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ORIGINAL RESEARCH

Stage-specific concurrent chemoradiotherapy with or without induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma: a retrospective, population-based study

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Purpose: This large population-based analysis aims to investigate whether the additional induction chemotherapy to concurrent chemoradiotherapy improved overall survival (OS) and disease-free survival (DFS) for locoregionally advanced nasopharyngeal carcinoma (LRANPC).

Patients and Methods: The study group comprised 3,980 patients who were treated either with IC+CCRT (1,888 patients) or CCRT alone (2,092 patients) between January 1998 and June 2013. Survival outcomes were compared using Cox proportional hazards regression models with adjustments for confounding provided by propensity score methods. Primary outcome variables included OS and DFS.

Results: Kaplan–Meier analysis showed that CCRT and IC+CCRT were of similar benefit to OS (P=0.099), whereas there was a marginal benefit of CCRT to DFS (P=0.063) in the overall cohort, which showed no differences between the two treatment regimens using multivariate Cox analysis and propensity score. Interestingly, for patients with 2D radiationtherapy (2DRT), CCRT had OS and DFS benefits for stage III, with 5-year and 10-year OS for CCRT vs IC +CCRT being 88% and 75% vs 81% and 67%, respectively (P=0.002); 5-year and 10-year DFS for CCRT vs IC+CCRT being 84% and 74% vs 76% and 66%, respectively (P=0.002). In contrast, IC + CCRT had OS and DFS benefits for stage IVa-b, with 5-year and 10-year OS for CCRT vs IC+CCRT being 71% and 55% vs 76% and 60%, respectively (P=0.037, HR=0.786); 5-year and 10-year DFS for CCRT vs IC+CCRT were 64% and 50% vs 69% and 58%, respectively (P=0.038, HR=0.801). No difference was found in intensity-modulated radiotherapy (IMRT) subgroup.

Conclusion: Our study indicates that CCRT and IC+CCRT may have similar OS and DFS benefits for overall LRANPC. Stage-specific chemoradiotherapy may be administered based on the greatest benefit of IC+CCRT for stage IVa-b patients and CCRT alone for stage III patients received 2DRT. The optimal chemotherapy pattern in combination with IMRT needs further investigation.

Trial registration: ClinicalTrials.gov ID: NCT02604472

Keywords: nasopharyngeal carcinoma, concurrent chemotherapy, radiation therapy, induction chemotherapy, prognosis, stage specific

Introduction

Nasopharyngeal carcinoma (NPC) is a specific head and neck cancer associated with the Epstein-Barr virus (EBV) that has a high incidence in Southern China, Southern Asia, the Middle East, North Africa, Alaska and Greenland; it has an aggressive

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natural locoregionally history and high frequency of distant metastasis.[1–4] With sensitivity to radiotherapy and chemotherapy, concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy (AC) can equally improve survival of locoregionally advanced NPC (LRANPC), and this has become the regimen recommended by the National Comprehensive Cancer Network guidelines (category 2A) for LRANPC.[5–7] However, the low compliance of AC because of the high toxicity and the uncertainty of survival benefit result in the recommendation of additional AC to CCRT being revised from category 1 to category 2A.[8]

Induction chemotherapy (IC) is another strategy to improve the efficacy of chemotherapy but is still controversial for use in NPC (category 3) despite facilitating organ preservation, improve locoregional control and may decrease distant metastasis.[9,10] The controversy associated with adding IC to CCRT is attributed to its unclear advantage in terms of overall survival (OS) without confirmation by large-scale randomized clinical trials (RCTs).[11–13] We suspect that appropriate patient selection in overall LRANPC, instead of ubiquitous application, is critical to balance the benefits and disadvantages of adding IC to CCRT.[14] Sun Yat-Sen University Cancer Center (SYSUCC) is located in a NPC endemic area in Southern China; also, CCRT and IC + CCRT have been used in this center for over 2 decades, which gives the opportunity to conduct a population-based study comparing CCRT with IC +CCRT for LRANPC in a real-world setting.

The aim of this study was to investigate whether the additional IC to CCRT improved OS and disease-free survival (DFS) and to find out whether stage-specific chemoradiotherapy regimens might be beneficial for LRANPC.

Materials and methods

Patient selection

The clinical data for all patients who were newly diagnosed with NPC in the SYSUCC between January 1, 1998 to June 1, 2013 were retrieved from the Department of Medical Information, SYSUCC. Additional information including demographics, pathological diagnosis and date, image diagnosis, TNM stage, family history, smoking history, Karnofsky Performance Status (KPS), chemotherapy pattern and drugs, radiation technology and dosage, and follow-up was collected through electronic and paper medical records. Patients were excluded if they had stage I-II disease, distant metastasis disease, missing medical data, not finish radiotherapy, died during radiotherapy period, not received CCRT, received adjuvant chemotherapy. Written informed consent for the use of clinical data and collected samples for future studies (including retrospective studies) was obtained when the patients were admitted to receive treatment as a general standard procedure for patients treated in our center. This study was approved by the Institutional Review Boards of SYSUCC (ClinicalTrials.gov ID: NCT02604472).

Outcome variables

The primary outcome measured was OS and DFS. OS was defined as the time period between the date of pathological diagnosis and the date of death from any cause. DFS was defined as the time period from the date of pathological diagnosis to treatment failure. Treatment failure was defined as the development of either distant metastasis, local-regional relapse, combined distant metastasis and local relapse, death due to treatment sequelae or unspecified treatment failure, whichever occurred first. All of the data, including the diagnosis of metastasis and/or local-regional relapse, were audited by the first three co-authors and the last author. In addition, any discrepancy between the paper medical records and electronic data was reviewed. Date of last follow-up was defined as the latest image study and/or clinic visiting and/or telephone follow-up. The last follow-up data were updated in October 1, 2015.

Study covariates

According to the clinical characteristics, the study population was divided into the following cohorts, including age cohorts: <45, 45–65 and >65 years at diagnosis; KPS cohorts: ≤70, 70–80 and ≥90; smoking cohorts: no or yes; family history cohorts: no cancer family history, NPC family history or cancer other than NPC family history; radiation technology cohorts: 2DRT and Iintensity-modulated radiotherapy (IMRT) and CCRT drugs cohorts: platinum-based and non-platinum based. The clinical stage was re-categorized according to the American Joint Committee on Cancer classification system 7th edition by XY, XW and LH. The pathologic diagnosis was re-evaluated according to WHO histology type by LY, YY and YJ. Because of the lack of EBV-DNA copy number data before 2008, EBV-DNA copy number was not used to classify risk levels.

Statistical methods

Continuous data were presented as medians with IQR. To compare the differences in the proportions of baseline

characteristics of categorical variables, Pearson χ^2 tests were used. The cumulative survival and survival curves were computed with life table, Kaplan–Meier analysis, log-rank tests and univariable Cox proportional hazards regression models. A multivariate Cox regression method (ENTER-method) was used to adjust for covariates including the basic clinical characteristics such as gender, age and TNM stage.

We estimated the effect of treatment on survival using the following two approaches: matching and weighting by inverse probability of treatment (IPTW). Propensity scores reflect the conditional probability that is intended to be uniform between patients receiving CCRT and IC+CCRT based on their baseline characteristics. The propensity score-matching (PSM) method was adopted to balance observed covariates between groups. Matching was performed based on nearest-neighbor matching, and each patient who received IC+CCRT with one who received CCRT using the logit of the propensity score, using calipers of width equal to 0.2 standard deviations of the logit of the estimated propensity score. The main limitation of PSM is that it limits the analysis to matched pairs only, thus reducing power. IPTW is another frequently used strategy which does not carry this limitation. For IPTW, each observation was weighted based on the propensity score by the inverse probability of receiving the treatment the patients received. A Cox proportional hazards model was then fitted with treatment regimen as the only predictor variable. Descriptive analysis, univariate analysis, multivariate analysis, PSM and IPTW were performed using SPSS 20.0 (IBM, Armonk, NY, USA). Statistical significance was set at 0.05, and all tests were two-tailed.

Results

Study population and baseline characteristics at diagnosis

Among the 11,618 cases, distant metastasis patients at first diagnosis (n=1,229), those who did not complete radiotherapy (n=132), those with missing medical data (n=556), and those who died during the RT period (n=6) were excluded. In total, 9,695 patients remained for further evaluation. According to their clinical stages, patients with stage I or II were excluded (18.5%, n=1,791). After the exclusion, a total of 7,904 patients with stage III or IVa-b remained. Among them, 2,281 were treated with IC and radiotherapy, 2,092 were treated with CCRT, 117 were treated with CCRT+AC, 1,888 received IC+CCRT, 99 received IC+CCRT+AC, 41 received IC+RT+AC, 13 received RT+AC, and the other 1,373 cases were treated with RT alone. In total, 3,980 patients (2,092 in CCRT and 1,888 in IC+CCRT) were eligible for this study (Figure 1). The baseline characteristics are shown in Table 1. The median follow-up was 67 months (IQR 42–96 months) for the overall cohort. Because of the chronological conduction of 2DRT and IMRT, the medians of follow-up in 2DRT cohort and IMRT cohort were 77 months (IQR 49–104 months) and 58 months (IQR 37–80 months), respectively. OS and DFS analysis were based on 858 (21.6%) deaths and 1,060 (26.6%) treatment failures out of 3,980 patients, respectively. Up to October 1, 2015, 3,443 (86.5%) patients received follow-up or confirmed death.

Survival outcome

The results showed that CCRT and IC+CCRT had a similar benefit for OS (P=0.099, HR =1.119, 95%CI 0.979–1.280), whereas there was a marginal benefit of CCRT with regard to DFS (P=0.063, HR =1.121, 95%CI 0.994–1.265) in the overall cohort. Three-year, 5-year, and 10-year OS for CCRT vs IC+CCRT were 91%, 84%, and 70% vs 89%, 82%, and 68%, respectively. Three-year, 5-year, and 10-year DFS for CCRT vs IC +CCRT were 85%, 78%, and 67% vs 81%, 75%, and 65%, respectively (Figure S1). After adjusting for age, gender, T stage, N stage, and clinical stage, the results showed that CCRT with or without IC had similar benefits for OS as well as DFS.

Propensity score

We defined the logic of the predicted probability of treatment as a propensity score using the following baseline characteristics: age, gender, WHO histological type, T stage, N stage, clinical stage, KPS, smoking history, family history, radiation technology, and CCRT drugs. In total, 1,722 pairs of patients were matched between CCRT and IC+CCRT groups at a 1:1 ratio with a caliper definition=0.1. The results showed that 3-year, 5-year and 10-year OS for CCRT vs IC+CCRT were 91%, 84%, and 70% vs 90%, 82%, and 69%, respectively (p=0.474, HR=1.057, 95%CI 0.908–1.230); 3-year, 5-year, and 10-year DFS for CCRT vs IC+CCRT were 84%, 78%, and 66% vs 82%, 76%, and 67%, respectively (p=0.377, HR=1.063, 95% CI 0.928–1.219) (Figure 2A and B). Both results were consistent with the results observed in the overall cohort (Table S1). Subsequently, a Cox

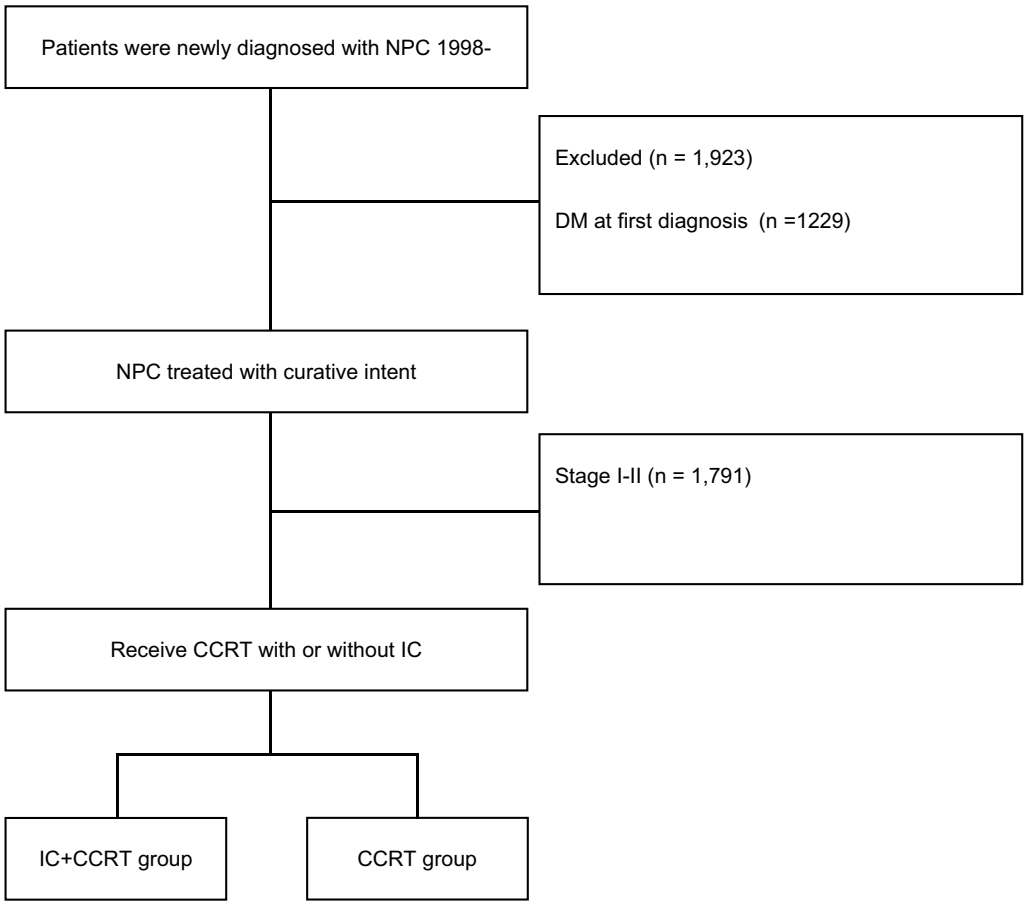

Figure 1 Flowchart of patients selection.
Abbreviations: NPC, nasopharyngeal carcinoma; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

proportional hazards model weighted on the inverse propensity for being treated with CCRT was fitted. This analysis also showed no survival advantage for CCRT (p=0.402, HR=1.060, 95% CI 0.925–1.215).

Stage-specific survival outcome in matched cohort

Stratifying the overall patients by clinical stage, no differences were found regarding OS or DFS (Figure S2). Based on the significant impact of radiation technology on the prognosis of NPC, we did a subset analysis regarding the different stages and radiation technologies. Intriguingly, for 2DRT patients, CCRT favored OS and DFS for stage III and IC+CCRT favored OS and DFS for stage IVa-b patients, which were similar both before and after adjusting for age, gender, T stage, and N stage; however, no significant difference was found for IMRT patients (Table S2).

For further confirmation, we stratified the subsets patients with different stages and radiation technologies in the PSM cohort. In 3,156 patients, 1,910 were stage III and 1,246 were stage IVa-b. Similarly, for patients used 2DRT, CCRT had OS and DFS benefits for stage III, which showed that 3-year, 5-year and 10-year OS for CCRT vs IC+CCRT were 94%, 88%, and 75% vs 88%, 81%, and 67%, respectively (p=0.002, HR=1.518, 95% CI 1.171–1.968); 3-year, 5-year, and 10-year DFS for CCRT vs IC+CCRT were 89%, 84%, and 74% vs 81%, 76%, and 66%, respectively (p=0.002, HR=1.465, 95% CI 1.146–1.871) (Figure 3A and B). In contrast, IC+CCRT had OS and DFS benefits for stage IVa-b, and the results showed that 3-year, 5-year and 10-year OS for CCRT vs IC+CCRT were 83%, 71%, and 55% vs 87%, 76%, and 60%, respectively (P=0.037, HR=0.786, 95% CI 0.628–0.985); 3-year, 5-year, and 10-year DFS for CCRT vs IC+CCRT were 73%, 64%, and 50% vs 79%, 69%, and 58%, respectively (p=0.038, HR=0.801, 95% CI 0.649–0.988)

Table 1 Clinical characteristics of 3,980 locoregionally advanced NPC patients undergoing CCRT with or without IC

Clinical characteristics		Total n=3,980	Overall cohort		SD*	*P*-value	PSM cohort		SD*	*P*-value
			CCRT n=2,092	IC + CCRT n=1,888			CCRT n=1,578	IC + CCRT n=1,578		
Sex	Male	29,71	1,541	1,430	0.039	0.132	1176	1176	0	1.000
	Female	1,009	551	458	0.046		402	402	0	
Ages(years)	<45	2,011	1,012	999	0.082	0.004	800	839	0.044	0.376
	45–65	1,814	985	829	0.059		730	692	0.045	
	>65	155	95	60	0.071		48	47	0.003	
WHO	I	7	3	4	0.016	0.849	3	4	0.013	0.716
	II	203	105	98	0.008		78	87	0.025	
	III	3,770	1,984	1,786	0.007		1497	1487	0.017	
T stage	T1	129	76	53	0.047	<0.001	50	48	0.007	0.584
	T2	451	232	219	0.016		186	162	0.047	
	T3	2,145	1222	933	0.165		837	854	0.019	
	T4	1,245	562	683	0.189		505	514	0.012	
N stage	N0	544	341	203	0.161	<0.001	189	193	0.008	0.965
	N1	1,380	812	568	0.177		531	537	0.008	
	N2	1,627	802	825	0.101		728	714	0.016	
	N3	429	137	292	0.280		130	134	0.009	
Clinical stage	III	2,402	1,416	986	0.287	<0.001	961	949	0.014	0.662
	Iva + b	1,578	676	902	0.291		617	629	0.015	
KPS	≤70	5	2	3	0.018	0.774	1	3	0.035	0.471
	70–80	72	36	36	0.014		23	28	0.025	
	≥90	3,903	2,054	1,849	0.009		1554	1,547	0.016	
Smoking	No	2,276	1,191	1,085	0.010	0.732	901	913	0.013	0.666
	Yes	1,704	901	803	0.010		677	665	0.014	
Family history	NO	3,077	1,594	1,483	0.045	0.207	1213	1,238	0.030	0.453
	NPC	437	242	195	0.039		168	165	0.006	
	Non-NPC	466	256	210	0.034		197	175	0.042	
Radiation Technology	2DRT	2,322	1,296	1,026	0.139	<0.001	916	884	0.036	0.250
	IMRT	1,658	796	862	0.142		662	694	0.037	
CCRT drug	Platinum	3,631	1,914	1,717	0.013	0.541	1,454	1,452	0.003	0.895
	Non-platinum	349	178	171	0.019		124	126	0.004	

(*Continued*)

Table 1 (Continued).

Clinical characteristics		Total n=3,980	Overall cohort		SD*	*P*-value	PSM cohort		SD*	*P*-value
			CCRT n=2,092	IC + CCRT n=1,888			CCRT n=1,578	IC + CCRT n=1,578		
Treatment	No	2,920	1,543	1,377	0.015	0.558	1,166	1,164	0.002	0.935
Failure	Yes	1,060	549	511	0.018		412	414	0.003	
Death	No	3,122	1,644	1,478	0.006	0.818	1,243	1,246	0.003	0.896
	Yes	858	448	410	0.007		335	332	0.005	

Note: * SD=(P1-P2)/square root of (P1[1-P1]+P2[1-P2]/2).
Abbreviations: NPC, nasopharyngeal carcinoma; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; KPS, Karnofsky performance status; SD, standardized difference.

(Figure 3C and D). Unsurprisingly, there were no significant differences for the stage-specific IMRT subgroups (Table 2 and Figure S3).

Discussion

This is the first study demonstrating that CCRT with or without IC is equally effective in the treatment of overall LRANPC and for those treated with IMRT in a large population-based cohort. Furthermore, selective application of IC+CCRT for stage IVa-b patients treated with 2DRT may produce the greater benefit with regard to OS and DFS. Meanwhile, CCRT alone may be optimal for stage III patients treated with 2DRT.

The strength of this study is its size, which allowed for subgroup and subset analyses to be performed. The major limitations of this study included its retrospective nature and its single academic center setting. Additionally, the analysis of relapse-free survival, distant-metastasis-free survival, and long-term toxicities was restricted due to the quality of the follow-up data.

The optimal combination of chemotherapy and radiotherapy in LRANPC has been controversial for the past two decades. With the strict control of clinical trials, CCRT has been confirmed by multiple clinical trials to benefit OS, with similar results both in endemic and non-endemic regions and most of the RCTs used 2DRT.[5,6] CCRT with AC has been deemed the standard of care for advanced NPC since 1998 and was initially confirmed by the landmark clinical trial of the INT-0099 study, which showed a 31% increase in 3-year OS.[5] Thereafter, more randomized-control Phase III clinical trials were conducted in NPC endemic regions. Some of them presented similar results, whereas others showed no or only marginal benefit.[6,15–17] The latest meta-analysis, including 19 trials and 4,806 patients, proved that CCRT with or without AC can similarly improve the survival of patients with LRANPC, for whom 5-year OS improved from 65.1% to 70.4%.[18] However, given the poor compliance with AC after CCRT, with only half to three-quarters of the patients finishing the planned chemotherapy cycles, the benefit of adding AC to CCRT remained uncertain.[6,8,15–17] Additionally, Phase III RCTs comparing RT and AC with RT alone did not show a positive effect on the OS of patients with advanced NPC.[19] Therefore, CCRT is still the most popular chemotherapy approach for LRANPC. IC is more tolerable than AC. However, IC application remains controversial. RCTs of ICRT have resulted in favorable relapse-free survival and improvement in DFS,

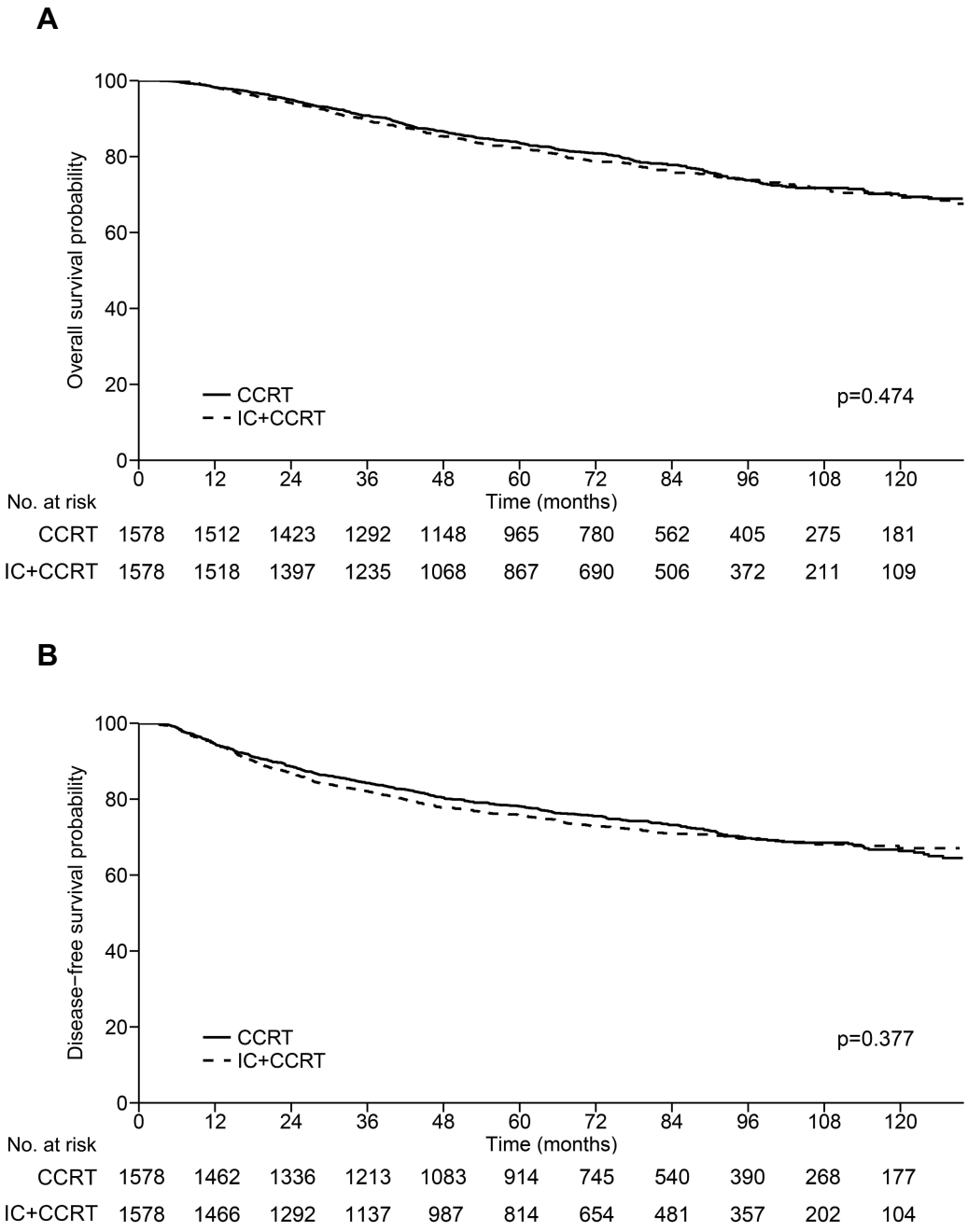

Figure 2 Kaplan–Meier overall and disease-free survival curves in matched pairs after propensity scoring. (**A**) overall survival curves and (**B**) disease-free survival curves for all matched patients.

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

but not OS, compared with RT alone.[20,21] A meta-analysis showed an enhancement of OS and distant metastasis rate compared with RT alone.[22] The combination of IC and CCRT is a reasonable chemotherapy approach for improving the prognosis of LRANPC. So far, there have been two reported clinical trials with different results comparing IC +CCRT with CCRT. One reported an improvement in OS following IC+CCRT treatment;[11] the other failed to observe any significant improvement in survival.[12] Recently, a meta-analysis reported that no significant improvement in OS was found for IC+CCRT vs CCRT, although improvement in the distant metastasis rate was observed following IC+CCRT.[13] However, with the small sample size of 206 cases, the benefit of IC+CCRT with regard to OS is still uncertain. The combination of IC and CCRT has been used for many years in clinical practice at

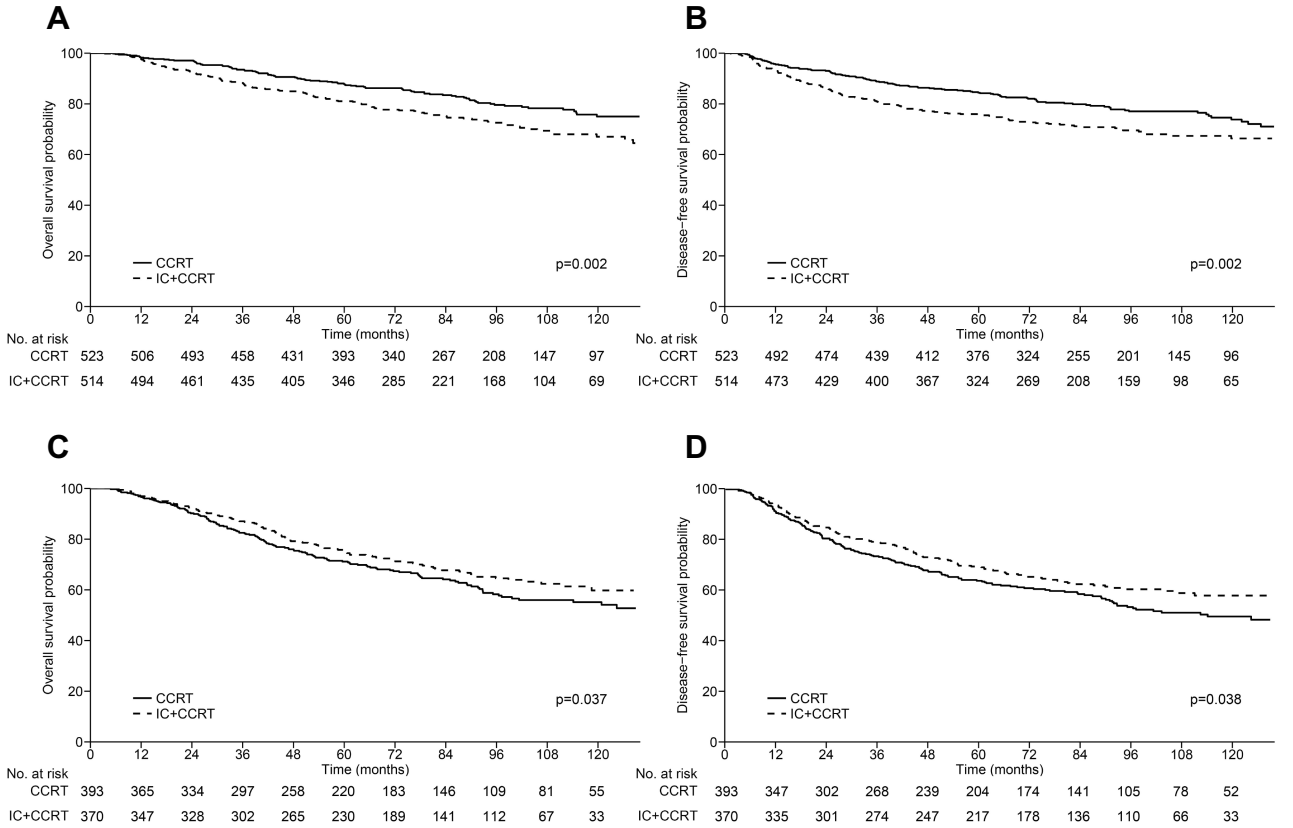

Figure 3 Stage-specific survival curves for locoregionally advanced nasopharyngeal carcinoma patients in matched pairs who received 2DRT and concurrent chemoradiotherapy with or without induction chemoradiotherapy. (**A**) Overall survival curves; (**B**) disease-free survival curves of stage III patients who received 2DRT; (**C**) overall survival curves; and (D) disease-free survival curves of stage IVa-b who received 2DRT.
Abbreviations: CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; 2DRT, 2 dimension radiotherapy.

SYSUCC; of all cases of LRANPC treated with chemoradiotherapy, 30% (1,987/6,561) received IC+CCRT. In the overall cohort, both CCRT and IC+CCRT have similar survival benefits for LRANPC, but it should be emphasized that CCRT and IC+CCRT have stage-specific benefits for LRANPC patients, respectively. We found that adding IC to CCRT had significant survival benefit for stage IVa-b patients; in contrast, CCRT was still optimal for stage III patients. Based on the inverse results for stage III and IVa-b patients, it is reasonable to conclude that the previous meta-analysis could not detect the difference between CCRT and IC+CCRT outcomes in patients at these stages. We suspect that for stage IVa-b with bulky primary tumors and/or extensive lymph node involvement, additional IC can not only early eradicate micrometastases but also improve locoregional control.[21] Additionally, shrinking the primary tumor to give a wider safe margin for the organs at risk is particularly needed for extensive local disease.[9,10,23] However, the addition of IC to CCRT for stage III patients treated with 2DRT produces worse outcomes than CCRT alone. Since stage III patients have a relatively small tumor burden and better survival than stage IVa-b, CCRT alone may be sufficient to achieve good survival. We suspect that the delay of the subsequent CCRT by IC in these patients and the toxicity of IC might consequently accelerate the proliferation of tumor cells and eventually result in worse survival outcomes rather than a benefit,[24] which has always been a concern of oncologists.

Radiotherapy is the standard treatment for NPC. Due to the anatomical location of NPC adjacent to the base of the skull, 2DRT cannot be effectively conducted at the sites that are in close proximity to radiation dose-limiting organs, such as the brain stem and spinal cord. For this reason, a regular fraction is usually conducted. With the advent of IMRT, radiation beams and treatment intensity can be modulated so that a high dose can be efficiently delivered to the tumor while limiting the dose to the surrounding normal tissue.[25–27] Except for the conformal distribution of radiation, simultaneous modulated

Table 2 Hazard ratios of risk of death and treatment failure for stage-specified locoregionally advanced NPC associated with CCRT and IC + CCRT after PSM

Radiation technology	Stage (n)	CCRT vs IC + CCRT				CCRT vs IC + CCRT			
		Death (n, %)	5 yr Overall survival	HR (95% CI)	*P*-value	Treatment failure (n, %)	5 yr Disease -free survival	HR (95% CI)	*P*-value
Overall	Stage III (1910)	312 (16%)	89% vs 86%	1.225 (0.985–1.522)	0.068	396 (21%)	84% vs 79%	1.192 (0.985–1.442)	0.072
	Stage IV (1246)	355 (29%)	75% vs 77%	0.863 (0.701–1.064)	0.168	430 (35%)	68% vs 70%	0.880 (0.728–1.064)	0.186
2DRT	Stage III (523 vs 514)	99 vs 135 (19% vs 26%)	88% vs 81%	1.518 (1.171–1.968)	0.002	113 vs 148 (22% vs 29%)	84% vs 76%	1.465 (1.146–1.871)	0.002
	Stage IV (393vs 370)	142 vs 116 (36% vs 31%)	71% vs 75%	0.786 (0.628–0.985)	0.037	169 vs 136 (44% vs 37%)	64% vs 69%	0.801 (0.649–0.988)	0.038
IMRT	Stage III (438 vs 435)	46 vs 32 (10% vs 7%)	91% vs 92%	0.763 (0.486–1.198)	0.240	72 vs 63 (16% vs 14%)	84% vs 84%	0.944 (0.673–1.323)	0.736
	Stage IV (224 vs 259)	48 vs 49 (21% vs 19%)	82% vs 80%	1.008 (0.677–1.502)	0.968	58 vs 67 (26% vs 26%)	77% vs 73%	1.067 (0.751–1.518)	0.716

Abbreviations: NPC, nasopharyngeal carcinoma; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; 2DRT, 2 dimension radiotherapy; IMRT, intensity modulated radiotherapy.

accelerated radiation therapy is usually used in NPC treatment, in which different doses are simultaneously delivered to different target lesions in an overall shorter treatment time.[28,29] As a result, the 5-year OS of CCRT in LRANPC with IMRT was over 80%, and the local-regional control rate was over 90%. Additionally, the development of distant metastases also significantly decreased subsequently.[30–32] Furthermore, a study reported that IMRT alone achieved a 5-year OS as high as 83.2%, which is similar to that for CCRT.[33] In this study, we found no differences between CCRT and IC+CCRT in patients receiving IMRT, regardless of stages. We speculate that on one hand the survival benefit of chemotherapy was limited by the upgrading of radiation technology, on the other hand, relatively shorter follow-up time and smaller sample size in IMRT subgroup than 2DRT subgroup may be insufficient to conclude. New regimens with higher potency that can decrease distant metastasis may result in better survival in NPC received IMRT, which is expected in future RCTs.

In conclusion, this large population-based analysis first demonstrates the similar benefit of CCRT with or without IC in the overall cohort and the IMRT cohort for LRANPC. For 2DRT, stage-specific chemoradiotherapy may be administered based on the greater benefit of adding IC to CCRT for stage IVa-b patients and of CCRT alone for stage III patients.

Data Sharing Statement

The key clinical data set that support the findings of this study are available from Research Data Deposit (RDD) of Sun Yat-Sen University Cancer Center (www.researchdata.org.cn), with the approval RDD number as RDDA2018000880. Data are, however, available from the corresponding author upon reasonable request and with the permission of Sun Yat-Sen University Cancer Center.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Bailet JW, Mark RJ, Abemayor E, et al. Nasopharyngeal carcinoma: treatment results with primary radiation therapy. *Laryngoscope*. 1992;102(9):965–972. doi:10.1288/00005537-199209000-00002
2. Lee AW, Lin JC, Ng WT Current management of nasopharyngeal cancer. Paper presented at: Seminars in radiation oncology 2012. doi:10.1094/PDIS-11-11-0999-PDN
3. Wei KR, Zheng RS, Zhang SW, Liang ZH, Ou ZX, Chen WQ. Nasopharyngeal carcinoma incidence and mortality in China in 2010. *Chin J Cancer*. 2014;33(8):381–387. doi:10.5732/cjc.014.10086
4. Zhang LF, Li YH, Xie SH, et al. Incidence trend of nasopharyngeal carcinoma from 1987 to 2011 in Sihui County, Guangdong Province, South China: an age-period-cohort analysis. *Chin J Cancer*. 2015;34(6):15. doi:10.1186/s40880-015-0018-6
5. Al-Sarraf M, LeBlanc M, Giri P, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. *J Clin Oncol*. 1998;16(4):1310–1317. doi:10.1200/JCO.1998.16.4.1310
6. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on cancer/international union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol*. 2005;23(27):6730–6738. doi:10.1200/JCO.2005.16.790
7. Chan ATC, Leung SF, Ngan RKC, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*. 2005;97(7):536–539. doi:10.1093/jnci/dji084
8. Chen L, Hu C-S, Chen X-Z, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. 2012;13(2):163–171. doi:10.1016/S1470-2045(11)70320-5
9. Bae WK, Hwang JE, Shim HJ, et al. Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer. *Cancer Chemother Pharmacol*. 2010;65(3):589–595. doi:10.1007/s00280-009-1152-0
10. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357(17):1705–1715. doi:10.1056/NEJMoa070956
11. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2009;27(2):242–249. doi:10.1200/JCO.2008.18.1545
12. Fountzilas G, Ciuleanu E, Bobos M, et al. Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Ann Oncol*. 2012;23(2):427–U409. doi:10.1093/annonc/mdr116
13. Chen Y-P, Guo R, Liu N, et al. Efficacy of the additional neoadjuvant chemotherapy to concurrent chemoradiotherapy for patients with locoregionally advanced nasopharyngeal carcinoma: a Bayesian network meta-analysis of randomized controlled trials. *J Cancer*. 2015;6(9):883. doi:10.7150/jca.11814
14. Ko EC, Genden EM, Misiukiewicz K, et al. Toxicity profile and clinical outcomes in locally advanced head and neck cancer patients treated with induction chemotherapy prior to concurrent chemoradiation. *Oncol Rep*. 2012;27(2):467–474. doi:10.3892/or.2011.1512
15. Lee AWM, Ngan RKC, Tung SY, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer*. 2015;121(8):1328–1338. doi:10.1002/cncr.29208
16. Lee AWM, Tung SY, Chan ATC, et al. A randomized trial on addition of concurrent-adjuvant chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. *Radiother Oncol*. 2011;98(1):15–22. doi:10.1016/j.radonc.2010.09.023
17. Lee AWM, Tung SY, Ngan RKC, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 trials. *Eur J Cancer*. 2011;47(5):656–666. doi:10.1016/j.ejca.2010.10.026
18. Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol*. 2015. doi:10.1016/S1470-2045(15)70126-9
19. Rossi A, Molinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol*. 1988;6(9):1401–1410. doi:10.1200/JCO.1988.6.9.1401
20. Ma J, Mai H-Q, Hong M-H, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2001;19(5):1350–1357. doi:10.1200/JCO.2001.19.5.1350
21. Chua DT, Ma J, Sham JS, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. *J Clin Oncol*. 2005;23(6):1118–1124. doi:10.1200/JCO.2005.12.081
22. OuYang P, Xie C, Mao Y, et al. Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials. *Ann Oncol*. 2013;24(8):2136–2146. doi:10.1093/annonc/mdt146
23. Machtay M, Rosenthal DI, Algazy KM, et al. Pilot study of organ preservation multimodality therapy for locally advanced resectable oropharyngeal carcinoma. *Am J Clin Oncol*. 2000;23(5):509–515.
24. Group INCS, Trial VI. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (≥ N2, M0) undifferentiated nasopharyngeal carcinoma: A positive effect on progression-free survival. *Int J Radiat Oncol Biol Phys*. 1996;35(3):463–469.
25. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol*. 2009;27(22):3684–3690. doi:10.1200/JCO.2008.19.9109
26. Zheng Y, Han F, Xiao W, et al. Analysis of late toxicity in nasopharyngeal carcinoma patients treated with intensity modulated radiation therapy. *Radiat Oncol*. 2015;10(1):17. doi:10.1186/s13014-014-0326-z
27. Tao CJ, Liu X, Tang LL, et al. Long-term outcome and late toxicities of simultaneous integrated boost-intensity modulated radiotherapy in pediatric and adolescent nasopharyngeal carcinoma. *Chin J Cancer*. 2013;32(10):525–532. doi:10.5732/cjc.013.10124
28. Xiao WW, Huang SM, Han F, et al. Local control, survival, and late toxicities of locally advanced nasopharyngeal carcinoma treated by simultaneous modulated accelerated radiotherapy combined with cisplatin concurrent chemotherapy. *Cancer*. 2011;117(9):1874–1883. doi:10.1002/cncr.25754

29. Yi J, Huang X, Gao L, et al. Intensity-modulated radiotherapy with simultaneous integrated boost for locoregionally advanced nasopharyngeal carcinoma. *Radiat Oncol*. 2014;9:56. doi:10.1186/1748-717X-9-56
30. Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. *Int J Radiat Oncol Biol Phys*. 2004;60(5):1440–1450. doi:10.1016/j.ijrobp.2004.05.022
31. Saleh-Ebrahimi L, Zwicker F, Muenter MW, et al. Intensity modulated radiotherapy (IMRT) combined with concurrent but not adjuvant chemotherapy in primary nasopharyngeal cancer–a retrospective single center analysis. *Radiat Oncol*. 2013;8:20. doi:10.1186/1748-717X-8-20
32. Tang -L-L, Chen L, Mao Y-P, et al. Comparison of the treatment outcomes of intensity-modulated radiotherapy and two-dimensional conventional radiotherapy in nasopharyngeal carcinoma patients with parapharyngeal space extension. *Radiother Oncol*. 2015;116(2):167–173. doi:10.1016/j.radonc.2015.07.038
33. Cao C-N, Luo J-W, Gao L, et al. Concurrent chemotherapy for T4 classification nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy. *PLoS One*. 2015;10(3):e0119101.

Supplementary materials

Table S1 Hazard ratios of risk of death and treatment failure for locoregionally advanced NPC associated with CCRT and IC+CCRT

Characteristics	CCRT vs IC + CCRT			
	Overall survival		Disease-free survival	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
Overall cohort				
Unadjusted model	0.099	1.119 (0.979–1.280)	0.063	1.121 (0.994–1.265)
Model adjusted for age, gender and stage	0.534	1.044 (0.911–1.197)	0.552	1.038 (0.918–1.174)
Propensity-matching cohort				
Unadjusted model*	0.474	1.057 (0.908–1.230)	0.377	1.063 (0.928–1.219)
Inverse probability weighting	0.402	1.060 (0.925–1.215)	0.481	1.056 (0.907–1.229)

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

Table S2 Hazard ratios of risk of death and treatment failure for stage-specific locoregionally advanced NPC associated with CCRT and IC+CCRT

Radiation technology	Characteristics	CCRT vs IC + CCRT			
		Overall survival		Disease-free survival	
		P-value	HR (95% CI)	*P*-value	HR (95% CI)
Overall	Unadjusted model				
	Stage III	0.109	1.177 (0.964–1.438)	0.092	1.164 (0.976–1.388)
	Stage IVa-b	0.121	0.865 (0.720–1.039)	0.178	0.891 (0.754–1.054)
2DRT	Unadjusted model				
	Stage III	0.003	1.416 (1.129–1.777)	0.010	1.325 (1.071–1.640)
	Stage IVa-b	0.106	0.838 (0.676–1.038)	0.088	0.841 (0.689–1.026)
	Model adjusted for age, gender, T stage and N stage				
	Stage III	0.009	1.358 (1.080–1.707)	0.027	1.276 (1.028–1.583)
	Stage IVa-b	0.035	0.792 (0.637–0.984)	0.038	0.807 (0.659–0.988)
IMRT	Unadjusted model				
	Stage III	0.185	0.749 (0.489–1.148)	0.711	0.943 (0.690–1.288)
	Stage IVa-b	0.991	1.002 (0.701–1.433)	0.659	1.074 (0.781–1.478)
	Model adjusted for age, gender, T stage and N stage				
	Stage III	0.094	0.691 (0.448–1.065)	0.342	0.858 (0.625–1.177)
	Stage IVa-b	0.553	0.893 (0.613–1.299)	0.620	0.919 (0.659–1.283)

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

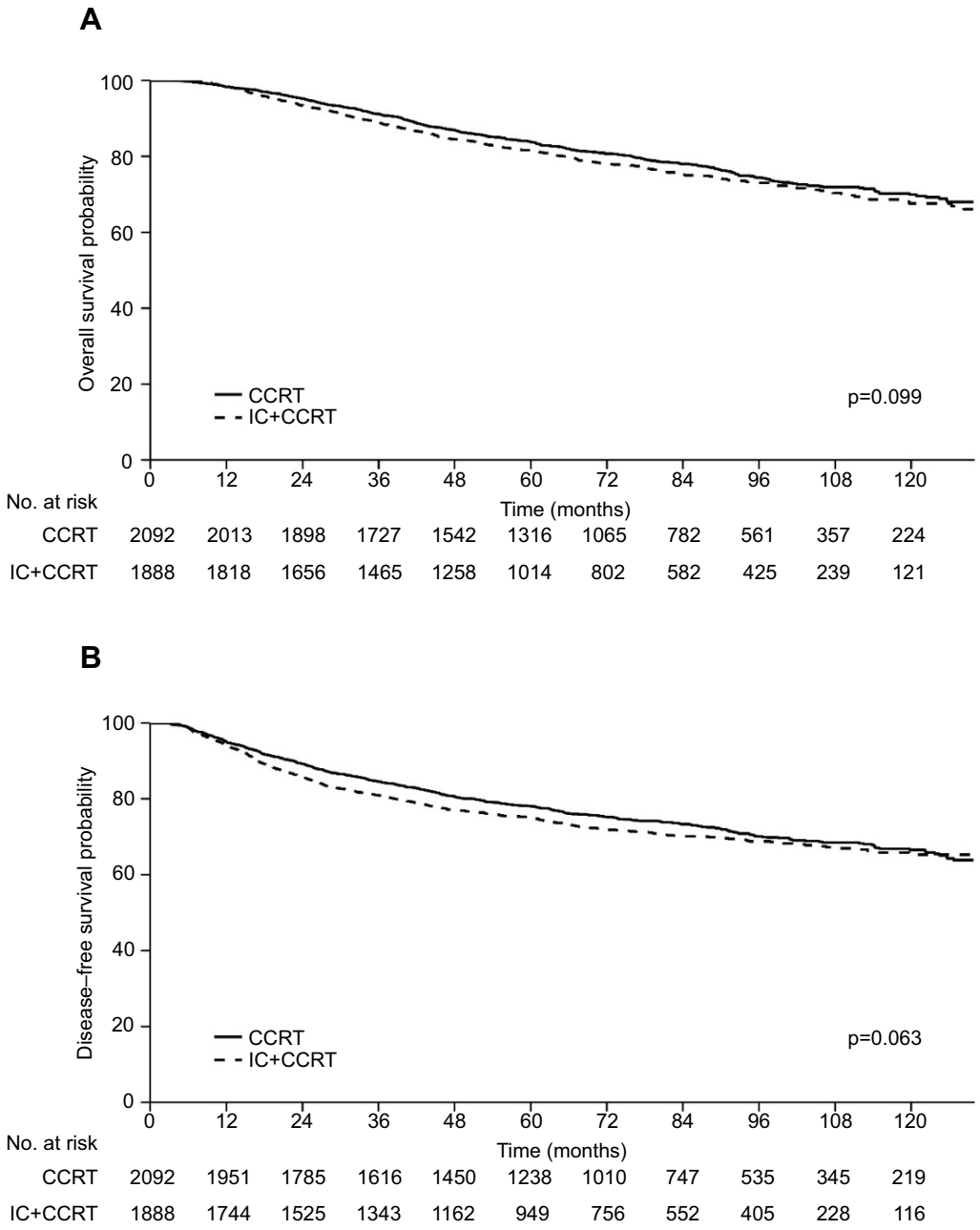

Figure S1 Survival curves for locoregionally advanced nasopharyngeal carcinoma patients received concurrent chemoradiotherapy with or without induction chemoradiotherapy before the propensity score matching. (**A**) Overall survival curves, (**B**) disease-free survival curves.
Abbreviations: NPC, nasophar7yngeal carcinoma; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

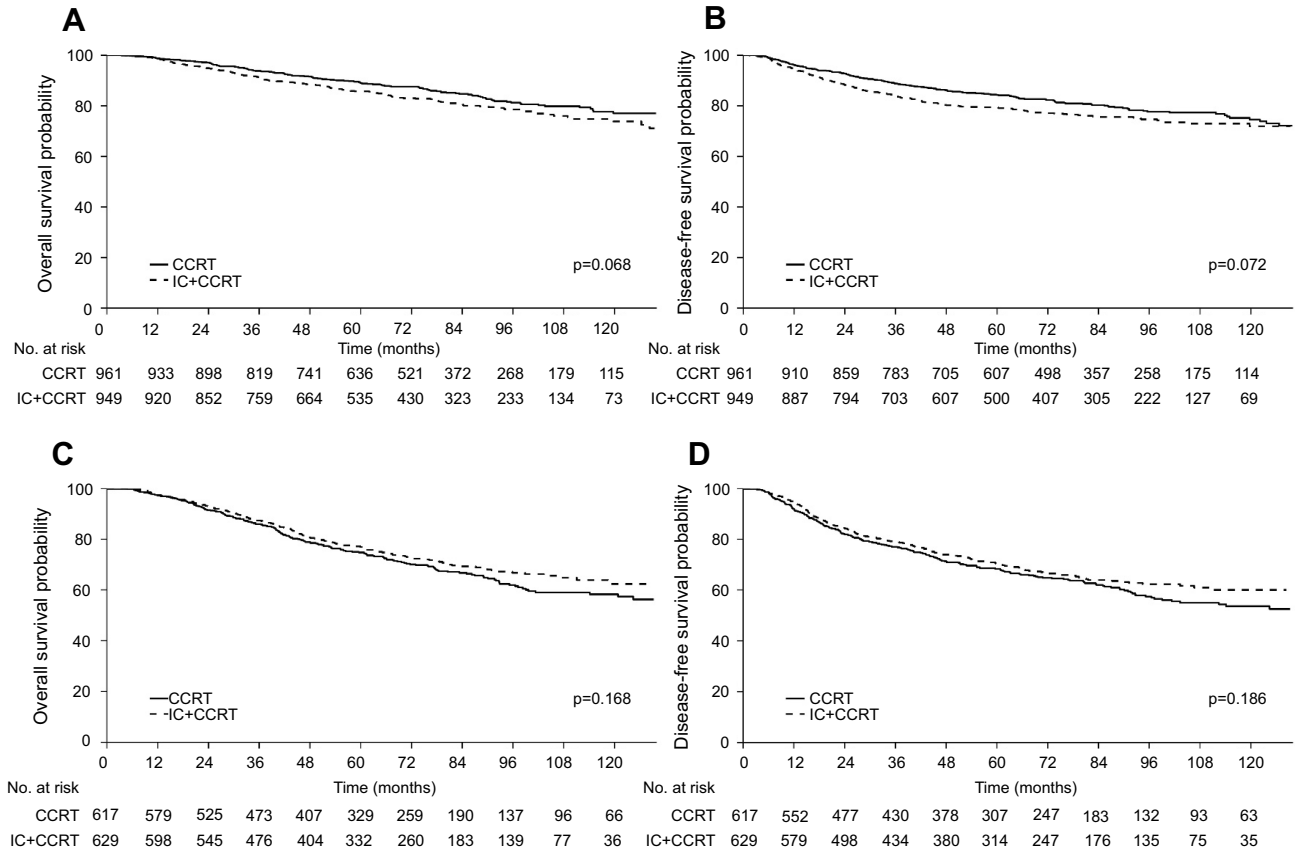

Figure S2 Stage-specific survival curves for locoregionally advanced nasopharyngeal carcinoma patients after the propensity score matching. (**A**) Overall survival curves and (**B**) disease-free survival curves of stage III; (**C**) overall survival curves and (**D**) disease-free survival curves of stage IVa-b.
Abbreviations: NPC, nasopharyngeal carcinoma; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

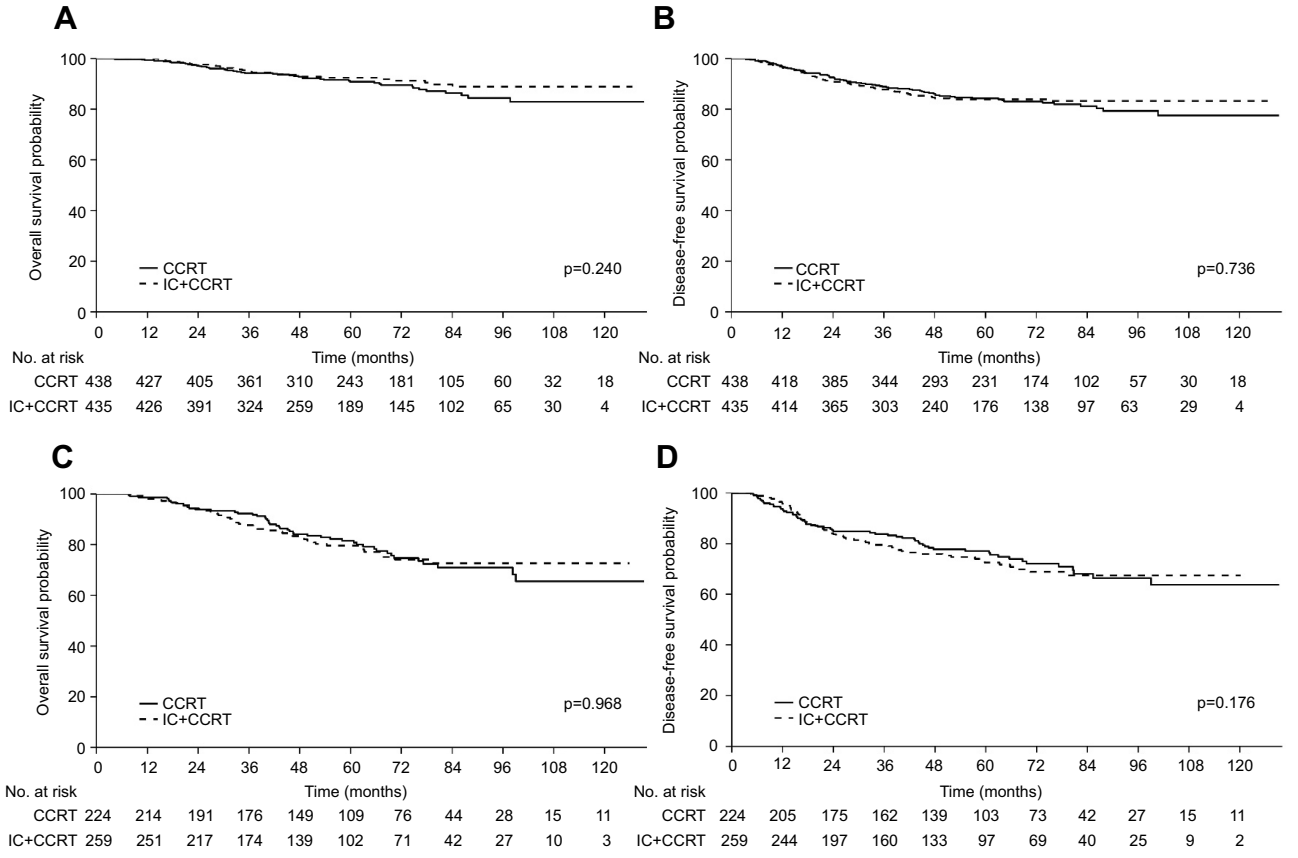

Figure S3 Stage-specific survival curves for locoregionally advanced nasopharyngeal carcinoma patients in matched pairs who received IMRT and concurrent chemoradiotherapy with or without induction chemoradiotherapy. (**A**) Overall survival curves; (**B**) disease-free survival curves of stage III patients who received IMRT; (**C**) overall survival curves; and (**D**) disease-free survival curves of stage IVa-b who received IMRT.

Abbreviations: CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; 2DRT, 2 dimension radiotherapy; IMRT, intensity modulated radiotherapy.