Neoadjuvant or Adjuvant Chemotherapy Plus Concurrent CRT Versus Concurrent CRT Alone in the Treatment of Nasopharyngeal Carcinoma: A Study Based on EBV DNA

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ABSTRACT

Background: The goal of this study was to explore the value of adding neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy (ACT) to concurrent chemoradiotherapy (CCRT) in patients with nasopharyngeal carcinoma (NPC) with different risks of treatment failure. **Patients and Methods:** A total of 2,263 eligible patients with stage III–IVb NPC treated with CCRT ± NACT or ACT were included in this retrospective study. Distant metastasis-free survival (DMFS), overall survival, and progression-free survival were calculated using the Kaplan-Meier method and differences were compared using the log-rank test. **Results:** Patients in the low-risk group (stage N0–1 disease and Epstein-Barr virus [EBV] DNA <4,000 copies/mL) who received NACT followed by CCRT achieved significantly better 5-year DMFS than those treated with CCRT alone (96.2% vs 91.3%; $P = .008$). Multivariate analyses also demonstrated that additional NACT was the only independent prognostic factor for DMFS (hazard ratio, 0.42; 95% CI, 0.22–0.80; $P = .009$). In both the intermediate-risk group (stage N0–1 disease and EBV DNA ≥4,000 copies/mL and stage N2–3 disease and EBV DNA <4,000 copies/mL) and the high-risk group (stage N2–3 disease and EBV DNA ≥4,000 copies/mL), comparison of NACT or ACT + CCRT versus CCRT alone indicated no significantly better survival for all end points. **Conclusions:** The addition of NACT to CCRT could reduce distant failure in patients with low risk of treatment failure.

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Background

Nasopharyngeal carcinoma (NPC), particularly the undifferentiated subtype, is prevalent in South Asia and South China.^{1,2} Radiotherapy (RT) is the mainstay treatment of NPC. With the innovation of modern imaging and radiation techniques, a high cure rate has been achieved for patients with early-stage NPC. However, due to its deep-seated location, 70% to 80% of patients are not diagnosed until the disease is at the advanced stage.³ For advanced-stage disease, RT in combination with concurrent chemotherapy has been shown to be the standard treatment protocol.^{4,5} Despite the use of concurrent chemotherapy, distant metastasis is still a major component of treatment failures, occurring in 18% to 27% of patients.^{5,6} To improve these results, additional systemic therapy has been explored, such as adding neoadjuvant or adjuvant chemotherapy (NACT or ACT, respectively) to concurrent chemoradiotherapy (CCRT).^{7–12} However, due to inconsistent results of several prospective randomized trials, the additional benefit of adding NACT or ACT to CCRT remains controversial.

Currently, therapeutic decisions are based primarily on TNM stage. However, given tumor heterogeneity, patients with similar stages and histologic classifications have markedly different survival outcomes. Infection with Epstein-Barr virus (EBV) is strongly linked to NPC.^{13,14} Previous studies have shown that patients with high levels of pretreatment plasma EBV DNA have higher rates of distant relapse and death.^{15,16} Thus, plasma EBV

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DNA level, as a supplement to disease stage, could help to stratify patients into different groups of risk of treatment failure. Patients in the high-risk group might benefit from the addition of NACT or ACT to CCRT. The ongoing NRG-HN001 study (ClinicalTrials.gov identifier: NCT02135042) is using EBV DNA to risk-stratify patients and determine ACT; no previous studies have used plasma EBV DNA to select eligible treatment participants. The goal of our study was to compare patients in different risk groups who received different chemotherapy treatments to determine the optimal therapeutic strategy for individuals with NPC.

Patients and Methods

From January 2004 to December 2012, we identified 6,996 patients in our institute who were newly diagnosed with NPC. Eligibility criteria included (1) biopsy-proven WHO histopathologic type II or III NPC; (2) age ≥ 18 years; (3) stages III–IVb disease according to the seventh edition of the International Union Against Cancer/AJCC TNM staging system; (4) ECOG performance status of 0 or 1; (5) treatment with intensity-modulated RT; (6) received CCRT $\pm$ NACT or ACT; (7) complete data of pretreatment plasma EBV DNA level; and (8) adequate hematologic, liver, and renal function. Exclusion criteria included history of previous or synchronous malignant tumors,

additional use of targeted therapy or immunotherapy, pregnancy or lactation, primary distant metastasis, and insufficient follow-up data. A total of 2,263 eligible patients were included in the study (Figure 1). This study was approved by Sun Yat-sen University Cancer Center's Clinical Research Committee.

Pretreatment Evaluation

All patients underwent a complete physical examination, fiberoptic nasopharyngoscopy, electrocardiography, MRI of the nasopharynx and neck, chest radiography, abdominal ultrasound, skeletal scintigraphy or whole-body fluorodeoxyglucose PET/CT, CBC count, biochemical profile, and EBV serology with plasma EBV DNA level.

RT and Chemotherapy

All patients were treated with concurrent cisplatin (100 mg/m²) at weeks 1, 4, and 7 of the RT cycle. Among them, 970 patients received CCRT alone, 1,073 received 2 or 3 cycles of NACT followed by CCRT, and 220 received CCRT followed by 1 to 4 cycles of adjuvant PF (cisplatin, 80 mg/m² on day 1 with 5-fluorouracil, 800–1,000 mg/m² for 96 hours of continuous intravenous infusion).¹⁷ The regimen of NACT included PF, TP (cisplatin with docetaxel, 75 mg/m² on day 1), and TPF (cisplatin, 75 mg/m² on day 1 and docetaxel, 75 mg/m² on day 1, with 5-fluorouracil, 750 mg/m² for 96 hours of continuous

Figure 1. Flowchart of patients included in the study.

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; EBV, Epstein-Barr virus; NACT, neoadjuvant chemotherapy; NPC, nasopharyngeal carcinoma.

intravenous infusion).^{7,9,18} The intensity-modulated RT plan was designed according to previous studies, and treatment followed the general design at our institute (supplemental eAppendix 1, available with this article at JNCCN.org).^{19,20}

Plasma EBV DNA–Level Assessment

Plasma EBV DNA concentrations were measured with real-time quantitative PCR before treatment.^{21,22} Pre-treatment EBV DNA levels were divided into a low and high group based on the cutoff value of 4,000 copies/mL, which was established as a prognostic value in previous studies.^{15,23}

Clinical Outcome and Follow-Up

Our primary study end point was distant metastasis–free survival (DMFS), which was calculated from the first day of treatment to the date of distant metastasis. The secondary end point included overall survival (OS), which was calculated from the start of treatment to the date of death of any cause, and progression-free survival (PFS), which was calculated from the first day of treatment to the date of any treatment failure or death of any cause. Patients were censored if they were still alive on August 4, 2017, the date of last follow-up. After treatment, patients were examined at 3-month intervals for the first 3 years and every 6 months thereafter or until death.

Statistical Analysis

Categorical variables were compared using the chi-square or Fisher exact test. The Kaplan-Meier method was used to estimate the cumulative survival rates, and survival curves were compared using the log-rank test. Hazard ratios (HRs) with 95% CIs were calculated using the Cox proportional hazards model. Univariate and multivariate analyses using Cox proportional hazards models were performed to evaluate the independent significance of the treatment group (different timing of chemotherapy to CCRT) and other potential prognostic factors, including age, sex, tumor stage, history of NPC, early antigen immunoglobulin A, and viral capsid antigen immunoglobulin A. Tests were 2-sided, and a *P* value < .05 was considered significant.

Results

The characteristics of the 2,263 patients in the different treatment groups are presented in Table 1. In the NACT + CCRT group (N=1,073), 81.5% of patients (n=875) received 3 cycles and 18.5% (n=198) received 2 cycles of NACT, and 45.5% (n=483) received 3 cycles and 55.0% (n=590) received 2 cycles of CCRT. In the CCRT + ACT group (N=220), 5.9% of patients (n=13) received 4 cycles, 31.4% (n=69) received 3 cycles, 44.5% (n=98) received 2 cycles, and 18.2% (n=400)

received 1 cycle of ACT, and 68.6% (n=151) received 3 cycles and 31.4% (n=69) received 2 cycles of CCRT. In the CCRT group (N=970), 55.1% of patients (n=534) received 3 cycles of CCRT and 44.9% (n=436) received 2 cycles. For the entire cohort (N=2,263), within the median follow-up of 68 months (range, 3–128 months), 17.8% of patients (n=403) died, 14.8% (n=335) developed distant metastasis, and 9.7% (n=220) exhibited locoregional relapse. For all end points, significant survival curve separations were not observed among the 3 treatment groups (supplemental eTable 1, Figure 2). Significant survival benefit was not achieved with the addition of NACT or ACT to CCRT (supplemental eFigure 1). In addition, the survival curves of different chemotherapy regimens of NACT were not significantly segregated (supplemental eFigure 2). Therefore, we further analyzed the relationship between treatment method and clinical outcome in different risk groups.

Risk Stratification

As we reported earlier,²⁴ N stage and pretreatment EBV DNA were significantly correlated with distant metastasis. Moreover, patients with N0–1 stage disease with high EBV DNA ($\geq 4,000$ copies/mL) and those with N2–3 stage disease with low EBV DNA ($< 4,000$ copies/mL) had similar likelihoods of developing distant metastasis.²⁴ In this study, 6.6% of patients (54 of 818) with N0–1 disease and low EBV DNA exhibited distant metastasis, 14.4% (118 of 818) with N0–1 disease and high EBV DNA or N2–3 disease and low EBV DNA exhibited distant metastasis, and 26.0% (163 of 627) with N2–3 disease and high EBV DNA developed distant metastasis. Thus, eligible patients in our study were divided into 3 different risk groups: low-risk (N0–1 and low EBV DNA), intermediate-risk (N0–1 disease and high EBV DNA or N2–3 disease and low EBV DNA), and high-risk (N2–3 disease and high EBV DNA). Characteristics of patients treated with different methods in different risk groups are shown in supplemental eTable 2. Survival curves were significantly segregated among patients in different risk groups for DMFS (*P*<.001), OS (*P*<.001), and PFS (*P*<.001) (supplemental eFigure 3).

Relationship Between Treatment and Clinical Outcome in Low-Risk Group

Patients who received NACT followed by CCRT achieved significantly better 5-year DMFS than those treated with CCRT alone (96.2% vs 91.3%; *P*=.008) (Table 2, eFigure 4). In multivariate analyses, additional NACT significantly reduced the risk of distant metastasis and was also the only independent prognostic factor for DMFS (HR, 0.42; 95% CI, 0.22–0.80; *P*=.009). Multivariate analyses also demonstrated that smoking was an independent prognostic factor for PFS (HR, 1.53; 95% CI, 1.02–2.31; *P*=.040) (Table 3).

Table 1. Patient Characteristics

Characteristic	CCRT n (%)	NACT + CCRT n (%)	CCRT + ACT n (%)	P Value
Total, N	970	1,073	220	
Median age (range), y	45 (18–79)	46 (18–77)	44 (18–68)	.039
Sex				.220
Female	262 (27.0%)	284 (26.5%)	47 (21.4%)	
Male	708 (73.0%)	789 (73.5%)	173 (78.6%)	
T stage				.453
1–2	114 (11.8%)	144 (13.4%)	25 (11.4%)	
3–4	856 (88.2%)	929 (86.6%)	195 (88.6%)	
N stage				<.001
0–1	586 (60.4%)	487 (45.4%)	110 (50.0%)	
2–3	384 (39.6%)	586 (54.6%)	110 (50.0%)	
Overall stage				<.001
III	764 (78.8%)	626 (58.3%)	165 (75.0%)	
IVa	158 (16.3%)	319 (29.7%)	44 (20.0%)	
IVb	48 (4.9%)	128 (11.9%)	11 (5.0%)	
Smoking history				.088
No	349 (36.0%)	437 (40.7%)	84 (38.2%)	
Yes	621 (64.0%)	636 (59.3%)	136 (61.8%)	
Family history				.177
No	867 (89.4%)	953 (88.8%)	187 (85.0%)	
Yes	103 (10.6%)	120 (11.2%)	33 (15.0%)	
VCA-IgA				.001
<1:80	206 (21.2%)	167 (15.6%)	31 (14.1%)	
≥1:80	764 (78.8%)	906 (84.4%)	189 (85.9%)	
EA-IgA				.004
<1:10	293 (30.2%)	267 (24.9%)	47 (21.4%)	
≥1:10	677 (69.8%)	806 (75.1%)	173 (78.6%)	
EBV DNA level				<.001
<4,000 copies/mL	614 (63.3%)	520 (48.5%)	137 (62.3%)	
≥4,000 copies/mL	356 (36.7%)	553 (51.5%)	83 (37.7%)	

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; EA, early antigen; EBV, Epstein-Barr virus; IgA, immunoglobulin A; NACT, neoadjuvant chemotherapy; VCA, viral capsid antigen.

Relationship Between Treatment and Clinical Outcome in Intermediate-Risk Group

Patients treated with NACT or ACT in addition to CCRT in the intermediate-risk group had no significantly better survival than those in the CCRT-alone group (Table 2). When adjusting for other factors at multivariate analysis, T stage was an independent prognostic factor for DMFS (HR, 2.17; 95% CI, 1.13–4.17; $P=.020$), OS (HR, 2.17; 95% CI, 1.20–3.93; $P=.011$), and PFS (HR, 2.12; 95% CI, 1.31–3.46; $P=.002$) (Table 3). Sex was an independent prognostic factor for DMFS (HR, 2.06; 95% CI, 1.21–3.51; $P=.008$) and OS (HR, 1.79; 95% CI, 1.10–2.90; $P=.019$). However, the treatment group was not an independent prognostic factor for all end points.

Relationship Between Treatment and Clinical Outcome in High-Risk Group

In the high-risk group, comparison of NACT or ACT + CCRT versus CCRT alone still indicated no significantly better survival (Table 2, eFigure 4). Multivariate analyses demonstrated that no prognostic factor was correlated with DMFS, OS, and PFS (Table 3).

Discussion

To our knowledge, the efficacy of systemic chemotherapy in addition to RT in patients with advanced-stage disease at different risk levels of distant metastasis was not well established in previous studies. Results of our study showed that NACT followed by CCRT could significantly

Figure 2. Comparison of the probability of different treatment methods with regard to (A) distant metastasis-free survival, (B) overall survival, and (C) progression-free survival rates.

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy.

reduce the risk of distant metastasis compared with CCRT alone in patients in the low-risk group. However, no significant OS benefit was observed for either the addition of NACT or ACT.

Since the landmark Intergroup 0099 trial,¹⁷ studies concerning the interaction between the timing of chemotherapy and the effect on various end points have been ongoing. Several meta-analyses showed that the survival benefit primarily comes from the concurrent phase.^{5,25} Although high locoregional control rates are currently achieved with CCRT for advanced-stage NPC, distant metastasis has become the leading cause of treatment failure.^{5,6} Our study investigated the efficacy of NACT or ACT in addition to CCRT. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers recommend CCRT followed by ACT for stages II–IVb NPC, and this recommendation is supported by level IIA evidence.²⁶ The combined analyses of the NPC-9901 and NPC-9902 trials also demonstrated that ACT contributed to improving distant control.²⁷ A retrospective study by Twu et al²⁸ showed that ACT could reduce distant failure and improve OS (71.6% vs 28.7%; $P<.001$) in patients with persistently detectable EBV DNA after CCRT. However, the phase III trial by Chen et al²⁹ showed no statistically significant improvement in failure-free survival with additional ACT. Notably, compliance with ACT is poor. In previous studies, only 52% to 61% of patients completed 3 cycles of ACT, and half of these had dose reductions.^{17,29–32} Theoretically, changing to NACT might improve tolerance and early eradication of potent micrometastases. Therefore, NACT followed by CCRT became the research focus. In 2009, a phase II trial conducted by Hui et al⁵ reported that adding neoadjuvant cisplatin and docetaxel to CRT increased PFS by 28.7%. Another phase II trial by Fountzilas et al⁸ and a phase II/III trial by Tan et al¹² both failed to show a significant survival benefit at 3 years. Preliminary results of the NPC-0501 trial indicated that the benefit of changing to an induction-concurrent sequence remains uncertain.⁹ However, Sun et al³³ more recently reported that NACT + CCRT could improve survival outcomes in NPC. Thus, there are differing opinions regarding whether the addition of NACT or ACT to CCRT should be recommended.

In our study, analysis of all 2,263 patients failed to show a significant survival benefit among the 3 treatment groups. We believe one possible reason for these controversial results was the therapeutic decisions in the aforementioned studies, which were simply based on TNM stage. As reported previously, pretreatment plasma EBV DNA level significantly correlated with clinical outcome. Patients with high pretreatment EBV DNA levels were more likely to develop treatment failure, especially distant metastases.^{15,16,23} N stage also correlated with distant

Table 2. Comparison of Cumulative Survival Rates

	n	%	5-Year DMFS (95% CI)	P Value	5-Year OS (95% CI)	P Value	5-Year PFS (95% CI)	P Value
Low-risk group ^a	818			.021		.209		.743
CCRT	435	53.2	91.3% (88.6%–94.0%)		91.6% (88.9%–94.3%)		85.8% (82.5%–89.2%)	
NACT + CCRT	303	37.0	96.2% (94.0%–98.4%)		93.3% (90.4%–96.2%)		85.2% (81.1%–89.3%)	
CCRT + ACT	80	9.8	94.7% (89.6%–99.8%)		94.5% (89.2%–99.8%)		88.3% (81.0%–95.6%)	
Intermediate-risk group ^b	818			.805		.475		.233
CCRT	330	40.3	87.3% (83.6%–91.0%)		85.5% (79.8%–91.3%)		79.1% (74.6%–83.6%)	
NACT + CCRT	401	49.0	85.8% (82.3%–89.3%)		83.3% (79.6%–87.0%)		74.8% (77.6%–92.4%)	
CCRT + ACT	87	10.6	89.4% (82.9%–95.9%)		91.2% (84.9%–97.5%)		85.0% (83.6%–91.0%)	
High-risk group ^c	627			.102		.128		.117
CCRT	205	32.7	70.2% (63.7%–76.7%)		69.4% (62.9%–75.9%)		60.9% (54.2%–67.6%)	
NACT + CCRT	369	58.9	75.2% (70.7%–79.7%)		76.8% (72.5%–81.1%)		66.9% (62.0%–71.8%)	
CCRT + ACT	53	8.5	82.4% (72.0%–92.8%)		74.1% (61.9%–86.3%)		67.7% (55.0%–80.4%)	

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; DMFS, distant metastasis-free survival; EBV, Epstein-Barr virus; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

^aLow-risk group: stage N0–1 disease and EBV DNA <4,000 copies/mL.

^bIntermediate-risk group: stage N0–1 disease and EBV DNA ≥4,000 copies/mL or stage N2–3 disease and EBV DNA <4,000 copies/mL.

^cHigh-risk group: stage N2–3 disease and EBV DNA ≥4,000 copies/mL.

metastasis.¹⁹ Therefore, taking these 2 factors into consideration, patients in our study were divided into 3 different risk groups. We further explored the efficacy of adding NACT and ACT to CCRT in patients with different risk levels. Interestingly, we found that patients in the low-risk group (N0–1 disease and EBV DNA <4,000 copies/mL) achieved significantly better DMFS from NACT + CCRT than from CCRT alone. Furthermore, NACT + CCRT was the only independent prognostic factor for DMFS. Similarly, the trial by Sun et al³³ also demonstrated a significant reduction in distant metastases in patients with N1 disease but not in those with N2–3b disease. The possible reason for these results is that patients with N2–3 or EBV DNA ≥4,000 copies/mL might have already had distant metastasis that could not be detected by imaging examination. In this case, an additional 2 or 3 cycles of NACT might not be enough to eradicate the metastasis. Therefore, a significant reduction in distant metastasis was not observed in these patients. The results could provide the basis for a trial that addresses additional NACT or ACT in the low-risk group.

In our study, patients in the high-risk group treated with CCRT + ACT experienced relatively higher DMFS rates than those treated with CCRT alone (82.4% vs 70.2%). This result was in line with findings of a recent meta-analysis conducted by Ribassin-Majed et al.³⁴ However, survival rates in our study failed to show significant differences between the 2 groups. Compliance with ACT and the small sample size of patients treated with ACT could potentially affect treatment outcome. In the high-risk group, only 53 patients underwent ACT, which underpowered the results. Furthermore, among them, 69.8% of patients (37 of 53) received only 1 to 2 cycles of ACT and had dose reductions, and therefore improvement

in survival benefit was inevitably hampered by the sub-optimal treatment intensity. Therefore, giving combinations of new drugs with low toxicities to improve compliance with ACT might result in further improvements in survival.

In addition, multivariate analyses showed that male patients had poorer prognosis than their female counterparts in the intermediate-risk group, suggesting that a biologic difference in tumor behavior might exist between male and female patients in this group. The sex difference in prognosis might be due to genetic variants, inappropriate diet, environmental tobacco smoke, and occupational exposures to formaldehyde and dusts in the intermediate-risk group.^{35–37} Future studies on the mechanisms of sex differences in NPC progression are needed.

Our study has several limitations. First, this was a retrospective study in a single center; therefore, results must be validated by other datasets and prospective studies. Second, only 220 patients in our study received CCRT + ACT; thus, the sample size in each risk group was relatively small. A larger sample size of patients treated with CCRT + ACT is needed to evaluate the long-term outcomes of these patients. Finally, the lack of integrated toxicity data for different treatment methods makes these results underpowered. In the future, a well-designed, multicenter, prospective, randomized study is needed to validate our results.

Conclusions

Our study demonstrated that patients with NPC in the low-risk group who were treated with NACT + CCRT had significantly reduced hazards of distant metastasis compared with patients treated with CCRT alone.

Table 3. Multivariate Analyses of Potential Prognostic Factors in Clinical Outcomes

End Point	Low-Risk Group ^a		Intermediate-Risk Group ^b		High-Risk Group ^c	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
DMFS						
Age (≥45 y vs <45 y)	1.11 (0.64–1.92)	.703	0.78 (0.54–1.14)	.203	1.15 (0.84–1.58)	.389
Sex (male vs female)	0.82 (0.41–1.63)	.568	2.06 (1.21–3.51)	.008	1.37 (0.88–2.11)	.161
T stage (T3–4 vs T1–2)	— ^d	— ^d	2.17 (1.13–4.17)	.020	1.24 (0.85–1.81)	.272
Smoking history (yes vs no)	1.45 (0.77–2.73)	.254	1.06 (0.71–1.57)	.787	1.05 (0.75–1.49)	.765
Family history (yes vs no)	0.66 (0.24–1.83)	.425	1.51 (0.91–2.51)	.110	1.05 (0.66–1.68)	.846
VCA-IgA (≥1:80 vs <1:80)	1.46 (0.49–4.34)	.494	1.04 (0.52–2.08)	.917	0.71 (0.41–1.24)	.226
EA-IgA (≥1:10 vs <1:10)	1.11 (0.45–2.75)	.818	0.94 (0.52–1.70)	.836	0.90 (0.55–1.50)	.695
NACT + CCRT vs CCRT	0.42 (0.22–0.80)	.009	0.99 (0.67–1.45)	.958	0.79 (0.57–1.09)	.154
CCRT + ACT vs CCRT	0.54 (0.19–1.51)	.240	0.72 (0.37–1.39)	.322	0.54 (0.26–1.08)	.082
OS						
Age (≥45 y vs <45 y)	1.56 (0.98–2.50)	.062	1.06 (0.76–1.48)	.724	1.29 (0.96–1.75)	.092
Sex (male vs female)	0.95 (0.52–1.74)	.877	1.79 (1.10–2.90)	.019	1.12 (0.75–1.68)	.573
T stage (T3–4 vs T1–2)	— ^d	— ^d	2.17 (1.20–3.93)	.011	1.09 (0.77–1.55)	.635
Smoking history (yes vs no)	1.51 (0.89–2.57)	.130	1.29 (0.90–1.85)	.172	1.12 (0.80–1.56)	.515
Family history (yes vs no)	0.56 (0.23–1.40)	.215	1.36 (0.86–2.17)	.193	0.93 (0.58–1.48)	.757
VCA-IgA (≥1:80 vs <1:80)	1.18 (0.49–2.86)	.713	1.03 (0.53–2.04)	.924	0.84 (0.49–1.44)	.526
EA-IgA (≥1:10 vs <1:10)	0.92 (0.43–1.98)	.827	1.21 (0.69–2.14)	.506	0.85 (0.53–1.36)	.502
NACT + CCRT vs CCRT	0.67 (0.42–1.13)	.139	1.06 (0.75–1.50)	.732	0.77 (0.56–1.05)	.102
CCRT + ACT vs CCRT	0.66 (0.28–1.55)	.339	0.69 (0.38–1.27)	.235	0.66 (0.36–1.21)	.181
PFS						
Age (≥45 y vs <45 y)	1.38 (0.97–1.97)	.710	0.96 (0.73–1.28)	.793	1.09 (0.84–1.42)	.536
Sex (male vs female)	0.82 (0.52–1.27)	.373	1.29 (0.88–1.87)	.189	1.04 (0.74–1.48)	.816
T stage (T3–4 vs T1–2)	— ^d	— ^d	2.12 (1.31–3.46)	.002	1.10 (0.81–1.51)	.533
Smoking history (yes vs no)	1.53 (1.02–2.31)	.040	1.22 (0.89–1.67)	.209	1.19 (0.89–1.60)	.249
Family history (yes vs no)	0.47 (0.23–0.96)	.038	1.06 (0.69–1.63)	.790	0.94 (0.62–1.41)	.753
VCA-IgA (≥1:80 vs <1:80)	1.00 (0.50–2.03)	.992	1.08 (0.61–1.90)	.786	0.80 (0.50–1.27)	.340
EA-IgA (≥1:10 vs <1:10)	1.19 (0.64–2.21)	.591	1.17 (0.73–1.87)	.528	0.87 (0.57–1.32)	.513
NACT + CCRT vs CCRT	0.87 (0.60–1.26)	.451	1.10 (0.82–1.47)	.519	0.78 (0.60–1.03)	.085
CCRT + ACT vs CCRT	0.98 (0.55–1.75)	.949	0.70 (0.41–1.19)	.189	0.69 (0.40–1.16)	.159

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; DMFS, distant metastasis-free survival; EA, early antigen; EBV, Epstein-Barr virus; HR, hazard ratio; IgA, immunoglobulin A; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; VCA, viral capsid antigen.

^aLow-risk group: stage N0–1 disease and EBV DNA <4,000 copies/mL.

^bIntermediate-risk group: stage N0–1 disease and EBV DNA ≥4,000 copies/mL or stage N2–3 disease and EBV DNA <4,000 copies/mL.

^cHigh-risk group: stage N2–3 disease and EBV DNA ≥4,000 copies/mL.

^dIn low-risk group, all patients have stage T3–4 disease.

Disappointingly, the addition of NACT or ACT failed to achieve OS benefit. Future results of the ongoing NRG-HN001 study using EBV DNA to risk-stratify patients might provide more information on individualized treatment of NPC. Further investigation is necessary to confirm our findings.

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Supplemental online content for:

Neoadjuvant or Adjuvant Chemotherapy Plus Concurrent CRT Versus Concurrent CRT Alone in the Treatment of Nasopharyngeal Carcinoma: A Study Based on EBV DNA

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eFigure 1: Comparison of CCRT Alone Versus CCRT + NACT or ACT

eFigure 2: Comparison of Different NACT Regimens

eFigure 3: Comparison of Different Risk Groups

eFigure 4: Comparison of Different Treatment Methods

eTable 1: Comparison of Cumulative Survival Rates Among Treatment Groups

eTable 2: Patient Characteristics Stratified by Risk Group

eAppendix 1: Design of the Intensity-Modulated Radiotherapy Plan

Figure 1. CCRT alone versus CCRT + NACT or ACT with regard to rates of (A) distant metastasis-free survival, (B) overall survival, and (C) progression-free survival.

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy.

eFigure 2. Comparison of NACT regimens with regard to rates of (A) distant metastasis-free survival, (B) overall survival, and (C) progression-free survival.
Abbreviations: PF, cisplatin (80 mg/m², day 1) with 5-fluorouracil (800–1,000 mg/m², 96 hours of continuous intravenous infusion); TP, cisplatin with docetaxel (75 mg/m², day 1); TPF, cisplatin (75 mg/m², day 1) and docetaxel (75 mg/m², day 1) with 5-fluorouracil (750 mg/m², 96 hours of continuous intravenous infusion).

eFigure 3. Comparison of different risk groups with regard to rates of (A) distant metastasis-free survival, (B) overall survival, and (C) progression-free survival.

(continued on next page)

eFigure 4. Comparison of the probability of different treatment methods in the (A, B, C) low-risk group, (D, E, F) intermediate-risk group, and (G, H, I) high-risk group with regard to distant metastasis-free survival, overall survival, and progression-free survival rates. Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy.

(continued)

eFigure 4. Comparison of the probability of different treatment methods in the (A, B, C) low-risk group, (D, E, F) intermediate-risk group, and (G, H, I) high-risk group with regard to distant metastasis-free survival, overall survival, and progression-free survival rates. Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy.

eTable 1. Comparison of Cumulative Survival Rates Among Treatment Groups								
Treatment Group	n	%	5-Year DMFS (95% CI)	P Value	5-Year OS (95% CI)	P Value	5-Year PFS (95% CI)	P Value
				.179		.184		.153
CCRT	970	42.9	85.6% (83.4%–87.8%)		84.8% (82.4%–87.2%)		78.3% (75.8%–80.8%)	
NACT + CCRT	1,073	47.4	85.0% (82.8%–87.2%)		84.0% (81.8%–86.2%)		75.1% (72.6%–77.6%)	
CCRT + ACT	220	9.7	89.7% (85.6%–93.8%)		90.0% (85.9%–94.1%)		82.6% (77.5%–87.7%)	

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; DMFS, distant metastasis-free survival; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival.

eTable 2. Patient Characteristics Stratified by Risk Group

Characteristic	Low-Risk Group ^a				Intermediate-Risk Group ^b				High-Risk Group ^c			
	CCRT n (%)	NACT + CCRT n (%)	CCRT + ACT n (%)	P Value	CCRT n (%)	NACT + CCRT n (%)	CCRT + ACT n (%)	P Value	CCRT n (%)	NACT + CCRT n (%)	CCRT + ACT n (%)	P Value
Total	435	303	80		330	401	87		205	369	53	
Median age (range), y	45 (18–79)	46 (18–72)	43 (18–71)	.567	47 (18–77)	45 (18–71)	44 (19–66)	.212	47 (18–77)	44 (18–77)	43 (22–66)	.033
Sex				.507				.117				.12
Female	116 (26.7%)	91 (30.0%)	25 (31.2%)		97 (29.4%)	106 (26.4%)	16 (18.4%)		49 (23.9%)	87 (23.6%)	6 (11.3%)	
Male	319 (73.3%)	212 (70.0%)	55 (68.8%)		233 (70.6%)	295 (73.6%)	71 (82.6%)		156 (76.1%)	282 (76.4%)	47 (88.7%)	
T stage				<.001				.581				.206
1–2	0 (0.0%)	0 (0.0%)	0 (0.0%)		57 (17.3%)	65 (16.2%)	11 (12.6%)		57 (27.8%)	79 (21.4%)	14 (26.4%)	
3–4	435 (100.0%)	303 (100.0%)	80 (100.0%)		273 (82.7%)	336 (83.8%)	76 (87.4%)		148 (72.2%)	290 (78.6%)	39 (73.6%)	
Overall stage				<.001				<.001				.001
II	376 (86.4%)	193 (63.7%)	63 (78.8%)		250 (75.8%)	245 (61.1%)	68 (78.2%)		138 (67.3%)	188 (50.9%)	34 (64.2%)	
III	59 (13.6%)	110 (36.3%)	17 (21.2%)		62 (18.8%)	128 (31.9%)	15 (17.2%)		37 (18.0%)	81 (22.0%)	12 (22.6%)	
IVa					18 (5.5%)	28 (7.8%)	4 (4.6%)		30 (14.6%)	100 (27.1%)	7 (13.2%)	
Smoking history				.455				.069				.382
No	284 (65.3%)	190 (62.7%)	56 (79.0%)		216 (65.5%)	229 (57.1%)	54 (62.1%)		121 (59.0%)	217 (59.8%)	26 (49.1%)	
Yes	151 (34.7%)	113 (37.3%)	24 (30.0%)		114 (34.5%)	172 (42.9%)	33 (37.9%)		84 (41.0%)	152 (34.5%)	27 (50.9%)	
Family history				.045				.305				.992
No	396 (91.0%)	264 (87.1%)	66 (82.5%)		290 (87.9%)	362 (90.3%)	74 (85.1%)		181 (88.3%)	327 (88.6%)	47 (88.7%)	
Yes	39 (9.0%)	39 (12.9%)	14 (17.5%)		40 (12.1%)	39 (9.7%)	13 (14.9%)		24 (11.7%)	42 (11.4%)	6 (11.3%)	
VCA-IgA				.389				.334				.009
<1:80	102 (23.4%)	60 (19.8%)	15 (18.8%)		60 (18.2%)	58 (14.5%)	12 (13.7%)		44 (21.5%)	49 (13.3%)	4 (7.5%)	
≥1:80	333 (76.6%)	243 (80.2%)	65 (81.2%)		270 (81.8%)	343 (85.5%)	75 (86.2%)		161 (78.5%)	320 (86.7%)	49 (92.5%)	
EA-IgA				.186				.302				.082
<1:10	146 (33.6%)	83 (27.4%)	23 (28.8%)		91 (27.6%)	101 (25.2%)	17 (19.5%)		56 (27.3%)	83 (22.5%)	7 (13.2%)	
≥1:10	289 (66.4%)	220 (72.6%)	57 (71.2%)		239 (72.4%)	300 (73.6%)	70 (75.9%)		149 (72.7%)	286 (77.5%)	46 (86.8%)	

Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; EA, early antigen; IgA, immunoglobulin A; NACT, neoadjuvant chemotherapy; VCA, viral capsid antigen.

^aLow-risk group: stage N0–1 disease and EBV DNA <4,000 copies/mL.^bIntermediate-risk group: stage N0–1 disease and EBV DNA ≥4,000 copies/mL or stage N2–3 disease and EBV DNA <4,000 copies/mL.^cHigh-risk group: stage N2–3 disease and EBV DNA ≥4,000 copies/mL.

eAppendix 1. Design of the Intensity-Modulated Radiotherapy Plan

All patients were immobilized in the supine position with a head, neck, and shoulder thermoplastic mask. Two sets of images, with and without contrast, were obtained from the CT simulator for treatment planning. All patients were scanned with serial 3-mm slices from the vertex through the clavicles. Inverse intensity-modulated radiotherapy planning was performed using CORVUS version 3.0 (Best NOMOS), and a MIMiC multileaf collimator (NOMOS) was used for planning and treatment.

The primary and nodal gross tumor volumes (GTV) included all gross diseases visualized by CT and/or MRI. The high-risk clinical tumor volume (CTV-1) included GTV plus a 5- to 10-mm margin and encompassed the entire nasopharyngeal mucosa plus 5-mm submucosal volume. CTV-2 was designed for potentially involved regions included in the nasopharyngeal cavity (limited only to the posterior part of the nasal cavity), maxillary sinus (limited to 5 mm anterior to the posterior nasal aperture and maxillary mucosa), pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of the clivus and cervical vertebra, inferior sphenoid sinus, and cavernous sinus, and it included the retropharyngeal lymph node regions from the base of the skull to the cranial edge of the second cervical vertebra. CTV of the neck nodal regions included levels II, III, IV, and V, which were outlined according to the recommendation by the RTOG/EORTC CTV delineation protocol for head and neck malignancies. The planning target volume (PTV) was created based on each volume with an additional 3-mm margin, allowing for setup variability. Critical normal structures, including the brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporo-mandibular joints, mandible, and hypophysis, were contoured and set as organs at risk during optimization.

The dose-volume histograms of the treatment targets and critical normal structures were evaluated. The prescribed dose was 68 to 70 Gy to the PTV of GTV of nasopharynx, 60 Gy to PTV-1, 54 Gy to PTV-2, and 60 to 70 Gy to PTV of the GTV of lymph nodes in 30 to 33 fractions. For GTV and CTV, the target volumes receiving 95% of the prescribed dose were used to reflect the target coverage, and the maximal, minimal, and mean doses delivered to the target volumes were also calculated. For critical organs with functional subunits organized in series, such as the brainstem, optic chiasm, and optic nerves, the dose delivered to 5% of the volumes was examined. For critical organs with functional subunits organized in parallel, the dose delivered to 33% of the volumes was evaluated. The dose distribution was also examined slice by slice on the CT image.