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Research Paper

Induction Chemotherapy Improved Long-term Outcomes of Patients with Locoregionally Advanced Nasopharyngeal Carcinoma: A Propensity Matched Analysis of 5-year Survival Outcomes in the Era of Intensity-modulated Radiotherapy

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Abstract

Background: The aim of this study is to evaluate the long-term therapeutic gain of induction chemotherapy (IC) in locoregionally advanced nasopharyngeal carcinoma (NPC) in the era of intensity-modulated radiotherapy (IMRT).

Methods: Data on 957 patients with stage T1-2N2-3 or T3-4N1-3 NPC treated with IMRT were retrospectively reviewed. Propensity score matching (PSM) method was adopted to balance influence of various covariates. Patient survival between IC and non-IC groups were compared.

Results: For the 318 pairs selected from the original 957 patients by PSM, the median follow-up duration was 57.13 months (range, 1.27-78.1 months). The 5-year overall survival (OS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and locoregional relapse-free survival (LRRFS) rates for IC group vs. non-IC group were 87.2% vs. 80.8% (P = 0.023), 88.1% vs. 83.2% (P = 0.071), 80.7% vs. 71.4% (P = 0.011) and 92.1% vs. 86.7% (P = 0.081), respectively. Multivariate analysis identify IC as an independent prognostic factor for OS (HR, 0.595; 95% CI, 0.397-0.891; P = 0.012) and DFS (HR, 0.627; 95% CI, 0.451-0.872; P = 0.006). After excluding the patients not receiving concurrent chemotherapy, IC was found to be an independent prognostic factor for OS (HR, 0.566; 95% CI, 0.368-0.872; P = 0.01), DMFS (HR, 0.580; 95% CI, 0.367-0.916; P = 0.02) and DFS (HR, 0.633; 95% CI, 0.444-0.903; P = 0.012).

Conclusions: IC is an effective treatment modality for patients with stage T1-2N2-3 and T3-4N1-3 NPC, and the incorporation of IC with standard CCRT could achieve the best therapeutic gain.

Key words: Nasopharyngeal carcinoma; induction chemotherapy; locoregionally advanced; intensity-modulated radiotherapy; prognosis.

Introduction

Nasopharyngeal carcinoma (NPC) is a tumor originating from nasopharynx epithelium and has an extremely unbalanced geographic distribution whereby in endemic regions, such as south China, its annual age-standard incidence rate is up to 20-50 per 100,000 males [1]. As a result of the anatomic

constraints and its high degree of radiosensitivity, radiotherapy (RT) has been the primary and only curative treatment for non-disseminated NPC. NPC also responses well to chemotherapy (CT), and randomized trials have demonstrated that a combination of CT with standard RT could improve the therapeutic outcome of patients with locoregionally advanced NPC [2-5] compared with RT alone. Therefore, concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy (ACT) has been established as the standard treatment for advanced NPC [6-8].

With the advent of intensity-modulated radiotherapy (IMRT), local control of advanced NPC has improved greatly and distant metastasis has emerged as the predominant mode of treatment failure pattern [9, 10]. Therefore, there has been a renewed interest in the re-exploration of induction chemotherapy (IC) in advanced NPC [11-16] as it may reduce distant metastasis and improve overall survival. However, results from previous randomized or non-randomized trials [11-18] were controversial with regard to the therapeutic gain of overall survival. Therefore, the prognostic value of IC remains to be addressed. Moreover, due to the insufficient follow-up duration in abovementioned studies, few 5-year survival outcomes were reported in previous studies.

According to previous findings, we conducted this retrospective study to establish the value of IC for patients with locoregionally advanced NPC treated by IMRT based on the 5-year survival outcomes. To balance the influence of covariates, propensity score matching (PSM) method was adopted to compare survival outcomes and decrease potential bias [19].

Materials and Methods

Study Patients

Data on 1811 patients with newly diagnosed stage I-IVB NPC, who were treated between November 2009 and February 2012 at Sun Yat-sen university cancer center, were retrospectively reviewed. The including criteria for this study were as follows: (1) stage T1-2N2-3 or T3-4N1-3 NPC; (2) World Health Organization (WHO) pathology type II/III; (3) with the data of pre-treatment Epstein-Barr virus (EBV) DNA (pre-DNA); (4) age 18 years or older. Finally, 957 (52.8%) patients were recruited for the current study. This study was approved by the Research Ethics Committee of Sun Yat-sen university cancer center. Informed consent was obtained from all the patients.

Clinical Staging Work

The conventional staging workups included a complete history and clinical examinations of the head and neck region, direct fibre-optic nasopharyngoscopy, magnetic resonance imaging (MRI), chest radiography, whole-body bone scan and abdominal sonography, as well as positron emission tomography (PET)-CT if necessary. Tumour-related markers like pre-DNA were quantified. All patients received a dental evaluation before radiotherapy.

All patients were restaged according to the 7th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) system [20]. All MRI materials and clinical records were reviewed to minimize heterogeneity in restaging. Two radiologists (L.Z.L. and L.T.) employed at our hospital separately evaluated all of the scans and disagreements were resolved by consensus.

Real-time quantitative EBV DNA PCR

Measurement of the plasma EBV DNA load was performed before treatment, and plasma DNA was extracted and assayed using real-time quantitative PCR which was described previously [21]. The real-time quantitative PCR system was developed for plasma EBV DNA detection, and targeted the *BamH*I-W region of the EBV genome using primers 5′-GCCAGAGGTAAGTGGACTTT-3′ and 5′-TACCA CCTCCTCTTCTTGCT-3′. The dual fluorescence-labelled oligomer 5′-(FAM) CACACCCAGGCAC ACACTACACAT (TAMRA)-3′ served as a probe. Sequence data for the EBV genome were obtained from the GeneBank sequence database.

Clinical Treatment

All patients received IMRT at Sun Yat-sen university cancer center. The prescribed doses were 66-72Gy at 2.12-2.43Gy/fraction to the planning target volume (PTV) of the primary gross tumour volume (GTVnx), 64-70Gy to the PTV of the GTV of the metastatic lymph nodes (GTVnd), 60-63Gy to the PTV of the high-risk clinical target volume (CTV1), and 54–56Gy to the PTV of the low-risk clinical target volume (CTV2). IC consisted of cisplatin (80 mg/m^2) with 5-fluorouracil (1000 mg/m^2) (PF), docetaxel (75 mg/m^2) with cisplatin (75 mg/m^2) (TP) every three weeks for two or more cycles. Concurrent chemotherapy was cisplatin weekly (30-40 mg/m^2) or on weeks 1, 4 and 7 (80-100 mg/m^2) of radiotherapy.

Follow-Up and Statistical Analysis

Follow-up was measured from first day of therapy to last examination or death, and patients were followed by MRI and plasma EBV DNA at least every 3 months during first 2 years, then every 6 months thereafter (or until death).

Propensity scores were computed by logistic regression for each patient using the following

covariates: age, gender, concurrent chemotherapy (CRT), smoking, drink, T category, N category, overall stage and pre-DNA. The cut-off value of pre-DNA was evaluated by receiver operating characteristic (ROC) analysis. Chi-square test or Fisher's exact test and non-parametric test were adopted to compare categorical and continuous variables. Overall survival (OS), distant metastasis-free survival (DMFS), disease-free survival (DFS) and locoregional relapse-free survival (LRRFS) curves were estimated using Kaplan-Meier analysis and compared using the log-rank test. The multivariate Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs); age, gender, CRT, smoking, drinking, T category, N category, overall stage, pre-DNA and IC were included as variables. All tests were two-sided; $P < 0.05$ was considered significant. Stata Statistical Package 12 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Results

Cut-off Value of Pre-treatment EBV DNA

Among the whole cohort, 158/957 (16.5%) patients had undetectable pre-DNA and the median pre-DNA load was 5200 copies/ml (interquartile range, 517-30950). According to the ROC curve analysis, the cut-off value of pre-DNA was 1595 copies/ml for OS (area under curve [AUC], 0.611; sensitivity, 0.791; specificity, 0.383).

Basic characteristics

In total, 542 (56.7%) patients received IC. From the original 957 NPC patients, 318 pairs were selected by PSM (Table 1). The median pre-DNA was 4260 copies/ml (interquartile range, 398-21900) and 5500 copies/ml (interquartile range, 544-26825) for the non-IC and IC groups ($P = 0.551$), respectively. No significant difference was found with regard to the host, tumor and treatment factors between the IC and non-IC groups ($P > 0.05$ for all rates). For the selected cohort, the male (n=488)-to-female (n=148) ratio was 3.0:1, and the median age was 45 (range, 18-78) years-old.

Failure Patterns

The median follow-up duration for the selected 318 pairs was 57.13 months (range, 1.27-78.1 months). Up to the last follow-up, 14/318 (4.4%) patients in IC group and 23/318 (7.2%) patients in non-IC group developed local recurrence; 15/318 (4.7%) patients in IC group and 17/318 (5.3%) patients in non-IC group experienced regional recurrence; and 36/318 (11.3%) patients in IC group and 51/318 (16.0%) patients in non-IC group experienced distant metastasis. Moreover, 39/318 (12.6%) patients and 60/318 (15.8%) patients died in IC and non-IC group, respectively.

Survival Analysis

For the selected 318 pairs, the 5-year OS, DMFS, DFS and LRRFS rates were 83.9%, 85.7%, 76.1% and 89.5%, respectively. The 5-year OS (87.2% vs. 80.8%; $P = 0.023$; Figure 1A) and DFS (80.7% vs. 71.4%; $P = 0.011$; Figure 1C) rates for patients receiving IC were significantly higher than the corresponding rates for patients not receiving IC. Moreover, the difference in the DMFS rate (88.1% vs. 83.2%; $P = 0.071$; Figure 1B) and LRRFS rate (92.1% vs. 86.7%; $P = 0.081$; Figure 1D) between the IC and non-IC groups nearly reached statistical significance.

Multivariate analysis was performed to adjust for various prognostic factors, and consistent with the results of univariate analysis, it revealed that IC could improve the therapeutic outcomes of OS (HR, 0.595; 95% CI, 0.397-0.891; $P = 0.012$) and DFS (HR, 0.627; 95% CI, 0.451-0.872; $P = 0.006$) (Table 2). Patients receiving IC also had a lower risk of distant metastasis (HR, 0.684; 95% CI, 0.446-1.048; $P = 0.081$) and locoregional relapse (HR, 0.634; 95% CI, 0.378-1.063; $P = 0.084$), and this difference was marginally statistically significant.

Table 1. Baseline characteristics of all 318 pairs of stage III-IVB NPC patients (except T3-4N0) with or without IC.

	IC	Non-IC	
Characteristics	No. (%)	No. (%)	*P*
Age (median, y)	46	44	0.293[a]
Gender			0.851[b]
Male	245 (77.0)	243 (76.4)	
Female	73 (23.0)	75 (23.6)	
Concurrent chemotherapy			0.232[b]
Yes	283 (89.0)	273 (85.8)	
No	35 (11.0)	45 (14.2)	
Smoking			0.807[b]
Yes	123 (38.7)	126 (39.6)	
No	195 (61.3)	192 (60.4)	
Drinking			0.802[b]
Yes	37 (11.6)	35 (11.0)	
No	281 (88.4)	283 (89.0)	
T category [c]			0.267[b]
T1	13 (4.1)	14 (4.4)	
T2	23 (7.2)	12 (3.8)	
T3	214 (67.3)	227 (71.4)	
T4	68 (21.4)	65 (20.4)	
N category [c]			0.984[b]
N1	209 (65.7)	211 (66.4)	
N2	76 (23.9)	75 (23.6)	
N3	33 (10.4)	32 (10.0)	
Overall stage [c]			0.931[b]
III	224 (70.4)	225 (70.8)	
IVA-IVB	94 (29.6)	93 (29.2)	
Pre-DNA (median, copies/ml)	5500	4260	0.551[a]

Abbreviations: NPC = nasopharyngeal carcinoma; IC = induction chemotherapy; Pre-DNA = pre-treatment Epstein-Barr virus DNA.

[a] *P*-values were calculated by Non-parametric test.

[b] *P*-values were calculated by Chi-square test or Fisher exact test if indicated.

[c] According to the 7th AJCC/UICC staging system.

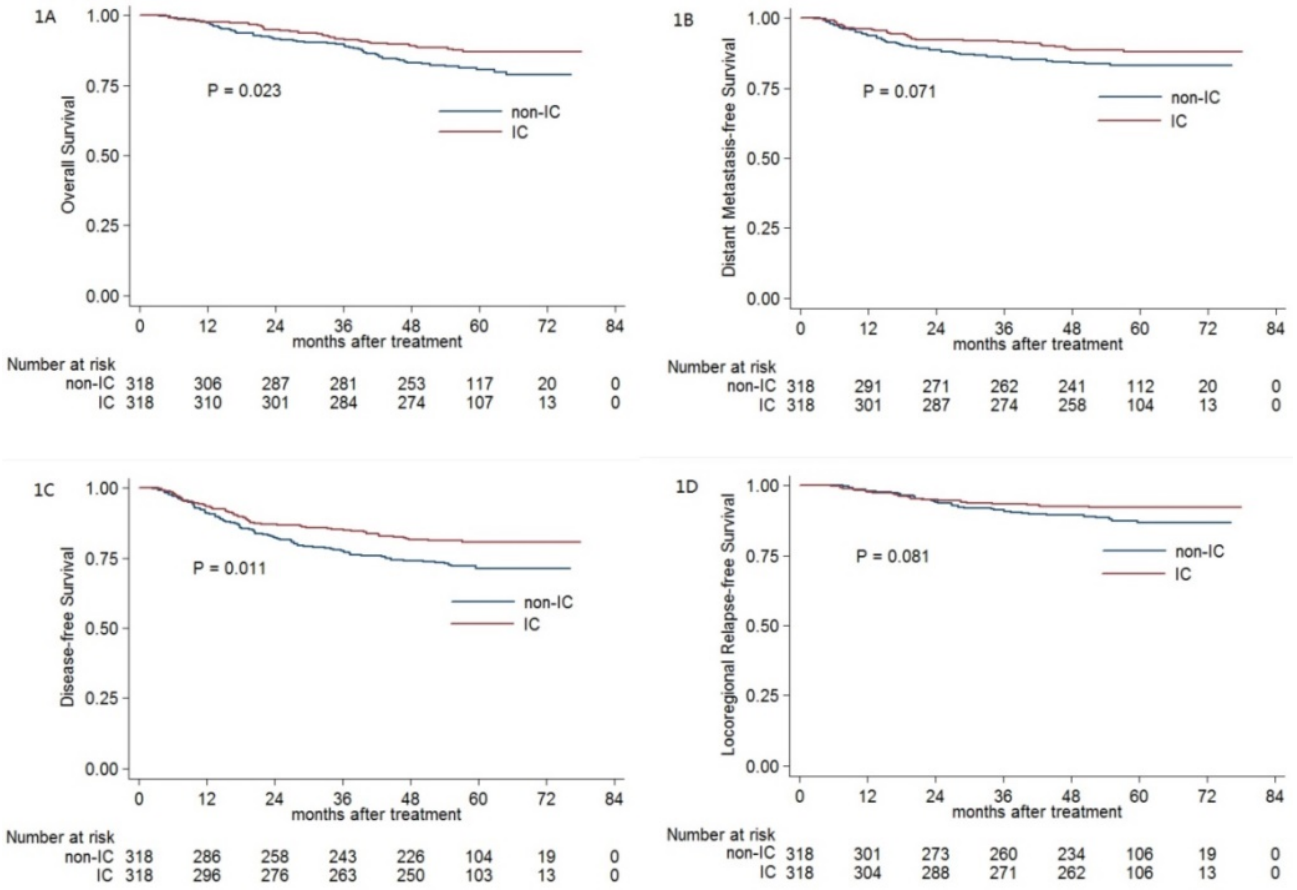

Figure 1. Kaplan-Meier OS (A), DMFS (B), DFS (C) and LRRFS (D) curves for the 318 pairs of stage III-IVB NPC with or without IC. Abbreviations: OS = overall survival; DMFS = distant metastasis-free survival; DFS = disease-free survival; LRRFS = locoregional relapse-free survival; IC = induction chemotherapy.

Table 2. Multivariate analysis of prognostic factors for all 318 pairs of stage III-IVB NPC patients (except T3-4N0) with or without IC.

Endpoints	Variable	HR (95% CI)	*P*[a]
OS	Age	1.849 (1.206-2.834)	0.005
	N category, N2 vs. N1	2.007 (1.274-3.161)	0.003
	Overall stage	2.299 (1.448-3.652)	< 0.001
	Pre-DNA	1.848 (1.155-2.957)	0.01
	IC	0.595(0.397-0.891)	0.012
DMFS	N category, N2 vs. N1	1.809 (1.113-2.941)	0.017
	Overall stage	1.814 (1.084-3.037)	0.023
	Pre-DNA	2.850 (1.630-4.985)	< 0.001
	IC	0.684 (0.446-1.048)	0.081
DFS	Age	1.408 (1.006-1.971)	0.046
	N category, N2 vs. N1	1.623 (1.116-2.360)	0.011
	Overall stage	1.743 (1.181-2.573)	0.005
	Pre-DNA	1.591 (1.103-2.293)	0.013
	IC	0.627(0.451-0.872)	0.006
LRRFS	IC	0.634(0.378-1.063)	0.084

Abbreviations: NPC = nasopharyngeal carcinoma; IC = neoadjuvant chemotherapy; HR = hazard ratio; CI = confidence interval; OS = overall survival; DMFS = distant metastasis-free survival; DFS = disease-free survival; LRRFS = locoregional relapse-free survival; Pre-DNA = pre-treatment Epstein-Barr virus DNA.

[a]: Multivariate *P*-values were calculated using an adjusted Cox proportional-hazards model with backward elimination and the following parameters: age (> 45y vs. ≤ 45y), gender (male vs. female), concurrent chemotherapy (yes vs. no), smoking (yes vs. no), drinking (yes vs. no), T category (T1-2 vs. T3-4), N category (N2 vs. N1, N3 vs. N1), overall stage (III vs. IVA-B), pre-DNA (≥ 1595 copies/ml vs. < 1595 copies/ml) and IC (yes vs. no).

Prognostic Value of IC in Patients Receiving CRT

Given the truth that CCRT has been the basic treatment for patients with advanced NPC, we therefore exclude the patients not receiving CCRT and re-evaluate the prognostic value of IC. Overall, 163 (17.0%) patients not receiving CRT from the originally entire cohort were excluded, and 276 pairs were selected by PSM (Table 3).

The 5-year OS, DMFS, DFS and LRRFS rates for IC group vs. non-IC group were 86.7% vs. 80.5% (P = 0.038, Figure 2A), 88.3% vs. 82.4% (P = 0.042, Figure 2B), 80.1% vs. 72.4% (P = 0.037, Figure 2C) and 91.6% vs. 88.1% (P = 0.319, Figure 2D), respectively. When entered into the multivariate analysis, IC was still found to be an independent prognostic factor for OS (HR, 0.566; 95% CI, 0.368-0.872; P = 0.01), DMFS (HR, 0.580; 95% CI, 0.367-0.916; P = 0.02) and DFS (HR, 0.633; 95% CI, 0.444-0.903; P = 0.012), respectively.

Table 3. Baseline characteristics of all 276 pairs of stage III-IVB NPC patients (except T3-4N0) receiving CCRT with or without IC.

	IC	Non-IC	*P*
Characteristics	No. (%)	No. (%)	
Age (median, y)	47	44	0.301[a]
Gender			1.000[b]
Male	216 (78.3)	216 (78.3)	
Female	60 (21.7)	60 (21.7)	
Smoking			0.794[b]
Yes	109 (39.5)	112 (40.6)	
No	167 (60.5)	164 (59.4)	
Drinking			0.900[b]
Yes	36 (13.0)	37 (13.4)	
No	240 (87.0)	239 (86.6)	
T category [c]			0.305[b]
T1	10 (3.6)	14 (5.1)	
T2	19 (6.9)	10 (3.6)	
T3	185 (67.0)	192 (69.6)	
T4	62 (22.5)	60 (21.7)	
N category [c]			1.000[b]
N1	180 (65.2)	180 (65.2)	
N2	66 (23.9)	66 (23.9)	
N3	30 (10.9)	30 (10.9)	
Overall stage [c]			1.000[b]
III	190 (68.8)	190 (68.8)	
IVA-IVB	86 (31.2)	86 (31.2)	
Pre-DNA (median, copies/ml)	6760	4590	0.430[a]

Abbreviations: NPC = nasopharyngeal carcinoma; IC = induction chemotherapy; CCRT = concurrent chemoradiotherapy; Pre-DNA = pre-treatment Epstein-Barr virus DNA.

[a] *P*-values were calculated by Non-parametric test.

[b] *P*-values were calculated by Chi-square test or Fisher exact test if indicated.

[c] According to the 7th AJCC/UICC staging system.

Table 4. Multivariate analysis of prognostic factors for all 276 pairs of stage III-IVB NPC patients (except T3-4N0) receiving CCRT with or without IC.

Endpoints	Variable	HR (95% CI)	*P*[a]
OS	Age	2.110 (1.334-3.336)	0.001
	Gender	0.460(0.244-0.870)	0.017
	Overall stage	1.890 (1.136-3.145)	0.014
	IC	0.566(0.368-0.872)	0.010
DMFS	Age	1.643(1.029-2.622)	0.037
	N category, N3 vs. N1	2.217 (1.223-4.018)	0.009
	Pre-DNA	1.996 (1.133-3.518)	0.017
	IC	0.580 (0.367-0.916)	0.02
DFS	Age	1.584 (1.096-2.288)	0.014
	Overall stage	1.729(1.215-2.461)	0.002
	Pre-DNA	1.493 (1.003-2.223)	0.048
	IC	0.633(0.444-0.903)	0.012
LRRFS	Overall stage	2.033(1.166-3.546)	0.012
	IC	0.751(0.429-1.132)	0.314

Abbreviations: NPC = nasopharyngeal carcinoma; IC = neoadjuvant chemotherapy; CCRT = concurrent chemoradiotherapy; HR = hazard ratio; CI = confidence interval; OS = overall survival; DMFS = distant metastasis-free survival; DFS = disease-free survival; LRRFS = locoregional relapse-free survival; Pre-DNA = pre-treatment Epstein-Barr virus DNA.

[a]: Multivariate *P*-values were calculated using an adjusted Cox proportional-hazards model with backward elimination and the following parameters: age (> 45y vs. ≤ 45y), gender (male vs. female), smoking (yes vs. no), drinking (yes vs. no), T category (T1-2 vs. T3-4), N category (N2 vs. N1, N3 vs. N1), overall stage (III vs. IVA-B), pre-DNA (≥ 1595 copies/ml vs. < 1595 copies/ml) and IC (yes vs. no).

Discussion

To the best of our knowledge, this is the first study with the largest sample and longest follow-up duration to established the prognostic value of IC in the era of IMRT, and the findings of this current study revealed IC was associated with significantly improved 5-year OS and DFS for patients with locoregionally advanced NPC. Moreover, after excluding the patients not receiving CRT, we further proved that IC could also improve therapeutic outcomes of 5-year DMFS. However, IC was not associated with better 5-year LRRFS no matter CRT was delivered or not.

Unlike previous studies which include all locoregionally advanced NPC (stage III-IVB) [13, 15, 17, 18, 22], we excluded patients with stage T3-4N0 disease because patients with negative lymph node metastasis stage have lower distant tumor burden and could not really benefit from IC. This recruiting criteria was also adopted in our previous work which appraised the contribution of adjuvant chemotherapy additional to CCRT in locoregionally advanced NPC [8]. For the selected 318 pairs, 80 (12.6%) patients did not accepted CRT. Refusal by patients after IC was the primary and main reason for uncompleted CRT. In addition, a part of patients (26/80 patients with age more than 60 years) avoided CRT as well because they could not tolerate CRT after IC according to clinicians' decisions.

With the adoption of CRT and IMRT being the standard RT technique, the control of locoregional is satisfactory and distant metastasis has been the predominant mode of treatment failure [9, 10]. Therefore, much attention had been paid to IC, and many combined regimens had been applied such as BEC (bleomycin, epirubicin and cisplatin) [14], BFC (bleomycin, fluorouracil and cisplatin) [15], TP (docetaxel and cisplatin) [13] and GCP (gemcitabine, carboplatin and paclitaxel) [16]. However, only one phase II trial by Hui et al. [13] showed an OS benefit. Of note, the sample in this study was too small (n = 65) and the results may not be solid conclusive. Moreover, other two phase III trials showed a benefit of DFS [12, 14] but not OS. However, the treatment modality was not the currently standard pattern. Furthermore, the follow-up duration in these three studies was insufficient. These shortages made the prognostic value of IC inconclusive. After making up for these deficiencies, our current study substantially established the efficacy of IC and the outcomes were similar to the meta-analysis by Ouyang et al. [23].

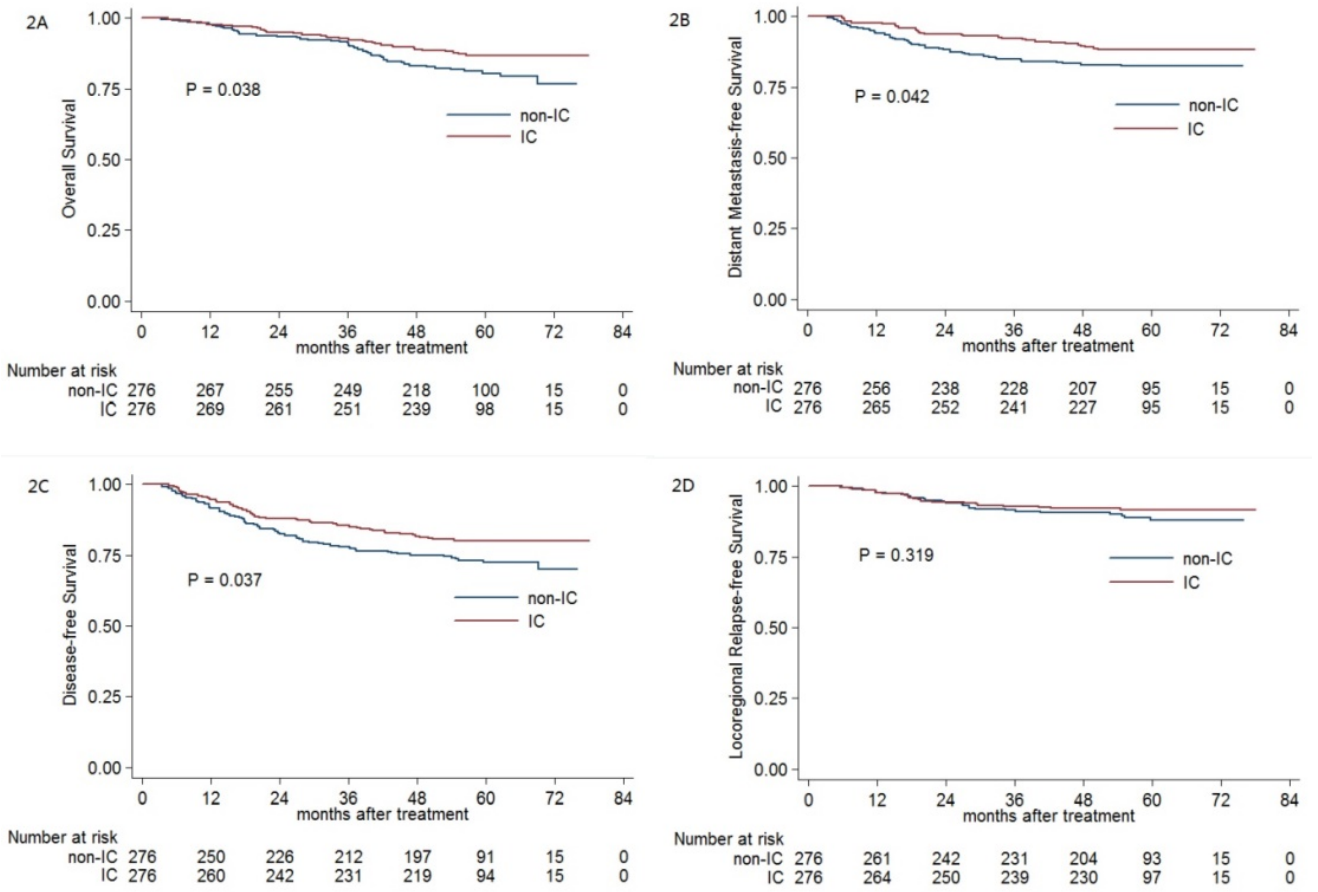

Figure 2. Kaplan-Meier OS (A), DMFS (B), DFS (C) and LRRFS (D) curves for the 276 pairs of stage III-IVB NPC patients receiving CCRT with or without IC. Abbreviations: OS = overall survival; DMFS = distant metastasis-free survival; DFS = disease-free survival; LRRFS = locoregional relapse-free survival; IC = induction chemotherapy; CCRT = concurrent chemoradiotherapy.

Since CCRT has been the mainly standard treatment for advanced NPC, we therefore excluded patients not receiving CRT and re-evaluated the prognostic value of IC. Consistent with the results of primary analysis, it revealed IC was still associated with significantly improved OS and DFS. Intriguingly, a significantly better 5-year DMFS was observed in patients receiving IC plus CCRT compared with patients receiving CCRT alone. As expected, IC did not influence the 5-year LRRFS, and this should be attributed to use of IMRT. These results indicate that IC prior to RT is an effective treatment strategy for the eradication of micro-metastasis and improving therapeutic outcomes in locoregionally advanced NPC. Therefore, IC combined with CCRT should be a promising treatment modality in advanced NPC with high risk of distant metastasis.

The major strength of our study is the use of PSM and multivariate analysis to establish the prognostic value of IC in advanced NPC; this addressed the potential limitations of divergent confounders, treatment heterogeneity, and selection bias associated with the direct retrospective analysis of observational data [19]. As the most important prognostic biomarker, plasma EBV DNA [24-27] was also well balanced between IC and non-IC groups. Therefore, the results of our study should be reliable. With regard to the limitations, first, the data was retrospectively collected from one single center. Second, the IC regimens were not uniform. However, this would not affect the outcomes of this study because no evidence has proven the efficacy difference of these two regimens so far. Future prospective trials are warrant to address this issue.

In conclusion, our findings suggest that IC prior to RT is an advantage for patients with stage III-IVB NPC (except T3-4N0) and receiving CRT. Based on the present evidence, it is recommended that IC combined with CCRT should be delivered to patients with advanced NPC, although future randomized trials are warrant to define the optimal IC regimen.

Conclusion

IC before RT is an effective treatment pattern for patients with stage III-IVB NPC (except T3-4N0), and the incorporation of IC with standard CCRT could achieve the best therapeutic gain. Further randomized trials are warrant to define the optimal IC regimen.

Abbreviations

NPC: nasopharyngeal carcinoma; RT: radiotherapy; CT: chemotherapy; CCRT: concurrent chemoradiotherapy; ACT: adjuvant chemotherapy; IMRT: intensity-modulated radiotherapy; IC: induction chemotherapy; PSM: propensity score matching; WHO: World Health Organization; EBV: Epstein-Barr virus; Pre-DNA: pre-treatment Epstein-Barr virus DNA; MRI: magnetic resonance imaging; PET: positron emission tomography; UICC/AJCC: International Union against Cancer/American Joint Committee on Cancer; PTV: planning target volume; GTV: gross tumour volume; GTVnx: primary gross tumour volume; GTVnd: gross tumour volume of the metastatic lymph nodes; CTV1: high-risk clinical target volume; CTV2: low-risk clinical target volume; PF: cisplatin with 5-fluorouracil; TP: docetaxel with cisplatin; OS: overall survival; DMFS: distant metastasis-free survival; DFS: disease-free survival; LRRFS: locoregional relapse-free survival; CRT: concurrent chemotherapy; HR: hazard ratio; CI: confidence interval; AUC: area under curve; BEC: bleomycin with epirubicin and cisplatin; BFC: bleomycin with fluorouracil and cisplatin; GCP: gemcitabine with carboplatin and paclitaxel.

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Competing Interests

The authors declare no competing financial interests.

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