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ORIGINAL RESEARCH

Outcomes of adding induction chemotherapy to concurrent chemoradiotherapy for stage T3N0-1 nasopharyngeal carcinoma: a propensity-matched study

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Objective: Our objective was to examine whether adding induction chemotherapy to concurrent chemoradiotherapy improved survival in stage III nasopharyngeal carcinoma (NPC) patients, especially in low-risk patients at stage T3N0-1.

Materials and methods: We retrospectively analyzed 687 patients with stage T3N0-1 NPC treated with intensity-modulated radiation therapy (IMRT) plus concurrent chemotherapy (CC) with or without induction chemotherapy (IC). Propensity score matching (PSM) method was used to select 237 pairs of patients from two cohorts. Overall survival (OS), locoregional relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) were assessed by using the Kaplan–Meier method, log-rank test, and Cox regression analysis.

Results: No significant survival differences were observed between IC plus CC and CC cohorts with similar 4-year OS (91.7% vs 92.6%, P=0.794), LRFS, (92.7% vs 96.8%, P=0.138), DMFS (93.5% vs 94.3%, P=0.582), and PFS (87.5% vs 91.1%, P=0.223). In a univariate analysis, lower Epstein–Barr virus deoxyribonucleic acid (EBV DNA; <4,000 copies/mL) significantly improved 4-year DMFS (95.5% vs 91.6%, P=0.044) compared with higher EBV DNA (≥4,000 copies/mL). No factors were associated with 4-year OS, LRFS, DMFS, and PFS in a multivariate analysis. IC plus CC group experienced higher rates of grade 3–4 leucopenia (P<0.001) and neutropenia (P<0.001).

Conclusion: The addition of IC to CC in stage T3N0-1 NPC patients treated with IMRT did not significantly improve their survival. The IC group experienced higher rates of grade 3–4 hematological toxicities. Therefore, further investigation is required.

Keywords: nasopharyngeal carcinoma, induction chemotherapy, intensity-modulated radiation therapy, propensity score matching, stage T3N0-1

Introduction

Nasopharyngeal carcinoma (NPC) occurs at a high incidence rate in Southern China, especially in Hong Kong and Guangdong.[1] NPC exhibits high radiosensitivity, and radiotherapy (RT) is the primary and most effective treatment for pathologically confirmed NPC. Intensity-modulated radiation therapy (IMRT) has significantly improved local control and lowered radiation-induced toxicities compared with two-dimensional RT.[2,3] A series of phase III clinical trials have established chemoradiotherapy as the standard treatment for locoregionally advanced NPC (LA-NPC) because it improves disease control and survival.[4–10]

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However, whether the addition of induction chemotherapy (IC) would improve survival in LA-NPC patients remains controversial. Differing results have been found in several trials.[11–14] Hui et al[14] showed that overall survival (OS) improved by adding IC (94.1% vs 67.7%, *P*=0.012), whereas 3-year progression-free survival (PFS) did not significantly improve (*P*=0.12). Fountzilas et al[12] and Tan et al[11] reported no significant survival benefit in LA-NPC patients treated with IC. Sun et al[13] recently published a phase III study showing that treatment with IC in LA-NPC patients (except T3-4N0) significantly improved 3-year failure-free survival, OS, and distant failure-free survival. Our recent retrospective study[15] showed that the addition of IC significantly improved 5-year OS (*P*=0.022) and 5-year distant metastasis-free survival (DMFS; *P*=0.018) in stage IVa-b NPC patients treated with IMRT.

IC may be associated with high incidences of hematological acute toxicity and could affect chemoradiotherapy. A previous study showed that IC exhibited grade 3 and 4 toxicities, including leukopenia (*P*=0.046), neutropenia (*P*=0.029), and thrombocytopenia (*P*<0.001).[11] Therefore, IC may not improve survival benefits but increase hematological acute toxicity in low-risk stage III NPC patients. In order to assess the benefit of IC, we retrospectively analyzed stage T3N0-1 NPC patients treated with IMRT plus concurrent chemotherapy (CC) with or without IC. The propensity score matching (PSM) method was used to mimic randomized trials to reduce potential bias.[16,17]

Materials and methods

Patients

A total of 687 patients with stage T3N0-1 NPC treated with IMRT plus CC with or without IC were retrospectively examined in our institution between January 19, 2005, and December 27, 2012. Before treatment, a complete history of each patient was noted. Clinical examinations of the head and neck, hematological studies and biochemical profiles, pretreatment plasma Epstein–Barr virus deoxyribonucleic acid (pre-EBV DNA) level, fiberoptic nasopharyngoscopy with biopsy, magnetic resonance imaging (MRI) of the nasopharynx and neck, chest radiography, abdominal sonography, and a whole body bone scan using single photon emission computed tomography (CT) or positron emission CT were performed for each patient. Plasma EBV DNA level was measured by using real-time quantitative polymerase chain reaction as previously described.[18,19] All the patients were restaged according to the seventh edition of the International Union against Cancer/American Joint Committee on Cancer staging system for NPC.[20] This study was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center. The requirement for written consent was waived as this is a retrospective study; however, oral consent was obtained via telephone.

Treatment

Radiation therapy

All the patients were treated using one daily fraction of IMRT for 5 days per week at our institution. Gross tumor volume (GTV) included the nasopharynx GTV (GTVnx) and the cervical lymph nodes GTV (GTVnd). High-risk clinical target volume (CTV-1) was defined as the GTVnx plus a 5–10 mm margin (2–3 mm posteriorly) to encompass the high-risk area and the whole nasopharynx, and low-risk clinical target volume (CTV-2) was defined as the CTV-1 plus a 5–10 mm margin (2–3 mm posteriorly) to encompass the low-risk area including parapharyngeal space, posterior parts of the nasal cavity, retropharyngeal nodal regions, clivus, pterygoid fossae, sphenoid sinus, pterygopalatine fossae, and the selective neck area. The prescribed doses were as follows: 66–72 Gy to the GTVnx, 60–68 Gy to the GTVnd, ≥60 Gy to the (CTV-1), and 54–56 Gy to the CTV-2 for >30–33 fractions.

Chemotherapy

Platinum-based chemotherapy was given to all the patients. IC consisted of docetaxel plus cisplatin (TP), paclitaxel plus carboplatin (TC), docetaxel plus cisplatin plus fluorouracil (TPF), or cisplatin/nedaplatin plus fluorouracil (PF) regimen for up to three cycles. Patients received a CC regimen of cisplatin/nedaplatin of 30–40 mg/m^2 weekly or every 3 weeks during RT. The three weekly regimens consisted of 80–100 mg/m^2 of cisplatin/nedaplatin, PF, or TP for up to seven cycles.

Follow-up

Patient follow-up was calculated from the first day of therapy to either the day of death or the last day of examination. The patients underwent physical examination, plasma EBV DNA level, endoscopy, MRI scans, chest radiography, abdominal sonography, and whole body bone scan every 3–6 months during the first 3 years and every 6–12 months thereafter until death. OS, locoregional relapse-free survival (LRFS), DMFS, and PFS were analyzed as end points, and these end points were measured from the date of the first therapy to the date of death, first locoregional relapse, distant metastasis, disease progression (locoregional relapse or distant metastasis), or

the date of the last follow-up visit. Patients not having recent examination records were followed-up via telephone calls.

Statistical analysis

SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. We used the PSM method to match the patients between the two groups (IC plus CC and CC) at the ratio of 1:1 based on propensity scores. The scores were computed by using logistic regression based on the following covariates: gender, age, World Health Organization (WHO) pathological types (types I + II and III), smoking history, NPC family history, pre-EBV DNA, chemotherapy strategy (IC plus CC and CC), and N category (ie, N0 and N1). The balance of the covariates between the two groups was examined by using independent-samples *t*-test (continuous variable), χ^2 test, or Fisher's exact test (categorical variable). A cutoff of 4,000 copies/mL of pre-EBV DNA was used to define low versus high levels because this threshold has previously been shown to be a good prognostic factor.[21] The χ^2 test or Fisher's exact test was used to compare the patient characteristics. Survival rates were estimated by using the Kaplan–Meier method, and differences were compared by using the log-rank test. Multivariate analyses were performed by using the Cox proportional hazards model to calculate hazard ratios (HRs) and 95% CIs and to identify significant independent prognostic factors. In the multivariate analyses, the following parameters were included in the model as covariates for each analysis: gender, age (≤50 vs >50 years), WHO pathological types (types I + II and III), smoking history, NPC family history, N category (N0 and N1), pre-EBV DNA (≤4,000 vs >4,000 copies/mL), and chemotherapy strategy (IC plus CC and CC). Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

Before PSM, we compared the characteristics of all the 687 patients between two groups. The analysis showed that age, pre-EBV DNA, and N category were not balanced between the two groups (P=0.031, P<0.001, and P<0.001, respectively). In order to balance the characteristics and reduce potential bias, we selected 237 patient pairs from 687 T3N0-1 NPC patients by using PSM method. In the PSM cohort, the median age of patients was 44 years (range =21–70 years), including 330 men and 144 women with a ratio of 2.29:1. No significant differences were found in gender, age, pathology type, smoking, NPC family history, pre-EBV DNA, and N category between the IC plus CC group and the CC group (Table 1).

Patterns of treatment failure

The median follow-up time was 49.4 months (range =1.4–117.7 months). Up to the last day of follow-up, 54 patients experienced disease progression. Furthermore, 33 of 54 (61.1%) patients showed disease progression in the IC plus CC group and 21 of 54 (38.9%) patients in the CC group. In total, 22 of 54 (40.7%) patients developed local/regional recurrence alone. A total of 5 of 22 (22.7%) patients in the IC plus CC group and 1 of 22 (4.5%) patients in the CC group developed both local and regional recurrence. Furthermore, 4 of 22 (18.2%) patients in the IC plus CC group and 5 of 22 (22.7%) patients in the CC group developed local recurrence, and 6 of 22 (27.3%) patients in the IC plus CC group and 1 of 22 (4.5%) patients in the CC group developed regional recurrence. In addition, 29 of 54 (53.7%) patients experienced distant metastases alone, which included 16 of 29 (55.2%) patients treated with IC plus CC and 13 of 29 (44.8%) patients treated with CC (P=0.565). Moreover, only two patients treated with IC plus CC and one patient treated with CC developed both distant metastases and recurrence. Table 2 shows the summary of treatment failure.

Prognostic value of IC

The 4-year OS, LRFS, DMFS, and PFS for the patient population were 92.1%, 94.7%, 93.9%, and 89.2%, respectively. Table 3 shows the summary of univariate analysis of prognostic factors, including gender, age, pathological type, smoking, NPC family history, pre-EBV DNA, chemotherapy strategy, and N category. Among these factors, gender, age, pathological type, smoking, NPC family history, and N category were not significantly associated with 4-year OS, LRFS, DMFS, and PFS. Patients with lower pre-EBV DNA (<4,000 copies/mL) demonstrated a significant improvement in 4-year DMFS (95.5% vs 91.6%, P=0.044) compared with those with higher EBV DNA (≥4,000 copies/mL). However, we did not detect a significant difference in pre-EBV DNA in 4-year OS, LRFS, and PFS rates. Patients treated with IC plus CC and CC alone resulted in similar 4-year OS (91.7% vs 92.6%, P=0.794; Figure 1A), 4-year LRFS (92.7% vs 96.8%, P=0.138; Figure 1B), 4-year DMFS (93.5% vs 94.3%, P=0.582; Figure 1C), and 4-year PFS (87.5% vs 91.1%, P=0.223; Figure 1D). Although there were no significant differences in survival improvement between the two groups, CC group was numerically superior to the IC plus CC group.

Multivariate analysis was performed to adjust for various prognostic factors. The factors were included as covariates in accordance with univariate analysis (Table 4). Consistent

Table 1 Characteristics of stage T3N0-1 NPC treatment with IC + CC or CC before and after propensity score matching

Characteristics	Before propensity score matching					After propensity score matching				
	IC + CC (n=260)		CC (n=427)		*P*-value[a]	IC + CC (n=237)		CC (n=237)		*P*-value[a]
	n	%	n	%		n	%	N	%	
Gender					0.859					0.424
Male	181	69.6	300	70.3		161	67.9	169	71.3	
Female	79	30.4	127	29.7		76	32.1	68	28.7	
Age (years)					0.031					0.756
≤50	195	75.0	287	67.2		172	72.6	175	73.8	
>50	65	25.0	140	32.8		65	27.4	62	26.2	
Pathology type[b]					0.884					0.724
Type I + II	8	3.1	14	3.3		5	2.1	3	1.3	
Type III	252	96.9	413	96.7		232	97.9	234	98.7	
Smoking					0.448					0.433
Yes	81	31.2	145	34.0		73	30.8	81	34.2	
No	179	68.8	282	66.0		164	69.2	156	65.8	
NPC family history					0.847					0.442
Yes	28	10.8	44	10.3		26	11	21	8.9	
No	232	89.2	383	89.7		211	89	216	91.1	
Pre-EBV DNA (copies/mL)					<0.001					0.456
<4,000	144	55.4	311	72.8		142	59.9	134	56.5	
≥4,000	116	44.6	116	27.2		95	40.1	103	43.5	
N category					<0.001					0.111
N0	27	10.4	90	21.1		27	11.4	39	16.5	
N1	233	89.6	337	78.9		210	88.6	198	83.5	

Notes: [a]*P*-values were calculated by using χ^2 test or Fisher exact test if indicated. [b]Based on WHO histological type: I – differentiated keratinizing carcinoma, II – differentiated nonkeratinizing carcinoma, and III – undifferentiated non-keratinizing carcinoma.

Abbreviations: CC, concurrent chemotherapy; EBV DNA, Epstein–Barr virus deoxyribonucleic acid; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma; WHO, World Health Organization.

with the univariate analysis, gender, age, pathological type, smoking, NPC family history, chemotherapy strategy, and N category were not associated with 4-year OS, LRFS, DMFS, and PFS. Only pre-EBV DNA showed an approximately significant difference in 4-year DMFS (HR =1.05; 95% CI =0.38–0.83; *P*=0.05).

Table 2 Patterns of treatment failure in 237 patient pairs with stage T3N0-1 NPC

Failure pattern	IC plus CC	CC	*P*-value[a]	Total
Local/regional recurrence alone			0.081	
Local	4	5		9
Regional	6	1		7
Local and regional	5	1		6
Total	15	7		22
Distant metastases alone			0.565	
Bone	5	5		10
Lung	4	5		9
Liver	3	3		6
Brain	1	0		1
Multiorgan	3	0		3
Total	16	13		29
Distant metastases and recurrence	2	1		3
Total	33	21	0.083	54

Note: [a]*P*-values were calculated by using χ^2 test or Fisher exact test if indicated.

Abbreviations: CC, concurrent chemotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma.

Grade 3–4 hematological toxicities

In the IC plus CC treatment group, 82 patients experienced grade 3–4 leucopenia, and 97 patients experienced grade 3–4 neutropenia. IC plus CC treatment significantly increased the incidence of grade 3–4 leucopenia ($P<0.001$) and neutropenia ($P<0.001$) compared with CC treatment. The rates of grade 3–4 anemia and thrombocytopenia exhibited no significant difference in either treatment group (Table 5).

Discussion

Previous phase II/III clinical trials showed conflicting outcomes when IC was added to concurrent chemoradiotherapy (CCRT) in LA-NPC patients.[11–14] Tan et al's[11] and Hui et al's[14] studies included stage III–IVB NPC patients and Fountzilas et al's study[12] included stage IIB–IVB patients, but only Hui et al's study significantly increased 3-year OS (94.1% vs 67.7%, *P*=0.012).[14] When stage T3-4N0 NPC patients were excluded to enhance the power for survival, the trial showed a significant improvement in 3-year PFS (*P*=0.034), OS (*P*=0.029), and DMFS (*P*=0.031) in LA-NPC patients.[13]

Table 3 Summary of prognostic factors in 237 patient pairs with stage T3N0-1 NPC by univariate analysis

Factors	n	4-year OS (%)	*P*-value[a]	4-year LRFS (%)	*P*-value[a]	4-year DMFS (%)	*P*-value[a]	4-year PFS (%)	*P*-value[a]
Gender			0.871		0.393		0.419		0.178
Male	300	91.7		95.7		94.6		91.4	
Female	144	93		92.3		92.1		84.6	
Age (years)			0.861		0.620		0.828		0.603
≤50	347	92.4		94.9		93.7		89.5	
>50	127	91		94.1		94.3		88.5	
Pathological type			0.37		0.465		0.416		0.286
Type I + II	8	100		100		100		100	
Type III	466	91.9		94.6		93.8		89	
Smoking			0.705		0.831		0.551		0.694
Yes	154	93.1		95.2		94.2		90.8	
No	320	91.6		94.4		93.7		88.5	
NPC family history			0.346		0.091		0.236		0.913
Yes	47	85.2		100		91.4		91.4	
No	427	92.7		94.1		94.2		89	
Pre-EBV DNA			0.887		0.358		0.044		0.118
<4,000	276	93.3		95.8		95.5		91.3	
≥4,000	198	90.5		93.1		91.6		86.4	
Chemotherapy			0.794		0.138		0.582		0.223
IC plus CC	237	91.7		92.7		93.5		87.5	
CC	237	92.6		96.8		94.3		91.1	
N category			0.732		0.598		0.373		0.226
N0	66	92.9		95.2		95.5		92.2	
N1	408	92		94.6		93.6		88.7	

Note: [a]*P*-values were calculated by using the unadjusted log-rank test.
Abbreviations: CC, concurrent chemotherapy; DMFS, distant metastasis-free survival; EBV DNA, Epstein–Barr virus deoxyribonucleic acid; IC, induction chemotherapy; LRFS, locoregional relapse-free survival; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival.

Therefore, no published study exists which assesses the effect of IC in stage T3N0-1 patients, which could be defined as low-risk LA-NPC because of low T and N categories. Therefore, our retrospective study is the first to analyze IC plus CC treatment and CC treatment alone in stage T3N0-1 NPC patients treated with IMRT.

As it is a propensity-matched study, the groups were shown to be well matched for prognostic factors. Other than exploring conventional prognostic factors (ie, gender, age, WHO pathological type, chemotherapy strategy, and N category), we also considered some carcinogenic factors, including smoking history and family history of NPC. Our previous study[22] revealed that pretreatment of cigarette smoking was a negative prognostic factor of death, locoregional recurrence, distant metastasis, and disease progression. Guo et al[23] reported that the ever-smokers suffered a higher risk of locoregional disease recurrence compared with never-smokers in LA-NPC patients. Ouyang et al[24] published that patients who had a first-degree family history of NPC had higher rates of OS and DMFS than those without a family history. However, smoking history and family history of NPC were not associated with survival in both univariate analysis and adjusted multivariate analysis. Plasma EBV DNA has been proven a prognostic biomarker in several studies.[25–27] Leung et al[28] demonstrated that high levels of EBV DNA pretreatment were associated with the incidence of distant metastasis. Moreover, pre-EBV DNA has been reported a prognostic factor using a cutoff of 4,000 copies/mL to define low versus high levels.[21] Our results showed an increased risk of distant metastasis in patients with high EBV DNA (≥4,000 copies/mL) compared with those with low EBV DNA (<4,000 copies/mL), whereas there was no significant difference in 4-year OS, LRFS, and PFS.

Chemoradiotherapy is the standard treatment for LA-NPC. Chemoradiotherapy has been shown to significantly improve patient survival in several phase III randomized clinical trials.[4–10] For patients with bulky and/or extensive nodal disease (N2-3), there is higher potential for metastasis; CC is not adequate.[29,30] Moreover, T4-classified tumors are considered to result in a poor prognosis.[31] Consequently, N2-3 and/or T4 patients can be defined as a high-risk group of LA-NPC; therefore, IC is needed to reduce metastasis and improve survival. Xu et al[32] demonstrated that CCRT achieved higher 3-year DMFS rates (94.9% vs 80.1%, *P*=0.03) in N0-1 LA-NPC patients, but not in N2-3 tumors. In the present study, we chose stage T3N0-1 NPC patients

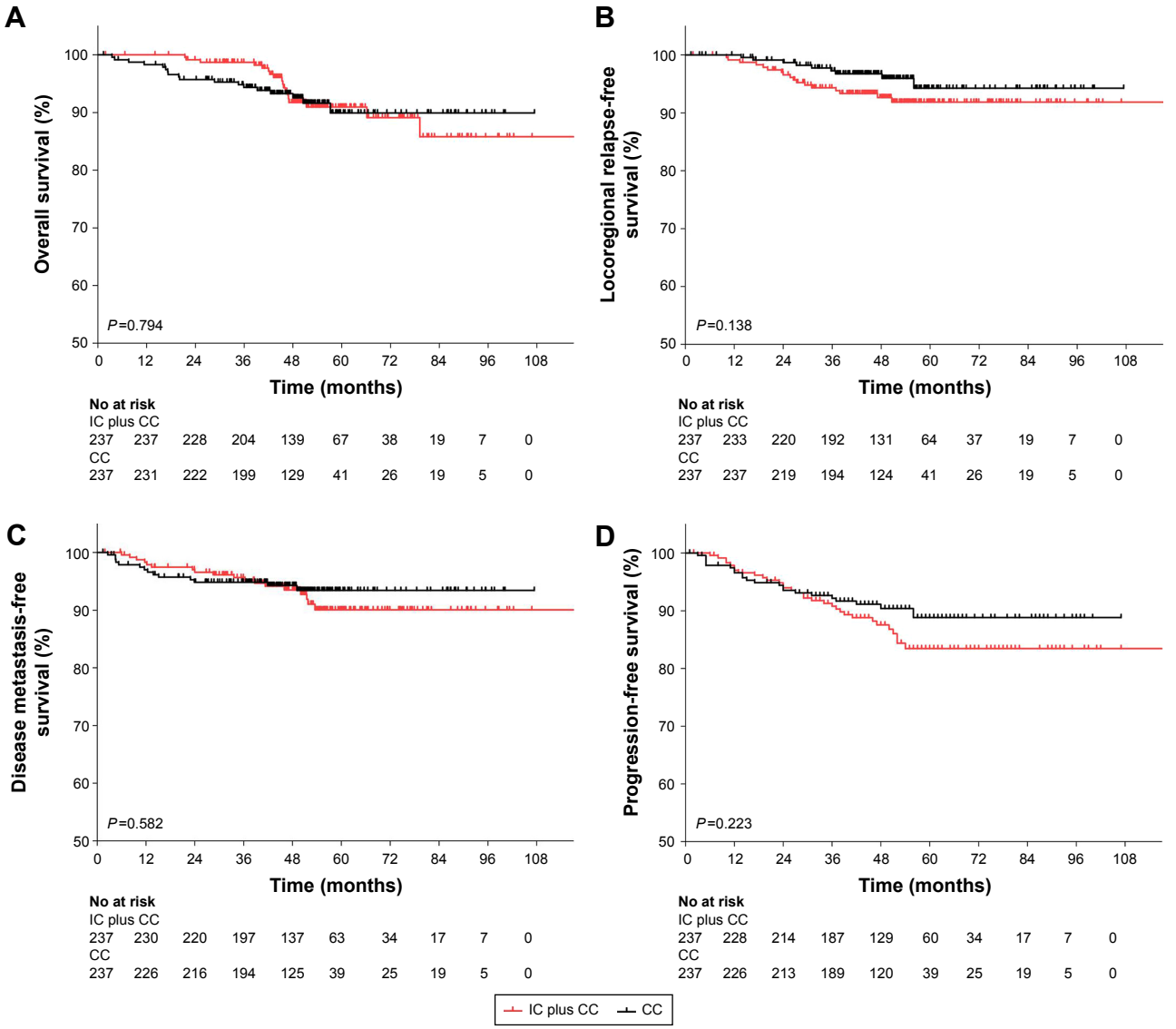

Figure 1 Kaplan–Meier survival curves for IC plus CC and CC alone in 237 patient pairs.
Notes: (**A**) Overall survival; (**B**) locoregional relapse-free survival; (**C**) distant metastasis-free survival; (**D**) progression-free survival.
Abbreviations: CC, concurrent chemotherapy; IC, induction chemotherapy.

Table 4 Summary of prognostic factors in 237 patient pairs with stage T3N0-1 NPC by multivariate analysis

Factors	OS			LRFS			DMFS			PFS		
	HR	95% CI	*P*-value[a]	HR	95% CI	*P*-value[a]	HR	95% CI	*P*-value[a]	HR	95% CI	*P*-value[a]
Gender	0.86	0.39–1.89	0.713	1.79	0.69–4.70	0.234	1.73	0.73–4.12	0.215	1.82	0.94–3.53	0.076
Age (years)	1.10	0.53–2.29	0.808	1.26	0.54–2.96	0.595	0.90	0.39–2.02	0.793	1.16	0.64–2.11	0.618
Pathological type	–	–	0.979	–	–	0.989	–	–	0.972	–	–	0.962
Smoking	0.81	0.37–1.79	0.608	1.40	0.53–3.76	0.499	1.59	0.67–3.81	0.295	1.45	0.73–2.85	0.286
NPC family history	1.57	0.60–4.06	0.357	–	–	0.976	1.88	0.72–4.92	0.202	0.94	0.37–2.38	0.901
Pre-EBV DNA	1.05	0.38–0.83	0.897	1.35	0.61–2.99	0.459	2.08	1.00–4.32	0.05	1.48	0.85–2.57	0.164
Chemotherapy	0.90	0.53–2.08	0.760	1.91	0.85–4.33	0.119	1.23	0.61–2.48	0.569	1.40	0.81–2.42	0.229
N category	1.17	0.45–3.10	0.745	1.05	0.30–3.64	0.945	1.29	0.38–4.38	0.683	1.40	0.54–3.60	0.485

Note: [a]*P*-values were calculated by using an adjusted Cox proportional hazard model with the forward conditional method.
Abbreviations: DMFS, distant metastasis-free survival; EBV DNA, Epstein–Barr virus deoxyribonucleic acid; HR, hazard ratio; LRFS, locoregional relapse-free survival; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival.

Table 5 Grade 3–4 hematological toxicities in 237 patient pairs with stage T3N0-1 NPC

Hematological toxicity	IC plus CC	CC	*P*-value
Leucopenia	82 (34.6%)	38 (16.0%)	<0.001
Neutropenia	97 (40.9%)	14 (5.9%)	<0.001
Anemia	10 (4.2%)	4 (1.7%)	0.104
Thrombocytopenia	27 (11.4%)	22 (9.3%)	0.451

Note: *P*-values were calculated by using χ^2 test or Fisher exact test if indicated.
Abbreviations: CC, concurrent chemotherapy; IC, induction chemotherapy; NPC, nasopharyngeal carcinoma.

treated with IMRT as a low-risk group to assess the value of IC. Results showed that IC plus CC did not improve survival compared with CC. However, the results showed that CC group was numerically superior to the IC plus CC group in 4-year OS (92.6% vs 91.7%), 4-year LRFS (96.8% vs 92.7%), DMFS (94.3% vs 93.5%), and PFS (91.1% vs 87.5%). We considered that IC increased hematological acute toxicities and reduced the tolerance of CC, which resulted in poor treatment intensity.

A previous trial showed that IC caused higher rates of grade 3 and 4 hematological toxicities, including leukopenia (52% vs 37%, P=0.046), neutropenia (24% vs 12%, P=0.029), and thrombocytopenia (14% vs 0%, P<0.01) compared with the chemoradiotherapy group in LA-NPC patients.[11] Our study showed that IC did not improve survival benefits and increased hematological acute toxicities. The IC group experienced a significantly higher incidence of grade 3–4 leucopenia (34.6% vs 16%, P<0.001) and neutropenia (40.9% vs 5.9%, P<0.001). These hematological toxicities may compromise the delivery of subsequent CC with dose reduction.

The present study had several limitations. First, our study is a single institutional retrospective study in an endemic area; therefore, a selection bias existed. Second, although all the patients in the cohort received platinum-based chemotherapy, the regimen and cycles of IC and CC were in disunity. IC included TP, TC, TPF, or PF regimens, whereas CC regimens consisted of cisplatin/nedaplatin, PF, or TP. Furthermore, there was no IMRT dose-fractionation consensus in NPC treatment. Third, only acute hematological toxicities were evaluated. Nonhematological mucositis, vomiting, and late toxicities were not acquired because of the long time interval of the cohort, and some information was missing. Fourth, besides plasma pre-EBV DNA,[33] pretreatment serum lactate dehydrogenase was reported to be associated with distant metastasis,[34,35] but we did not include this factor into our analysis. Finally, we assessed only 4-year survival; however, the investigation should be 5 years or longer to evaluate the survival.

Conclusion

IC did not significantly improve survival in stage T3N0-1 NPC patients treated with CC. Furthermore, IC increased the incidence of grade 3–4 hematological toxicities, and it is not recommended for low-risk LA-NPC patients. Further confirmation is warranted in prospective studies.

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Disclosure

The authors report no conflicts of interest in this work.

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