Supplementary Material

Pretreatment evaluation

Pretreatment evaluation included complete history; physical examination, and fiber-optic endoscopic examination of the nasopharynx, oropharynx, and larynx; magnetic resonance imaging (MRI) or computerized tomography (CT) of the head and neck; a conventional work-up including chest x-ray, abdominal ultrasound, and skeletal scintigraphy. Loco-regional lesions were confirmed by biopsy or aspiration. If metastasis was suggested by the conventional work-up, the patient underwent additional evaluations, including [18F]fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT), CT, MRI, biopsy, or aspiration at the site in question. If discrepancies were noted between imaging modalities, the measure value based on MRI, or CT was given priority according to RECIST guidelines [1, 2].

Treatment at referral

All patients received irradiation by IMRT. The target volumes were delineated according to a previously described institutional treatment protocol, which is in accordance with the International Commission on Radiation Units and Measurements reports 50 and 62. Briefly, the primary nasopharyngeal gross tumor volume (GTVnx) and corresponding cervical lymph nodes were determined based on MRI/CT imaging as well as clinical and endoscopic findings. The enlarged retropharyngeal nodes together with primary gross tumor volume (GTV) were outlined as the GTVnx on the

IMRT plans. The first clinical tumor volume (CTV1) was defined as the GTV within 0.5-1.0 cm margin (0.2 to 0.3 cm posterior margin) to encompass the high-risk sites of microscopic extension and the whole nasopharynx. Clinical target volume 2 (CTV2) was defined as the CTV1 plus a 0.5-1.0 cm margin (0.2 to 0.3 cm posterior margin) to encompass the low-risk sites of microscopic extension, the level of the lymph node, and the elective neck area (bilateral levels IIa, IIb, III, and Va are routinely covered for all N0 patients, whereas ipsilateral levels IV, Vb, and supraclavicular fossae were also included for the N1-3 patients). The prescribed doses were 66–70 Gy to the planning target volume (PTV), 60 Gy to PTV1, 54 Gy to PTV2, and 60–66 Gy to the PTV of the involved cervical lymph nodes in 28 to 33 fractions. All patients were treated once daily with five fractions weekly. Dose constraints to the critical structures were within the tolerance according to the RTOG 0225 protocol, and efforts were made to meet the criteria as closely as possible.

According to the 2013 NCCN guidelines for head and neck cancer, CCRT is the standard treatment for NPC patients with II-IVb stage [3]. The study-defined concurrent chemotherapy regimen was 100 mg/m^{2}cisplatin on day 1 every 3 weeks for 3 cycles [4]. Nimotuzumab was administered concomitantly with IMRT at a dose of 200 mg weekly, which was diluted in 250 mL saline to obtain a 200 mg suspension and was intravenously infused over 1 hour [5]. Intravenous cetuximab was administered at an initial dose of 400 mg/m2 followed by 250 mg/m2 weekly throughout RT weekly [6].

Statistical analysis

All analyses were performed using Stata version 10.0, software and a 2-tailed *P* value of less than 0.05 was considered to be statistically significant.

The clinicopathological characteristics of the cohort are described, and the differences in these characteristics between CTX/NTZ plus CCRT arm and CCRT arm were compared. Complete response was defined as no unequivocal soft tissue mass in the local region and all cervical lymph nodes were less than 10 mm in the short axis. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions (an absolute increase of at least 5 mm), or the appearance of one or more new lesions. Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. The relative dose intensity of CTX, NTZ, or CDDP was calculated as the proportion of the prescribed total dose of each drug in the protocol actually received by the patients in the current analysis. Categorized variables were compared using the χ^2 test, the correction χ^2 test, or Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U*-test.

The events for overall survival (OS), distant metastasis-free survival (DMFS), and loco-regional relapse-free survival (LRRFS) were death from any cause, distant metastasis, and loco-regional recurrence, respectively. The duration was calculated from the date of treatment initiation to the date of each event or last follow-up.

Disease–free survival (DFS) was calculated from the date of treatment initiation to loco-regional relapse, distant relapse or tumor-related death (whichever occurred first), or the final follow-up. Survival results were calculated using the Kaplan–Meier method, and differences were compared by log-rank test.

We then performed a multivariate Cox regression analysis to identify independent prognostic factors for survival outcome [7], with the assumption of proportional hazards confirmed based on Schoenfeld residuals [8]; cumulative hazard plots estimated for both groups were parallel, verifying that the assumption of proportional hazards was appropriate. Treatment regimen status (CTX/NTZ plus CCRT vs. CCRT), gender, age, KPS, T and N stages, disease stage were used as covariates. Furthermore, the treatment regimen status and other independent prognostic factors were entered into the multivariate Cox regression model to test their primary effects, and an interaction term between the treatment regimens status and the independent prognostic factors was then added into the model to test the effect of their interaction.

Reference

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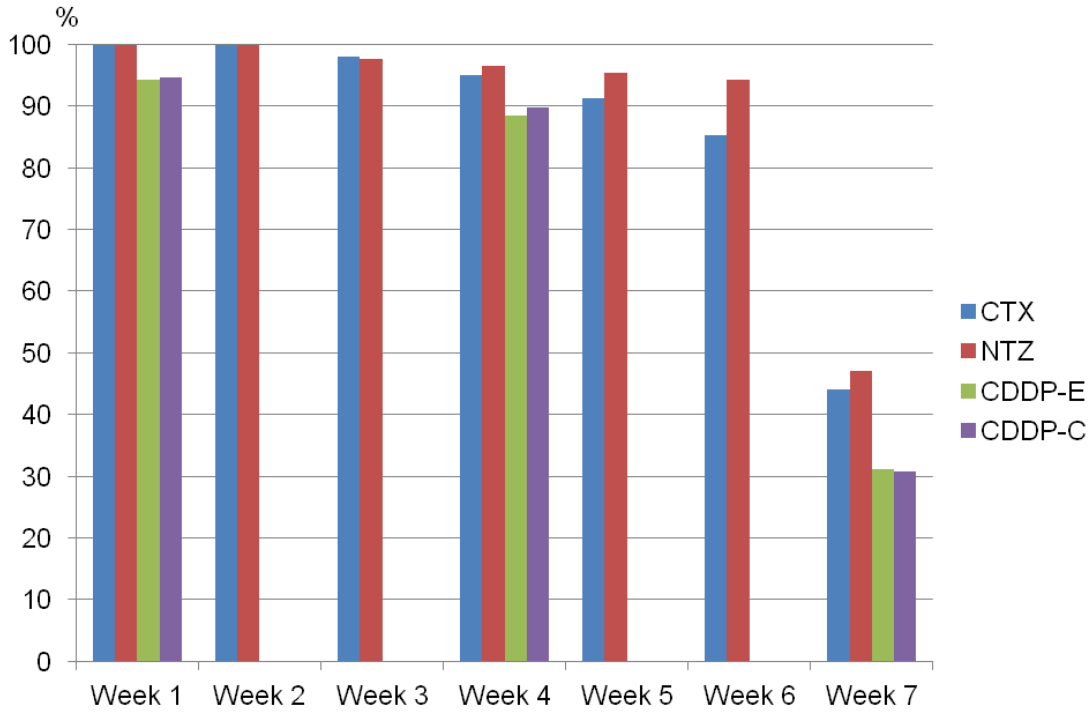

Supplementary Figure 1. Mean relative dose intensity. CTX, Cetuximab, at an initial dose of 400 mg/m2 followed by 250 mg/m2 weekly throughout RT; NTZ, Nimotuzumab, 200 mg weekly; CDDP-E, Cisplatin used in the CTX/NTZ plus CDDP arm, 100 mg/m^2 on weeks 1, 4, 7; CDDP-C, Cisplatin used in the CDDP arm, 100 mg/m^2 on weeks 1, 4, 7.

Supplementary Table 1. Baseline characteristics of patients in 1628 eligible cases

Characteristic	CTX/NTZ plus CCRT N = 249	CCRT N = 1379
Gender		
Female	51 (20.5%)	362 (26.3%)
Male	198 (79.5%)	1017 (73.7%)
Age ——yr		
Median	44.6	46.0
Range	11.8-68.5	15.0-78.0
Karnofsky performance status		
90-100	225 (90.4%)	1256 (91.1%)
70-80	24 (9.6%)	123 (8.9%)
T classification		
T1	18 (7.2%)	77 (5.6%)
T2	44 (17.7%)	222 (16.1%)
T3	153 (61.4%)	858 (62.2%)
T4	34 (13.7%)	222 (16.1%)
N classification		
No	28 (11.2%)	222 (16.1%)
N1	113 (45.4%)	642 (46.6%)
N2	94 (37.8%)	445 (32.3%)
N3	14 (5.6%)	70 (5.1%)
Disease stage		
II	31 (12.4%)	157 (11.4%)
III	171 (68.7%)	936 (67.9%)
IV	47 (18.9%)	286 (20.7%)

Data are the median or n (%), unless otherwise stated. CCRT, Concurrent Chemoradiotherapy; NTZ, Nimotuzumab; CTX, Cetuximab.

Supplementary Table 2. Imaging methods in the two treatment groups of the 878-patient well-balanced cohort

Techniques	CTX/NTZ plus CCRT N = 189	CCRT N = 689	P*
Nasopharynx and neck			ns
Patient receiving MRI	188 (99.5%)	688 (99.9%)	
Patient receiving CT	1 (0.5%)	1 (0.1%)	
Skeleton			ns
Patient receiving skeletal acintigraphy	100 (52.9%)	393 (57.0%)	
Patient receiving skeletal MRI	10 (5.3%)	28 (4.1%)	
Patient receiving PET/CT	79 (41.8%)	268 (38.9%)	
Thorax			Ns
Patient receiving chest X-ray	101 (53.4%)	395 (57.3%)	
Patient receiving chest CT	9 (4.8%)	26 (3.8%)	
Patient receiving PET/CT	79 (41.8%)	268 (38.9%)	
Abdomen			Ns
Patient receiving abdominal ultrasound	87 (46.0%)	361 (52.4%)	
Patient receiving abdominal MRI	12 (6.3%)	26 (3.8%)	
Patient receiving abdominal CT	11 (5.8%)	34 (4.9%)	
Patient receiving PET/CT	79 (41.8%)	268 (38.9%)	

CCRT, Concurrent Chemoradiotherapy; NTZ, Nimotuzumab; CTX, Cetuximab. *χ^2test or Fisher's exact test. Ns,non-significant.

Supplementary Table 3. Concurrent CTX/NTZ Characteristics and Compliance

Variable	CTX plus CCRT N = 102	NTZ plus CCRT N = 87	P*
Patients completing at least one cycle	102 (100.0%)	87 (100.0%)	ns
Patients completing two to five cycles	15 (14.7%)	5 (5.7%)	0.046
Patients completing six to seven cycles	87 (85.3%)	82 (94.3%)	0.046
Patients completing at least one cycle with dose reductions, no	0 (0.0%)	0 (0.0%)	ns

CCRT, Concurrent Chemoradiotherapy; NTZ, Nimotuzumab; CTX, Cetuximab. *χ^2test or Fisher's exact test. ns, non-significant.

Supplementary Table 4. Concurrent Chemoradiotherapy Characteristics and Compliance

	CTX/NTZ plus CCRT N = 189	CCRT N = 689	P*
Patients receiving IMRT	189 (100%)	689 (100%)	ns
Patient completing IMRT	189 (100%)	689 (100%)	ns
Median (IQR) dose of IMRT (Gy)	70 (70-70)	70 (70-70)	ns
Median (IQR) dose per fraction (Gy)	2.19 (2.12-2.26)	2.19 (2.12-2.26)	ns
Median (IQR) duration of IMRT (days)	46 (44-49)	46 (44-49)	ns
Patients starting concurrent cisplatin			ns
Patients completing at least two cycles CC	178 (94.2%)	655 (95.1%)	ns
Patients completing three cycles CC	59 (31.2%)	212 (30.8%)	ns
Patients receiving concurrent cisplatin $\geq$ 200mg/m^2	123 (75.1%)	473 (72.7%)	ns

CCRT, Concurrent Chemoradiotherapy; NTZ, Nimotuzumab; CTX, Cetuximab. *χ^2test or Fisher's exact test. ns, non-significant.

Supplementary Table 5. Survival outcomes in the 878-patient well-balanced cohort

	CTX/NTZ plus CCRT N = 189	CCRT N = 689	HR (95%CI)	P value
Disease–free survival				
Failures	18 (9.5%)	113 (16.4%)		
Proportion of patients disease-free at 3 years	93.5%	86.9%	0.57 (0.35-0.94)	0.028
Loco-regional relapse–free survival				
Loco-regional failures	7 (3.7%)	45 (6.5%)		
Proportion of patients alive without loco-regional failure at 3 years	97.8%	94.7%	0.57 (0.25-1.25)	0.160
Distant metastasis-free survival				
Distant failures	13 (6.8%)	89 (12.9%)		
Proportion of patients alive without distant failure at 3 years	94.6%	89.3%	0.52 (0.29-0.94)	0.030
Overall survival				
Deaths	8 (4.2%)	73 (10.6%)		
Proportion of patients alive at 3 years	96.6%	92.9%	0.40 (0.19-0.84)	0.015
Response to treatment (16 weeks after the end of chemotherapy)				
Overall response	189 (100%)	687 (99.7%)	------	ns*
Complete response	187 (98.9%)	680 (98.7%)	------	ns*
Partial response	2 (1.1%)	7 (1.0%)	------	ns*

*χ^2test or Fisher's exact test. ns, non-significant

Supplementary Table 6. Univariate analysis of variables correlated with the treatment regimen status and other prognostic factors in 1628 cases

	HR	Cl (95%)	P value
Disease–free survival			
Treatment regimen status			
CCRT	Reference		
CTX/NTZ plus CCRT	0.58	0.36-0.94	0.028
Gender			
Female	Reference		
Male	1.28	0.94-1.75	0.119
Age			
<45	Reference		
≥45	1.18	0.91-1.54	0.202
Karnofsky performance status score			
70-80	Reference		
90-100	1.09	0.62-1.67	0.507
Tumor stage			
T1	Reference		
T2	1.37	0.66-2.85	0.397
T3	1.28	0.65-2.51	0.476
T4	2.36	1.17-4.76	0.017
Node stage			
N0	Reference		
N1	1.31	0.85-2.02	0.216
N2	1.76	1.14-2.72	0.011
N3	3.22	1.85-5.63	<0.001
Disease stage			
II	Reference		
III	1.01	0.64-1.59	0.962
IV	2.01	1.25-3.23	0.004
Loco-regional relapse–free survival			
Treatment regimen status			
CCRT	Reference		
CTX/NTZ plus CCRT	0.55	0.26-1.19	0.131
Gender			
Female	Reference		
Male	1.17	0.73-1.89	0.517
Age			
<45	Reference		
≥45	1.07	0.72-1.61	0.734
Karnofsky performance status score			
70-80	Reference		
90-100	0.88	0.52-2.96	0.577
Tumor stage			
T1	Reference		
T2	2.24	0.67-7.54	0.193
T3	1.46	0.46-4.69	0.521
T4	2.46	0.73-8.26	0.144
Node stage			
N0	Reference		

N1	1.09	0.59-2.01	0.779
N2	1.27	0.68-2.38	0.450
N3	1.87	0.76-4.65	0.175
Disease stage			
II	Reference		
III	0.70	0.38-1.27	0.240
IV	1.12	0.58-2.19	0.732
Distant metastasis-free survival			
Treatment regimen status			
CCRT	Reference		
CTX/NTZ plus CCRT	0.49	0.28-0.90	0.028
Gender			
Female	Reference		
Male	1.59	1.08-2.35	0.019
Age			
<45	Reference		
≥45	1.13	0.83-1.52	0.442
Karnofsky performance status score			
70-80	Reference		
90-100	1.11	0.72-1.88	0.662
Tumor stage			
T1	Reference		
T2	1.03	0.46-2.28	0.951
T3	1.05	0.51-2.17	0.891
T4	2.06	0.97-4.37	0.060
Node stage			
N0	Reference		
N1	1.58	0.92-2.72	0.100
N2	2.16	1.25-3.73	0.006
N3	4.87	2.54-9.33	<0.001
Disease stage			
II	Reference		
III	1.22	0.68-2.18	0.501
IV	2.83	1.56-5.15	0.001
Overall survival			
Treatment regimen status			
CCRT	Reference		
CTX/NTZ plus CCRT	0.42	0.21-0.86	0.018
Gender			
Female	Reference		
Male	1.41	0.93-2.14	0.102
Age			
<45	Reference		
≥45	1.51	1.07-2.12	0.018
Karnofsky performance status score			
70-80	Reference		
90-100	0.84	0.29-2.06	0.582
Tumor stage			
T1	Reference		
T2	1.46	0.49-4.31	0.496

T3	1.65	0.61-4.52	0.327
T4	3.36	1.20-9.39	0.021
Node stage			
N0	Reference		
N1	1.22	0.70-2.12	0.483
N2	1.94	1.12-3.36	0.017
N3	3.83	1.93-7.61	<0.001
Disease stage			
II	Reference		
III	1.46	0.73-2.91	0.284
IV	3.27	1.61-6.63	0.001

HR, hazard ratio; 95% CI, 95% confidence interval.