

Survival without concurrent chemotherapy for locoregionally advanced nasopharyngeal carcinoma treated with induction chemotherapy plus intensity-modulated radiotherapy

Single-center experience from an endemic area

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Abstract

Although induction chemotherapy (IC) combined with intensity-modulated radiotherapy (IMRT) plus concurrent chemotherapy (CC) is the new standard treatment option in locoregionally advanced nasopharyngeal carcinoma (NPC), many patients fail to receive CC. The aim of this study was to investigate long-term survival outcomes and toxicities in these patients who are treated with IC before IMRT without CC.

We retrospectively reviewed 332 untreated, newly diagnosed locoregionally advanced NPC patients who received IC before IMRT alone at our institution from May 2008 through April 2014. The IC was administered every 3 weeks for 1 to 4 cycles. Acute and late radiation-related toxicities were graded according to the acute and late radiation morbidity scoring criteria of the radiation therapy oncology group. The accumulated survival was calculated according to the Kaplan–Meier method. The log-rank test was used to compare the difference in survival.

With a median follow-up duration of 65 months (range: 8–110 months), the 5-year estimated locoregional relapse-free survival, distant metastasis-free survival, progression-free survival (PFS), and overall survival rates were 93.4%, 91.7%, 85.8%, and 82.5%, respectively. Older age and advanced T stage were adverse prognostic factors for overall survival, and the absence of comorbidity was a favorable prognostic factor for PFS. However, acceptable acute complications were observed in these patients.

IC combined with IMRT alone provides promising long-term survival outcomes with manageable toxicities. Therefore, the omission of CC from the standard treatment did not affect survival outcomes.

Abbreviations: AC = adjuvant chemotherapy, AJCC/UICC = American Joint Committee for Cancer/Union International against Cancer, CC = concurrent chemotherapy, CCRT = concurrent chemoradiotherapy, CIs = confidence intervals, DMFS = distant metastases-free survival, FP = cisplatin + 5-fluorouracil, GP = gemcitabine + cisplatin, HRs = hazard ratios, IBM SPSS = International Business Machines Corporation Statistical Package for the Social Sciences, IC = induction chemotherapy, IMRT = intensity-modulated radiotherapy, LRRFS = locoregional relapse-free survival, MRI = magnetic resonance image, NPC = nasopharyngeal carcinoma, OS = overall survival, PFS = progression-free survival, PGTV = planning gross tumor volume, PTV = planning target volume, RT = radiotherapy, RTOG = the radiation therapy oncology group, TP = docetaxel + cisplatin, TPF = docetaxel + cisplatin + 5-fluorouracil.

Keywords: efficacy, induction chemotherapy, intensity-modulated radiotherapy, nasopharyngeal carcinoma, safety

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a unique cancer of the head and neck, with an incidence of 15 to 50 cases per 100,000 persons annually in endemic regions such as southern China, Singapore, and Malaysia.^[1] In some endemic areas, the rates of incidence and mortality of NPC have reduced owing to lifestyle changes.^[2,3] Nevertheless, NPC is one of the main causes of cancer death with a global mortality rate of about 50,000 persons per year.^[1,4]

Because of the high sensitivity to radiation and complicated anatomical structure, radiotherapy (RT) is the primary therapy for NPC. Approximately 60% to 70% of all NPC patients at diagnosis belong to the category of locoregionally advanced disease.^[5] Previous studies showed that compared with 2-dimensional RT, intensity-modulated radiation therapy (IMRT) was beneficial for locoregional control but did not prolong survival or reduce distant failure.^[6,7] A meta-analysis conducted by Al-Sarraf et al^[8] demonstrated that a combination of RT and chemotherapy improves the 5-year survival from 4% to 6% and reduces the risk of mortality by 18%. Concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy (AC) is beneficial for overall survival (OS), and it is the standard treatment for locoregionally advanced NPC, despite acute toxicities.^[9–11] A previous meta-analysis showed that compared with CCRT alone, the addition of induction chemotherapy (IC) to CCRT reduces distant failure in locoregionally advanced NPC patients.^[12,13] Another current meta-analysis confirmed that IC followed by CCRT significantly improved progression-free survival (PFS) and OS,^[14] although its efficacy in patients with locoregionally advanced NPC remains controversial.^[15–17] Therefore, the IC followed by CCRT is an encouraging treatment option in locoregionally advanced NPC patients in the era of IMRT.

Unfortunately, few patients do not receive concurrent chemotherapy (CC) for reasons such as treatment-associated toxicities, economic conditions, and patient refusal without due cause. It is unclear whether IC before IMRT alone is inferior to CCRT with or without IC. Komatsu et al^[18] observed similar survival outcomes between CCRT and IC plus RT. A randomized study by Huang et al^[17] showed that the efficacy of IC plus RT was not less than that of IC plus CCRT in these patients with respect to OS and PFS.^[17] In addition, Wu et al^[19] indicated that IC before RT provided similar long-term outcomes with CCRT in locoregionally advanced NPC.^[19] A phase III randomized study conducted by Xu et al^[20] showed that IC added to IMRT plus AC had similar OS and PFS outcomes but less acute toxicities than CCRT plus AC. The 2-dimensional RT technology was used in the above studies. However, IMRT had better survival outcomes than 2-dimensional RT.^[21,22] Hence, the addition of IC to IMRT alone may be a promising option with encouraging outcomes and reduced toxicity. There are few studies on the safety and efficacy of IC plus IMRT alone in locoregionally advanced NPC. Therefore, we conducted an observational study to investigate the long-term outcomes and tolerability of IC plus IMRT alone in patients with locoregionally advanced NPC.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the patients who received treatment in the Department of Radiation Oncology at Zhejiang Cancer

Hospital between May 2008 and April 2014. The patients who met the following criteria were included in the study:

- (1) untreated, newly diagnosed locoregionally advanced NPC,
- (2) Eastern Cooperative Oncology Group performance status ≤ 1 ,
- (3) completion of radical IMRT,
- (4) received NAC plus IMRT alone, and
- (5) no previous anticancer treatment.

This retrospective study was approved by the Medical Ethics Committee and the institutional review board of the Zhejiang Cancer Hospital. All the patients provided written informed consent.

Patients had pretreatment evaluations that included complete medical histories, physical examinations, hematology and biochemistry profiles, chest radiographs, sonography of the abdomen, bone scans, magnetic resonance imaging (MRI) of the nasopharynx, and nasopharyngoscopy. All patients were staged according to the 2010 American Joint Committee on Cancer staging system. Tumor histology was classified according to the World Health Organization classification.

The flowchart of the patients is shown in Figure 1. A total of 3022 newly diagnosed, locoregionally advanced NPC patients were registered at the Zhejiang Cancer Hospital. A total of 332 NPC patients who were treated with additional IC followed by IMRT were enrolled in this study. All patients received definitive IMRT alone without CC.

2.2. IMRT

All patients were immobilized in a supine position with thermoplastic masks. Computed tomography scans with intravenous contrast (2.5 mm slices from the head to 2 cm below the sternoclavicular joints) were performed for IMRT planning. All patients underwent radical IMRT with a simultaneous integrated boost technique that used 6-MV photons within 2 to 3 weeks of IC. The delineation of target volumes of NPC during the treatment of IMRT was described previously.^[23–25] The prescribed radiation doses were 69 to 72 Gy to planning gross target volume (PGTV)nx, 66 to 69 Gy to PGTVnd, 63 to 66 Gy to planning target volume (PTV)nx, 60 to 63 Gy to PTV1, and 51 to 54 Gy to PTV2 delivered in 30 to 33 fractions. Radiation was delivered once daily in 5 fractions per week, over 6 to 6.5 weeks according to the IMRT planning. The dose to organs at risk was limited based on the radiation therapy oncology group (RTOG) 0225 protocol.

2.3. Chemotherapy

All patients were given 1 to 4 cycles of 3-weekly platinum-based IC. The available IC regimens included TPF (docetaxel 60 mg/m²/d on day 1 and cisplatin 25 mg/m²/d and 5-fluorouracil 500 mg/m²/d on days 1–3), TP (docetaxel 60 mg/m²/d on day 1 and cisplatin 25 mg/m²/d on days 1–3), GP (gemcitabine 1 g/m²/d on day 1 and cisplatin 25 mg/m²/d on days 1–3), and FP (cisplatin 25 mg/m²/d and 5-fluorouracil 500 mg/m²/d on days 1–3).

2.4. Patient evaluation and follow-up

The assessment of tumor response was performed thrice: after the completion of IC, at the end of IMRT, and 3 months after RT. The assessment was based on MRI and nasopharynx fiberoptic

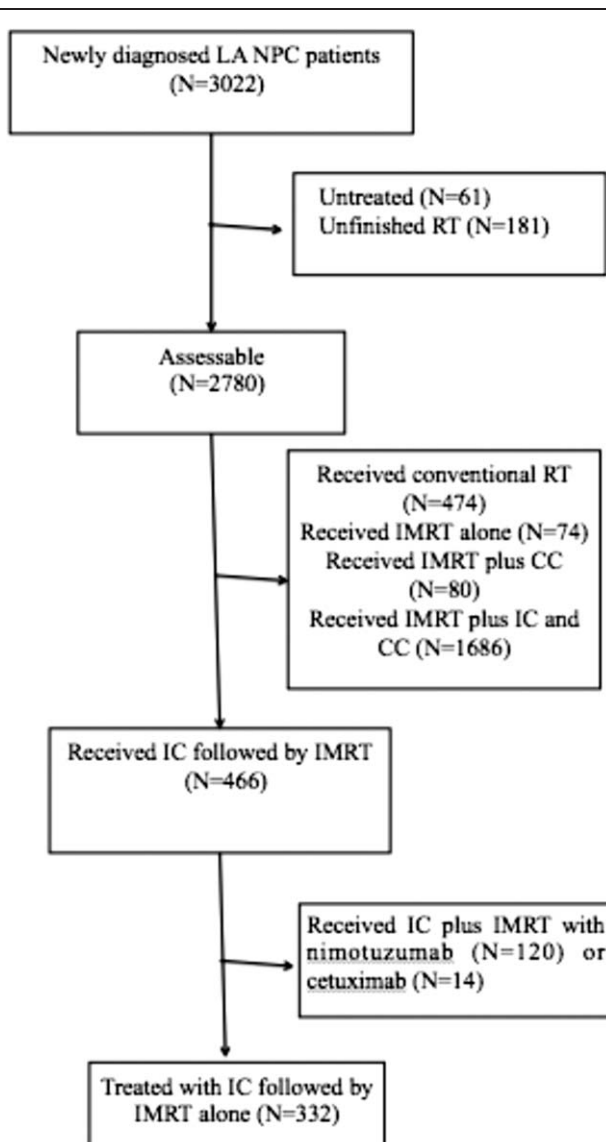


Figure 1. Flowchart of patients. CC=concurrent chemotherapy, IC=induction chemotherapy, IMRT=intensity-modulated radiotherapy, NPC=nasopharyngeal carcinoma, RT=radiotherapy.

according to the response evaluation criteria for solid tumors criteria. Systemic chemotherapy adverse effects were graded using the National Cancer Institute Common Toxicity Criteria (version 3.0) whereas RT-induced toxicities were scored according to the acute and late radiation morbidity scoring criteria of the RTOG.

All the subjects underwent weekly examinations for treatment response and toxicities during IMRT. Patients were followed-up every 3 months in the first 2 years; every 6 months from the third to the fifth year; and then annually. Each follow-up included careful examination of the nasopharynx and neck nodes by an experienced doctor, MRI scan of the nasopharynx, nasopharynx fibroscope, and chest computed tomography radiograph. Additionally, ultrasound of the abdomen was performed 3 months after the completion of IMRT and every 6 to 12 months thereafter. Additional examinations were performed when it was necessary to evaluate local relapse or distant metastasis.

2.5. Statistical analysis

The endpoints of this study included locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS), PFS, OS, and acute toxicities from IC and RT. OS was calculated from the date of enrollment in the trial to the date of death or last follow-up. LRRFS, DMFS, and PFS were calculated from the date of enrollment in the trial to the date of locoregional relapse, distant metastasis occurrence, and diagnosed evidence of disease progression or the last follow-up, respectively. After recurrence or metastasis, patients were given salvage therapy as determined by their physicians.

IBM SPSS Statistics version 19.0 was used for all data analyses. Survival curves were generated using the Kaplan–Meier method. The curves were compared using log-rank tests. Multivariate analysis was performed using Cox regression models to identify significant prognostic factors. Hazard ratios and 95% confidence intervals were calculated for each prognostic factor. A $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

From May 2008 to April 2014, the clinical data of 332 untreated, newly diagnosed, locoregionally advanced NPC patients who were initially treated with additional IC followed by IMRT in the Department of Radiation Oncology, Zhejiang Cancer Hospital (Hangzhou, People's Republic of China) were collected and retrospectively reviewed. The basic characteristics of patients are summarized in Table 1. All patients completed a full course of radical IMRT and received 1 to 4 cycles of IC.

3.2. Survivals

At a median follow-up duration of 65 months (range, 8–106 months), the 5-year estimated rates of LRRFS, DMFS, PFS, and OS for the entire cohort of patients were 93.4%, 91.7%, 85.8%, and 82.5%, respectively. Figure 2 shows the Kaplan–Meier curves of the survival in these patients. The 3-, 5-, 7-year LRRFS, DMFS, PFS, and OS rates are summarized in Table 2.

3.3. Patterns of treatment failure

Out of all patients, 45 patients (13.6%) experienced “any” treatment failure at last follow-up. Only locoregional relapse was observed in 19 (5.7%) patients. Only distant metastases occurred in 22 (6.6%) patients. Both locoregional relapse and distant metastases were observed in 4 (1.2%) patients. These details are shown in Table 3.

3.4. Prognostic factors

The common potential prognostic factors included patient age, patient gender, T category, N category, clinical-stage, comorbidity, and AC. We identified which factors influenced survival outcome and evaluated the prognostic significance of these factors by univariate and multivariate analyses. Univariate analysis showed that the 5-year OS of patients aged <60 years was better than those aged ≥ 60 years (5-year OS: 86.2% vs 72.8%, $P = .009$); T4 was associated with poor OS (5-year OS:

Table 1
Basic characteristic of 332 patients with locoregionally advanced NPC.

Characteristic	N (%)
Gender	
Male	209 (63.0)
Female	123 (37.0)
Age, yr	
Range	10–81
Median	52
<60	233 (70.2)
≥60	99 (29.8)
WHO pathology	
Type I	13 (4.0)
Type II	7 (2.1)
Type III	312 (93.9)
ECOG performance status	
0	287 (86.4)
1	45 (13.6)
T stage*	
T1	23 (6.9)
T2	68 (20.5)
T3	146 (44.0)
T4	95 (28.6)
N stage*	
N0	24 (7.2)
N1	77 (23.2)
N2	182 (54.8)
N3	49 (14.8)
Clinical stage*	
III	197 (59.3)
IVA	86 (25.9)
IVB	49 (14.8)
Comorbidity	
No	246 (74.1)
Yes	86 (25.9)
AC	
No	145 (43.7)
Yes	187 (56.3)
IC regimens	
TPF	39 (11.7)
TP	128 (38.6)
GP	19 (5.7)
FP	130 (39.2)
Other	16 (4.8)
Cycle of IC	
1	123 (37.0)
2	126 (38.0)
3–4	83 (25.0)

AC=adjuvant chemotherapy, ECOG=Eastern Cooperative Oncology Group, FP=cisplatin + 5-fluorouracil, GP=gemcitabine + cisplatin, IC=induction chemotherapy, TP=docetaxel + cisplatin, TPF=docetaxel + cisplatin + 5-fluorouracil, WHO=World Health Organization.

*The 7th American Joint Committee for Cancer/Union International against Cancer (AJCC/UICC) staging system.

72.7% vs 86.3%, $P=.006$); and 5-year PFS in patients with comorbidity was worse than those without comorbidity (5-year PFS: 77.2% vs 88.8%, $P=.025$). Table 4 lists the prognostic factors of survival outcomes in 332 patients with locoregionally advanced NPC using univariate analysis. Multivariate analysis indicated that older age and T4 were adverse independent predictors of OS ($P=.045$ and $P=.009$, respectively), and the absence of comorbidity was a favorable prognostic factor of PFS (Table 5).

3.5. Safety and toxicity

The most common treatment-related toxicities include hematologic and nonhematologic adverse effects during IC or IMRT. The profile of complications is shown in Table 6. Grade 3 to 4 leukopenia and neutropenia during IC were reported in 121 (36.4%) and 123 (37.0%) patients, respectively and during IMRT were reported in 46 (13.9%) and 45 (13.6%) patients, respectively. The rates of grade 3 to 4 mucositis during IC and IMRT only were 1.2% and 4.8%, respectively.

4. Discussion

To the best of our knowledge, the addition of IC to CC and IMRT is regarded as the current standard treatment option for locoregionally advanced NPC. However, many patients failed to receive CC. This is the first observational study to investigate the long-term survival and toxicities in these patients. The results showed that the addition of IC to IMRT alone provides promising long-term survival outcomes with manageable toxicities. Thus, the omission of CC from the standard treatment does not affect survival outcomes.

In this study, we examined survival over a median follow-up period of 65 months; the 5-year LRRFS, DMFS, PFS, and OS rates for locoregionally advanced NPC patients were 93.4%, 91.7%, 85.8%, and 82.5%, respectively. In addition, univariate and multivariate analyses indicated that older age and T4 were adverse independent predictors of OS ($P=.045$ and $P=.009$, respectively), and the absence of comorbidity was a favorable prognostic factor of PFS.

CCRT is a standard treatment option recommended by the National Comprehensive Cancer Network because it has improved survival benefits.^[26] However, a phase III randomized trial from China indicated that the addition of TPF IC to CCRT significantly improved failure-free survival in locoregionally advanced NPC patients with manageable toxicities.^[27] Zhang et al showed that GP IC added to CCRT significantly improved recurrence-free survival and OS in locoregionally advanced patients, as compared with CCRT alone.^[28] A recent meta-analysis showed that although adding IC to CCRT improved PFS and OS significantly, it was associated with frequent adverse events in locoregionally advanced NPC.^[29] As a result, some patients were unable to receive CC owing to these toxicities. Thus, the effect of omission of CC on the survival outcomes in locoregionally advanced NPC remains unclear.

Komatsu et al^[18] found that IC following RT and CCRT had similar survival outcomes in locoregionally advanced NPC. A randomized study showed that the efficacy of IC plus RT was not less than that of IC plus CCRT in locoregionally advanced NPC patients with respect to OS and PFS.^[17] Moreover, Wu et al^[19] indicated that the addition of IC to RT had similar long-term outcomes as CCRT for locoregionally advanced NPC. A phase III randomized study by Xu et al^[20] showed that IC added to IMRT plus AC had similar OS and PFS but less acute toxicities than CCRT plus AC. It is important to note that the above-mentioned studies used the 2-dimension RT technology for NPC patients. A retrospective study conducted by Qu Yang et al^[30] investigated IC plus IMRT in 94 NPC patients versus CC plus IMRT in 302 NPC patients and observed comparable survival outcomes.

In addition, we conducted a phase II trial and found that the efficacy of TPF and TP before IMRT with CC or without CC was

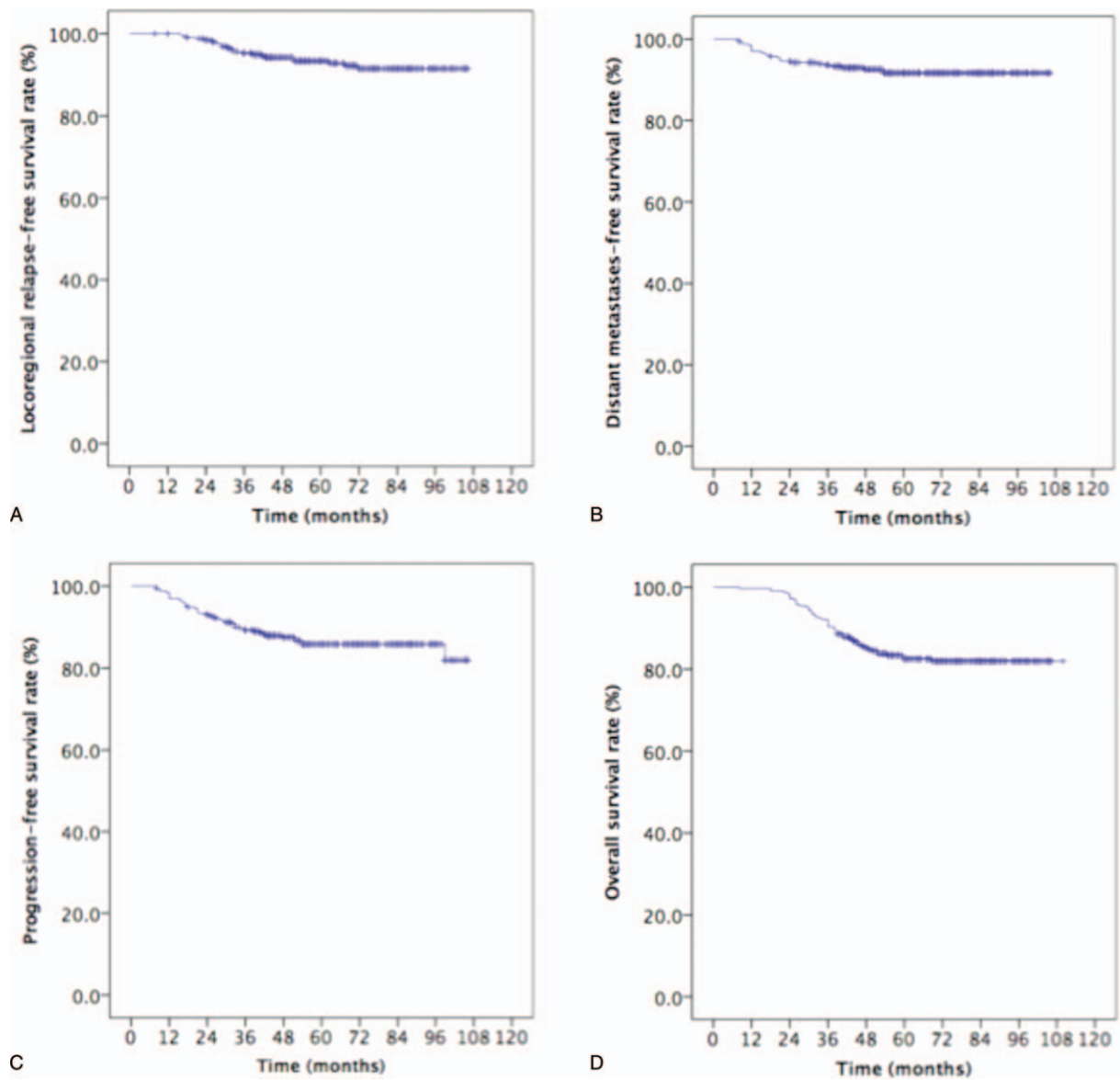


Figure 2. Kaplan-Meier estimates of the survival in 332 patients with locoregionally advanced nasopharyngeal carcinoma. (A) Locoregional relapse-free survival rate; (B) distant metastases-free survival rate; (C) progression-free survival rate; (D) overall survival rate.

comparable; the 3-year PFS and OS rates were 85.5% and 93.2%, respectively.^[31] Another phase II study of GP-base IC followed by IMRT with or without CC showed that the 4-year PFS and OS rates were 77.0% and 81.9%, respectively.^[32] In

retrospective studies from our hospital, the 5-year PFS and OS rates were approximately 81% to 91% and 85% to 93%, respectively.^[33-35] Therefore, the results of the addition of IC to IMRT were similar to previous data.

Table 2
3-, 5-, 7-yr rates of survival for 332 locoregionally advanced NPC patients receiving IC plus IMRT.

Endpoint	3-yr rates (%)	5-yr rates (%)	7-yr rates (%)
LRRFS	95.3	93.4	91.5
DMFS	93.6	91.7	91.7
PFS	89.3	85.8	85.8
OS	90.4	82.5	82.0

DMFS=distant metastasis-free survival, LRRFS=locoregional relapse-free survival, OS=overall survival, PFS=progression-free survival.

Table 3
Site and incidence of treatment failure.

Sites	Number of patients (n=45)
Locoregional only	19
Locoregional and distant	4
Distant only	22
Lung only	6
Bone only	7
Liver only	4
Lung, liver, bone, and other	5

Table 4**Prognostic factors of survival outcomes in 332 NPC patients using univariate analysis.**

Characteristics	n	OS (%)	P	LRRFS (%)	P	DMFS (%)	P	PFS (%)	P
Age			.009		.900		.264		.504
<60	233	86.2		93.6		90.7		85.3	
≥60	99	72.8		92.6		93.8		86.4	
Gender			.308		.258		.554		.853
Male	209	80.6		92.3		92.3		85.8	
Female	123	85.8		95.2		90.6		85.9	
T stage			.006		.338		.733		.497
T1–3	237	86.3		94.4		91.9		89.3	
T4	95	72.7		90.9		91.1		84.6	
N stage			.201		.731		.242		.314
N0–2	283	80.9		36.3		92.5		86.7	
N3	49	88.0		93.7		87.1		80.9	
Clinical stage			.175		.370		.834		.683
III	197	84.6		94.3		92.0		86.3	
IVA/B	135	79.5		92.2		91.2		85.2	
Comorbidity			.084		.125		.125		.025
No	246	84.4		93.9		93.2		88.8	
Yes	86	77.1		89.7		87.1		77.2	
IC regimen			.199		.554		.835		.434
TPF	57	96.4		87.7		86.0		94.7	
TP	75	90.3		91.9		85.2		92.0	
AC			.593		.431		.595		.460
No	145	83.6		93.7		92.7		87.3	
Yes	187	81.7		93.0		90.9		84.7	

DMFS = distant metastases-free survival, IC = induction chemotherapy, LRRFS = locoregional relapse-free survival, OS = overall survival, PFS = progression-free survival, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/5-fluorouracil.

Table 5**Summary of multivariate analyses of prognostic factors in the 332 NPC patients.**

Endpoint	Factor	HR	95% CI	P
LRRFS	Age: <60 yr versus ≥60 years	1.250	0.464–3.368	.660
	Gender: male versus female	1.587	0.619–4.064	.336
	T category: T1–3 versus T4	0.570	0.235–1.380	.213
	N category: N0–2 versus N3	0.879	0.293–2.638	.818
	AC: No versus Yes	0.720	0.297–1.749	.469
	Comorbidity: No versus Yes	1.068	0.311–3.661	.917
DMFS	Age: <60 yr versus ≥60 yr	2.044	0.727–5.748	.175
	Gender: male versus female	0.716	0.325–1.576	.406
	T category: T1–3 versus T4	0.728	0.313–1.696	.462
	N category: N0–2 versus N3	0.595	0.235–1.506	.273
	AC: No versus Yes	0.954	0.421–2.161	.912
	Comorbidity: No versus Yes	0.448	0.197–1.020	.056
PFS	Age: <60 yr versus ≥60 yr	1.501	0.725–3.107	.274
	Gender: male versus female	0.975	0.526–1.808	.936
	T category: T1–3 versus T4	0.683	0.357–1.306	.249
	N category: N0–2 versus N3	0.704	0.335–1.483	.356
	AC: No versus Yes	0.873	0.466–1.634	.671
	Comorbidity: No versus Yes	0.453	0.243–0.846	.013
OS	Age: <60 yr versus ≥60 yr	0.555	0.312–0.988	.045
	Gender: male versus female	1.257	0.709–2.230	.434
	T category: T1–3 versus T4	0.480	0.277–0.832	.009
	N category: N0–2 versus N3	1.618	0.638–4.104	.311
	AC: No versus Yes	0.695	0.396–1.222	.206
	Comorbidity: No versus Yes	0.659	0.368–1.182	.162

The 7th AJCC/UICC staging system.

AC = adjuvant chemotherapy, CI = confidence interval, DMFS = distant metastasis-free survival, HR = hazard ratio, IC = induction chemotherapy, LRRFS = locoregional relapse-free survival, OS = overall survival, PFS = progression-free survival, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/5-fluorouracil.

Table 6**Profile of toxicities during IC or IMRT.**

Adverse events	During IC (n)				During IMRT (n)			
	1	2	3	4	1	2	3	4
Hematologic								
Leukopenia	70	89	86	35	86	60	35	11
Neutropenia	66	83	92	31	78	57	32	13
Anemia	82	21	9	0	46	11	3	0
Thrombocytopenia	4	10	5	2	6	8	2	0
Liver function	14	7	2	0	5	1	0	0
Renal function	2	1	0	0	0	0	0	0
Non-hematologic								
Mucositis	26	15	4	0	176	105	16	0
Dermatitis	22	1	0	0	257	69	6	0
Diarrhea	24	13	5	0	7	0	0	0
Nausea/vomiting	78	45	19	0	25	12	8	0

IC=induction chemotherapy, IMRT=intensity-modulated radiotherapy.

This large-scale observational study was conducted at a single center in an endemic area. The major limitation was that the results of this single-arm retrospective study had relatively low power and therefore, did not indicate noninferior outcomes of IC plus IMRT. This study evaluated only acute treatment-associated toxicities based on medical record information. Besides, the IC regimens and doses were heterogeneous owing to the retrospective design. Therefore, our results should be regarded as preliminary. Further prospective and large sample clinical trials are warranted.

5. Conclusion

In summary, this study indicated that locoregionally advanced NPC patients who were treated with IC plus IMRT had encouraging survival outcomes with respect to LRRFS, DMFS, PFS, and OS and a low incidence of grade 3/4 acute toxicities. Therefore, the omission of CC does not affect survival outcomes. However, further randomized, controlled, multicenter phase III clinical trials are needed to assess the efficacy and toxicity of IC plus IMRT.

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