPC). However, the population used was small; therefore, there is an urgent need to confirm the result in a larger population because IC is still widely used in certain sections of china for stage II NPC. *METHODS AND MATERIALS:* We retrospectively analyzed an additional 272 patients. Therefore, in total, we report the results for 445 patients with stage II NPC treated with IC + CCRT or CCRT between June 2003 to June 2016 at the Zhejiang Cancer Hospital and Sun Yat-Sen University Cancer Center. *RESULTS:* This study included 445 patients treated with IC + CCRT (n = 195) or CCRT (n = 250). By last analysis, 22 (11.3%) patients in the IC + CCRT group developed local-regional recurrence and 23 (11.8%) patients developed distant metastases. Twenty-four (9.6%) patients in the CCRT group developed local-regional recurrence and 12 (4.8%) patients developed distant metastases. Univariate analyses showed that adding IC to CCRT significantly decreased the 5-year disease-free survival (DFS) (80.6% vs. 88.5%, $P = .043$); however, there was no statistically significant difference in 5-year overall survival (OS) (90.5% vs. 95.0%, $P = .375$). *CONCLUSION:* Using a larger population, the present study showed that adding IC to CCRT had a negative effect on patients with stage II NPC, which warrants further investigation.

Translational Oncology (2020) 13, 25–31

Introduction

Worldwide, nasopharyngeal carcinoma (NPC) accounted for approximately 0.7% of new cancer diagnoses and 0.8% of all cancer deaths in 2018 [1]. It is estimated that approximately 129,079 new cases were diagnosed and 72,987 deaths occurred worldwide in 2018 [1]. NPC is unsuitable for surgery but sensitive to chemo-radiation; therefore, the combination of radiotherapy (RT) and chemotherapy (CT) is the primary treatment for NPC. Screening for plasma target

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Received 15 April 2019; Revised 6 August 2019; Accepted 7 August 2019

1936-5233/19
https://doi.org/10.1016/j.tranon.2019.08.007

EBV DNA levels has resulted in more patients being detected with early stage NPC [2]. Current NCCN guidelines recommend that the therapeutic choices for the management of stage II tumors in cancer of the nasopharynx are: (a) Clinical trials (preferred); (b) concurrent chemo/RT (CCRT) followed by adjuvant chemotherapy (AC) (category 2A); (c) induction chemotherapy (IC) followed by CCRT (category 2A); and (d) CCRT not followed by AC (category 2B) [3]. Therefore, the appropriate management of stage II NPC is still uncertain. In particular, the value of the neo-adjuvant chemotherapy remains controversial. Xu et al. [4] carried out a propensity score-matched analysis and revealed that compared with CCRT, 5-year distant metastasis free survival (DMFS) and 5-year overall survival (OS) were significantly increased for patients with stage II NPC receiving IC + RT. Guo et al. [5] carried out a retrospective analysis and revealed that the addition of chemotherapy (more than half of patients received neo-adjuvant chemotherapy) improved loco-regional relapse-free survival (LRRFS) [hazard ratio (HR) 0.263, 95% confidence interval (CI) 0.083−0.839, $P = .024$], especially for T1 N1 patients (HR 0.209, 95% CI 0.046−0.954, $P = .043$). Chua et al. [6] carried out a subgroup analysis of two phase III trials and revealed that the addition of neo-adjuvant chemotherapy improved OS and DMFS for patients with early T and N (T1-T2 N0-N1) stage disease ($P = .048$ and $P = .0053$).

By contrast, our previous retrospective study, which was published in 2018, showed that adding IC to CCRT significantly decreased the 5-year OS (87.9% vs. 95.5%, $P = .033$), 5-year progression free survival (PFS) (74.0% vs. 86.1%, $P = .035$) and 5-year locoregional failure-free survival (LRFFS) (80.0% vs. 91.2%, $P = .016$) in patients with stage II NPC who received intensity modulated radiotherapy (IMRT) [7]. The results were somewhat controversial. However, the population used was small, and there is an urgent need to confirm the result in a larger population because IC is still widely used in certain regions of China for stage II NPC. Therefore, we combined data from our previous study with data from 272 additional patients. In the present study, we report the results for 445 patients with stage II NPC treated between June 2003 to June 2016 from the Zhejiang Cancer Hospital and Sun Yat-Sen University Cancer Center who received IC + CCRT or CCRT.

Materials and Methods

Patients

This study integrated records from the Zhejiang Cancer Hospital and Sun Yat-Sen University Cancer Center. This was a non-randomized hypothesis-generating study. To confirm the value of adding induction chemotherapy (IC) to concurrent chemoradiotherapy (CCRT), the inclusion criteria of our present study were (1) pathologically biopsy-proven NPC, (2) American Joint Committee on Cancer (AJCC) 8th 2017 stage II (T2 N0, T1 N1, or T2 N1) disease, (3) completion of curative CCRT or IC + CCRT, and (4) complete information on patterns of failure and survival. We excluded patients who were not compliant with the above four inclusion criteria. From June 2003 to June 2016, this study finally included 445 patients treated with IC + CCRT (n = 195) or CCRT (n = 250). The patient and tumor characteristics are listed in Table 1.

Chemotherapy and Radiotherapy

Patients in the IC + CCRT group received IC regimens including cisplatin and fluorouracil (PF), gemcitabine and cisplatin (GP), paclitaxel and cisplatin and fluorouracil (TPF), or paclitaxel and cisplatin (TP), repeated every 3 weeks. Patients in IC + CCRT group or CCRT group received CCRT regimens including cisplatin (80−100 mg/m^2) on day 1 every 3 weeks or cisplatin (25−30 mg/m^2) on day 1 every week. Chemotherapy was postponed or discontinued for patients who experienced serious side effects and did not recover before the next cycle. Patients received two-dimensional conformal radiation therapy (2D-CRT) in two courses. The design of the 2D-CRT plan was based on those of previous studies [8]. Patients received IMRT using simultaneous modulated accelerated radiation therapy (SMART) technology. The design of the IMRT plan was based on those of previous studies [9−11].

Outcome and Follow-Up

Details of the assessment and monitoring of our patients were the same as those described in our previous study [7].

Statistical Analysis

Overall survival was, defined as the duration from the date of starting treatment to the date of death from any cause or the censoring of the patient at the date of the last follow-up. Disease-free survival was defined as the date of starting treatment to first failure at any site or death of any cause or patient censoring at the date of last follow-up. We used Kaplan−Meier survival curves to analyze the time-to-event endpoints, and the log-rank test to compare the differences between two groups. A multivariate analysis using the Cox proportional hazards model was performed to identify covariates that were significantly associated with the aforementioned endpoints. Chi-squared tests were used to compare categorical variables. Analyses were performed using the statistical software package SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, and $P < .05$ was considered statistically significant.

Results

Patient Characteristics

Among the 445 cases of patients with stage II NPC, 195 cases received IC + CCRT and 250 received CCRT. The distribution of T1 N1 M0, T2N0M0, and T2N1M0 were 34.4, 13.2, and 52.4%, respectively. There were no statistically significant differences in the proportional distribution of sex, age, and T stages (all $P > .05$), while the differences in the proportional distribution of radiation technique, as well as N stages and clinical stages, in the two groups were statistically significant (all $P < .05$). In the IC + CCRT group, there are more patients with stage N1 disease (93.3% vs. 81.6%, $P < .001$). Compared with the CCRT group, more patients received IMRT (47.2% vs. 37.2%, $P < .001$) in the IC + CCRT group. A comparison of the balance of patient characteristics in the two groups is shown in Table 1.

Follow-Up Results

The last follow-up time was June 30, 2018; the median follow-up time was 77.85 months (4 to 180 months). Up to the last day of follow-up, 19 patients died in the IC + CCRT group and 23 died in the CCRT group. The detailed failure patterns for the patients in the two groups are presented in Table 2. There were 38 cases of treatment failure in the IC + CCRT group and 35 cases of treatment failure in the CCRT group. Twenty-two patients in the IC + CCRT group and 24 in the CCRT group developed locoregional recurrence; however, the difference between the two groups was not significant

Table 1. Baseline characteristics of the 445 patients with stage II nasopharyngeal cancer in each treatment arm

Variable	IC + CCRT ($n = 195$)	CCRT ($n = 250$)	*P*-value *
Sex			.761
Male	141 (72.3)	184 (73.6)	
Female	54 (27.7)	66 (26.4)	
Age			.657
< 60	172 (88.2)	217 (86.8)	
≥ 60	23 (11.8)	33 (13.2)	
radiation technique			.034
2D-CRT = 3	103 (52.8)	157 (62.8)	
IMRT = 1	92 (47.2)	93 (37.2)	
T category			.156
T 1	60 (30.8)	93 (37.2)	
T 2	135 (69.2)	157 (62.8)	
N category			<.001
N 0	13 (6.7)	46 (18.4)	
N 1	182 (93.3)	204 (81.6)	
Stage			<.001
T1N1M0	60 (30.8)	93 (37.2)	
T2N0M0	13 (6.7)	46 (18.4)	
T2N1M0	122 (62.5)	111 (44.4)	

* Calculated using the χ^2 test. Values are shown as *n* (%). IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; 2D-CRT, two-dimensional conformal radiation therapy; IMRT, intensity modulated radiotherapy.

(11.3% vs. 9.6%, $P = .563$). Twenty-three patients developed distant metastases in the IC + CCRT group and 12 in the CCRT group, which was significantly different (11.8% vs. 4.8%, $P = .007$).

Survival Outcomes

The 3-, 5-, and 10-year OS rates of all patients were 95.2, 93.2, and 86.5% (Figure 1*A*), while the 3-, 5-, and 10-year DFS rates of all patients were 89.2, 85.1, and 79.5% (Figure 1*B*), respectively. Univariate analysis showed that the 5-year DFS was significantly worse in the IC + CCRT group compared with that in the CCRT group (80.6 vs. 88.5%, $P = .043$, Figure 1*C*), while multivariate analysis showed that different treatments were not independent prognostic factors (Tables 3, 4). No statistically significant difference in OS rates was found between the two groups (90.5% vs. 95.0%, $P = .375$, Figure 1*D*). The survival curves are shown in Figure 1.

Adverse Events During Induction Chemotherapy and Chemoradiotherapy

All the patients in both groups completed the prescribed dose of radiation. The overall incidence of grade 3−4 hematological toxic effects in the CCRT arm was statistically significantly lower than that in the IC + CCRT arm (6.4% vs. 23.6%, $P < .001$; anemia: 1.2% vs. 5.1%, $P = .015$; thrombocytopenia: 1.2% vs. 4.6%, $P = .027$; neutropenia: 5.6% vs. 20.5%, $P < .001$). In the IC + CCRT group, the main grade 3 or 4 hematological adverse event during IC was neutropenia (15.4%). Among the IC + CCRT group, 26.2% of patients experienced grade 1 or 2 liver dysfunction and 1.5% experienced grade 1 or 2 kidney dysfunction. Grade 1 or 2 liver dysfunction occurred in 35.9% of the IC + CCRT group and in 6.0% of the CCRT group ($P < .001$), and grade 1 or 2 kidney dysfunction occurred in 11.3% of the IC + CCRT group and 0.8% of the CCRT group ($P < .001$). The details of the adverse events in the two groups are shown in Table 5.

Table 2. Comparison of the treatment outcome of the different chemotherapy regimens

Variable	IC + CCRT ($n = 195$)	CCRT ($n = 250$)	χ^2	*P*-value *
Distant metastases			7.397	.007
no	172 (88.2)	238 (95.2)		
yes	23 (11.8)	12 (4.8)		
Locoregional failure			0.334	.563
no	173 (88.7)	226 (90.4)		
yes	22 (11.3)	24 (9.6)		

* Calculated using the χ^2 test. Values are shown as *n* (%). IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.

Discussion

In the present study, we retrospectively analyzed 445 patients with a longer follow-up than our previous retrospective study and found that adding IC to CCRT significantly decreased the 5-year DFS (80.6% vs. 88.5%, $P = .043$); however, there was no statistically significant difference in 5-year OS (90.5% vs. 95.0%, $P = .375$). In addition, IC + CCRT remarkably increased treatment-associated adverse events during CCRT when compared with CCRT alone.

To improve the prognosis of patients with stage-II NPC, CT is widely used in clinical practice because it could improve sensitivity to RT. A systemic review and meta-analysis of 2138 patients conducted by Xu et al. [12] found that CRT induced a significantly higher OS and LRRFS ($P = .04$ and $P = .0003$) than RT alone. Wang et al. [13] carried out a systemic review including 16 studies with 3038 patients to evaluate the efficacy and toxicity of adding CT to RT to treat stage-II NPC. They revealed that compared with RT alone, CRT could significantly improve OS, PFS, and LRFS (Risk ratios of 1.04, 1.05 and 1.05, respectively). With the combination of IMRT and concurrent chemotherapy, the 5-year progression free survival was only 86.1%, which still requires improvement [7].

One possible strategy to further improve patients' prognosis is a CCRT+ AC sequence. Chen et al. [14] carried out a retrospective study to explore whether CCRT with or without AC could improve the survival of patients with stage II NPC. Compared with CCRT+ AC, they reported that CCRT could achieve equivalent rates of OS (93.9% and 95.0%, $P = .937$), LRRFS (96.8% and 94.9%, $P = .756$) DMFS (91.1% and 97.5%, $P = .185$), and failure free survival (FFS) (84.9% and 92.5%, $P = .597$). Wu et al. [15] reported a phase II prospective study of withholding AC in patients with stage II and III NPC. Their results showed that the 5-year OS, DFS, and DMFS were 94.1%, 85.9%, and 92.9% for patients with stage II NPC, respectively. Based on the results of the above two studies, adding AC to CCRT does not provide additional benefit for patients with stage II NPC.

The other strategy is an IC + CCRT sequence. In 2015, Kang et al. [16] carried out a retrospective study including 138 patients with stage II NPC who were treated with curative radiotherapy in 12 hospitals in South Korea and found that IC failed to improve the LRRFS, DMFS, PFS, and OS rates. Notably, patients in the IC arm had more N1 disease and less AC compared with the without IC arm (100% vs. 81.6% $P = .025$ and 8.3% vs. 35.1% $P = .010$) and only 17 patients received IC + CCRT among 138 patients. In 2018, Fangzheng et al. [17] carried out a retrospective study including 242 patients with stage II NPC who were treated with curative IMRT in a single hospital in South China and found that the IMRT alone, IC + IMRT, IC + CCRT, and CCRT treatment groups had similar 5-year LRRFS, DMFS, PFS, and OS rates. In addition, among 242 patients, only 25 patients received CCRT, although the baseline characteristics were well balanced between the four treatment arms.

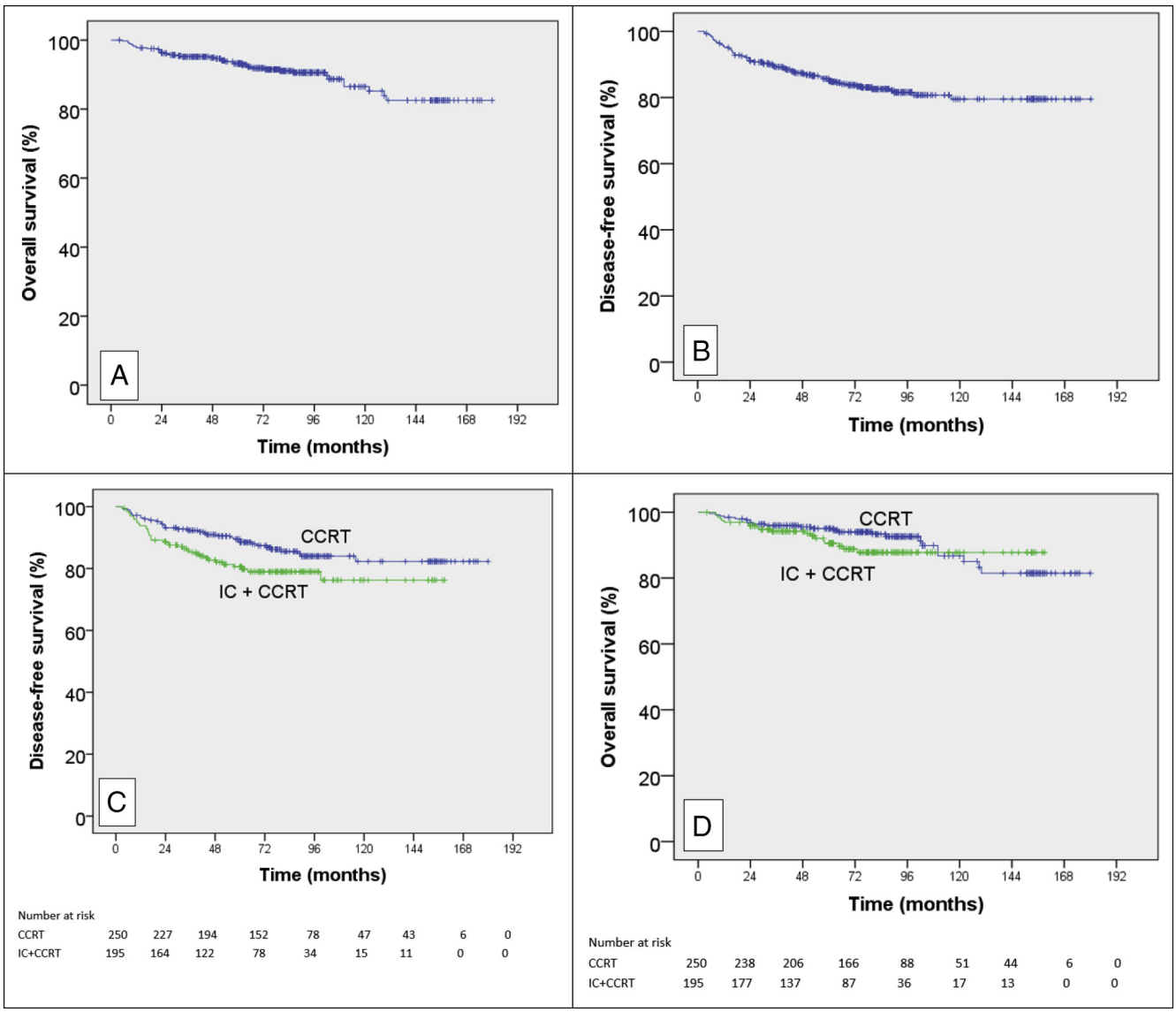

Figure 1. Kaplan–Meier estimates of (A) Overall survival for all patients. (B) Disease-free survival for all patients. (C) Disease-free survival for patients receiving IC + CCRT and CCRT alone ($P = .043$). (D) Overall survival for patients receiving IC + CCRT and CCRT alone ($P = .375$). IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.

By contrast, Xu et al. [4] carried out a propensity score-matched analysis and revealed that compared with that of CCRT, the 5-year DMFS and 5-year OS were significantly increased by 17.2% ($P = .047$) and 13.0% ($P = .020$) for patients with stage II NPC receiving IC + RT and the baseline characteristics were well balanced between the two treatment arms. In the present study, we found that the IC + CCRT group had worse prognosis compared with that of the CCRT group. That the baseline characteristics were not balanced between the two arms could be the main explanation for this. On the one hand, the IC + CCRT arm had more N1 disease compared with that in the CCRT arm (N1: 93.3% vs. 81.6% $P < .001$). Patients with N1 disease have worse survival than patients with N0 disease [18–20]. Ahmed et al. [19] carried out a retrospective study including 611 patients with stage II NPC who were treated with curative RT in the USA and found that patients with positive lymph node status (HR 1.6; 95% CI 1.04–2.46; $P = .0340$) were associated with poor OS using multivariable analysis. Chua et al. [18] carried out a retrospective study including 91 patients with stage II NPC (57 patients had lymph node disease) who were treated with RT alone in Hong Kong, and found that patients with T1–2N1 NPC appeared to have a worse prognosis compared with patients who had T2 N0 NPC. Xiao et al. [20] carried out a retrospective study including 362 early-stage (T1-T2 N0-N1 M0, 1992 Fuzhou, China staging system) patients who were treated with RT alone in the Sun Yat-Sen University Cancer Center. They found that compared with patients who had T1 N0, T2 N0, or T1 N1, those with T1–2N1 NPC had a worst prognosis (5-year OS rate: 73.1% and 5-year DMFS rate: 81.2%). However, our research showed that patients with T1–2N1 NPC appeared to have a similar prognosis to those who had T2 N0 NPC (5-year DFS: 84.2% vs. 90.9% $P = .145$ and 5-year OS: 92.8% vs. 95.8% $P = .436$). One possible reason is that more patients with T1–2N1 NPC received IC + CCRT compared with those who had T2 N0 NPC (47.2% vs. 22.0% $P < .001$). On the other hand, there were more patients in the IC + CCRT arm that received IMRT compared with those in the CCRT arm (47.2% vs. 37.2% $P = .034$). In 2011, Lai et al. [21] carried out a retrospective study including

Table 3. Univariate analysis of prognostic factors for DFS and OS

Prognostic factor	No. of patients	Disease progression	5-year DFS	χ^2	Hazard ratio (95% CI)	P*	Deaths	5-year OS	χ^2	Hazard ratio (95% CI)	P*
Gender				0.323	0.857 (0.503−1.460)	.570			0.337	0.811 (0.398−1.650)	.562
Male	325	55 (16.9%)	85.0%				32 (9.8%)	92.9%			
Female	120	18 (15.0%)	85.3%				10 (8.3%)	93.9%			
Age				0.275	1.384 (0.581−3.293)	.600			0.544	1.195 (0.613−2.332)	.461
< 60	389	63 (16.2%)	85.0%				36 (9.3%)	92.8%			
≥ 60	56	10 (17.9%)	85.3%				6 (10.7%)	96.4%			
radiation technique				1.804	1.182 (0.925−1.511)	.179			0.997	1.191 (0.844−1.679)	.318
2D-CRT	260	49 (18.8%)	82.8%				30 (11.5%)	91.4%			
IMRT	185	24 (13.0%)	88.5%				12 (6.5%)	96.0%			
T category				0.338	0.869 (0.540−1.397)	.561			2.356	0.624 (0.340−1.146)	.125
T 1	153	27 (17.6%)	85.8%				19 (12.4%)	92.1%			
T 2	292	46 (15.8%)	84.7%				23 (7.9%)	93.7%			
N category				2.122	1.843 (0.799−4.248)	.145			0.607	1.502 (0.536−4.211)	.436
N 0	59	6 (10.2%)	90.9%				4 (6.8%)	95.8%			
N 1	386	67 (17.4%)	84.2%				38 (9.8%)	92.8%			
Stage				2.150	0.994 (0.772-1.279)	.341			2.483	0.806 (0.582-1.117)	.289
T1N1M0	153	27 (17.6%)	85.8				19 (12.4%)	91.1			
T2N0M0	59	6 (10.2%)	90.9				4 (6.8%)	95.8			
T2N1M0	233	40 (17.2%)	83.1				19 (8.2%)	93.2			
treatment				4.109	1.048 (1.001-1.098)	**.043**			0.786	1.028 (0.967-1.093)	.375
IC + CCRT	195	38 (19.5%)	80.6				19 (9.7%)	90.5			
CCRT	250	35 (14.0%)	88.5				23 (9.2%)	95.0			

OS, overall survival; DFS, disease free survival; CI, confidence interval; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; 2D-CRT, two-dimensional conformal radiation therapy; IMRT, intensity modulated radiotherapy.

* Log-rank test.

1276 patients with NPC who were treated with either IMRT or 2D-CRT, and found that the LRFS in the IMRT group was significantly higher than that in the 2D-CRT group in stage T1 patients (100% vs. 94.4%; $P = .016$). Moon et al. [22] reported that compared with 2D-CRT (77.3%), both 3D-CRT and IMRT were associated with significantly better 5-year LPFS (91.1%, $P = .001$ and 92.3%, $P < .001$) In T1−2 patients. Zhang et al. [23] carried out a retrospective study including 7081 patients with non-metastatic NPC and reported that compared with 2D-CRT, IMRT provided an improved LRFS, LRRFS, and PFS in the early T classifications. By contrast, in 2011, Pan et al. [8] reported that IMRT and 2D-CRT had similar 5-year LRRFS, DMFS, PFS, and OS rates, not only in an unmatched cohort of 251 patients, but also in a propensity-matched cohort of 146 patients. Co et al. [24] carried out a systemic review and meta-analysis of the literature to assess the effectiveness of IMRT versus 2D-CRT in primary treatment of early stage NPC, and revealed that the risk ratio when using IMRT compared with 2D-CRT was 0.25 (CI = 0.04−1.45) for local failure and 0.02 (CI = 0.93−1.05) for regional failure and distant metastasis.

Table 4. Multivariate analysis for DFS using the Cox proportional hazards model

Variable	DFS		
	HR	95% CI *	$P^\dagger$
Age	1.179	0.604−2.301	0.630
Sex	0.820	0.481−1.400	0.468
Treatment	1.047	0.999−1.097	0.057
N stage	1.635	0.683−3.915	0.269
T stage	0.940	0.572−1.544	0.806
Radiotherapy equipment	1.200	0.937−1.537	0.148

DFS, disease free survival.

* CI, confidence interval.

† Cox regression model.

Previously published data also identified that older patients (age ≥ 60−65 years) were associated with increased risk for statistically significant decreased LRRFS and FFS, mortality, and poor OS [14,16,19,25]. Ahmed et al. [19] revealed that older patients (age ≥65 years) were associated with increased risk for mortality (HR 2.41; 95% CI 1.71−3.4; $P < .0001$) using a Cox multivariate proportional hazards model. Xu et al. [25] carried out a retrospective study including 392 patients with T2N1M0 NPC and reported that older patients (age ≥60 years) had poor 5-years OS compared with that of younger patients (age <60 years) (67.6% vs. 80.2; % $P = .007$). Kang et al. [16] carried out a retrospective study including 138 patients with stage II NPC and found that age (≤60 years vs. >60 years) was a significant prognostic factor in both univariate and multivariate analysis ($P = .014$ and .041, respectively). In contrast to the above studies, our results showed that older patients (age <60 years) had similar 5-years DFS and OS to younger patients (age ≥60 years) (85.0% vs. 85.3%; $P = .600$ and 92.8% vs. 96.4%; $P = .461$, respectively), which possibly reflected the small sample size in the older patients group.

The results of our research showed that the adverse events in the two groups during IC and/or CCRT were acceptable and no fatal adverse events occurred. The degrees of adverse events were significantly higher in the IC + CCRT group than in the CCRT group, which mainly manifested as grade 3 or 4 neutropenia and grade 1 or 2 liver dysfunction and kidney dysfunction. The patients in the IC + CCRT group had a similar frequency of grade 3 or 4 anemia and thrombocytopenia, but lower frequencies of grade 3 or 4 neutropenia during IC compared with the study conducted by Sun et al. [26] and Chen et al. [27]. This could be explained by the fact that our IC regimens contained less chemotherapeutic drugs and fewer cycles of IC. The dose of cisplatin received by our CCRT group was lower than that the study conducted by Sun et al. [26] and Chen et al. [27] (cisplatin 80−100 mg/m^2 vs. 100 mg/m^2 on day 1 every

Table 5. Adverse events

	IC + CCRT ($n = 195$)	CCRT ($n = 250$)	*P*-value *
Adverse events during induction chemotherapy, *n* (%)			
Hematological			
Anemia (grade 3 or 4)	5 (2.6)		
Thrombocytopenia (grade 3 or 4)	4 (2.0)		
Neutropenia (grade 3 or 4)	30 (15.4)		
Febrile neutropenia	8 (4.1)		
Liver dysfunction (grade 1 or 2)	51 (26.2)		
Kidney dysfunction (grade 1 or 2)	3 (1.5)		
Adverse events during chemoradiotherapy			
Hematological			
Anemia (grade 3 or 4)	10(5.1)	3 (1.2)	.015
Thrombocytopenia (grade 3 or 4)	9 (4.6)	3 (1.2)	.027
Neutropenia (grade 3 or 4)	40 (20.5)	14 (5.6)	<.001
Febrile neutropenia	5 (2.6)	2 (0.8)	.248 †
Liver dysfunction (grade 1 or 2)	70 (35.9)	15 (6.0)	<.001
Kidney dysfunction (grade 1 or 2)	22 (11.3)	2 (0.8)	<.001
Cycles of concurrent chemotherapy			.001
One	18 (9.2)	5 (2.0)	
Two or three	177 (90.8)	245 (98.0)	

IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.
* Calculated using the χ^2 test.
† Calculated using Fisher's exact test.

three weeks or cisplatin 25−30 mg/m^2 vs. 40 mg/m^2 on day 1 every week).

There were several limitations to our study: First, it was a retrospective study, but with large sample size and long follow-up period; second, non-hematological toxicity reactions could not be completely collected for analysis; last, some important baseline characteristics were not balanced between the two arms.

In conclusion, IC + CCRT did not improve, but might even worsen, the survival of patients with stage II NPC, and significantly increased treatment-associated adverse events when compared with CCRT alone. Therefore, well-designed phase 3, multi-center, prospective, randomized, controlled trials should be carried out for further verification.

Acknowledgments

We thank Doctor Hui-Zhang Li from the Zhejiang Cancer Hospital for his excellent advice.

Funding sources

This work was supported by the Zhejiang Province Medical and Health Science and Technology Project [Grant No. 2017RC016]; the National Natural Science Foundation of China [Grant No. 81672971]; the National Natural Science Foundation of China [Grant No. 81372437]; the Key Research Program of Zhejiang Province [Grant No. 2018C04009]; and the Excellent Talents Project of Zhejiang Cancer Hospital, P. R. China [Grant No. 2013 to T.J.].

Declarations of interest

None.

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