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Neoadjuvant Chemotherapy of Three Cycles or More Improve Survival of Patients with N2-3 Nasopharyngeal Carcinoma

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Abstract

Background: Concurrent chemo-radiation is now the standard treatment of nasopharyngeal carcinoma. However, distant metastases remain the major cause of death. The purpose of this study was to evaluate the impact of neoadjuvant chemotherapy of 3 cycles or more on survival of patients with N2-3 nasopharyngeal carcinoma.

Methods: In this study, a total of 553 consecutive patients with non-metastatic N2-3 nasopharyngeal carcinoma were recruited. 102 patients with neoadjuvant chemotherapy of 3 cycles or more (NACT≥3 group) were matched 1:2:1 to 204 patients with neoadjuvant chemotherapy of 2 cycles (NACT=2 group) and 102 patients without neoadjuvant chemotherapy (NACT=0 group), according to age, N stage, histological subtype, neoadjuvant chemotherapy regimen. Five candidate variables (sex, T stage, concurrent chemotherapy, intensity-modulated radiation therapy and cycle number of neoadjuvant chemotherapy) were analyzed for association with survival.

Results: After matching, 5-year overall survival, 5-year disease-free survival, 5-year local-recurrence-free survival and 5-year distant-metastasis-free survival of NACT≥3 group were better than those of NACT=2 group and those of NACT=0 group. In multivariate analysis, sex, T stage and cycle number of neoadjuvant chemotherapy maintained statistical significance on 5-year overall survival (P values were 0.029, <0.001 and <0.001), 5-year disease-free survival (P values were 0.020, <0.001 and 0.002), 5-year local-recurrence-free survival (P values were 0.048, 0.001 and 0.002) and 5-year distant-metastasis-free survival (P values were 0.017, <0.001 and <0.001).

Conclusion: For N2-3 nasopharyngeal carcinoma, neoadjuvant chemotherapy of 3 cycles or more appeared to be an independent factor associated with improvement of survival.

Keywords: Neoadjuvent chemotherapy; Cycle number; Nasopharyngeal carcinoma; Overall survival; Disease-free survival; Local-recurrence-free survival; Distant-metastasis-free survival

Abbreviations: NPC: Nasopharyngeal Carcinoma; NACT: Neoadjuvant Chemotherapy; 5y-OS: 5-Year Overall Survival; 5y-DFS: 5-Year Disease-Free Survival; 5y-RFS: 5-Year Local-Recurrence-Free Survival; 5y-MFS: 5-Year Distant-Metastasis-Free Survival; IMRT: Intensity-Modulated Radiation Therapy; CCT: Concurrent Chemotherapy; HN-MRI: Magnetic Resonance Imaging of Head and Neck; G3/4: Grade 3 To 4; CTCAE V4.0: Common Terminology Criteria for Adverse Events Version 4.0; HR: Hazard Ratio; 95% CI: 95% Confidence Interval

Introduction

Nasopharyngeal carcinoma (NPC) is the most common cancer originating from the epithelial cells that cover the surface of nasopharynx [1]. It is a rare malignancy with an average incidence under 1 per 100,000 person-years except certain regions of East Asia and Africa, where the incidence may reach 80 per 100,000 person-years [2]. Due to anatomical complexity of NPC and its tendency to metastasize, radiotherapy instead of surgery is the mainstay of treatment [3]. Since advent of intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy (CCT), the 5-year overall survival of NPC has reached 83.0% now [4]. Unfortunately, distant metastases remain the major causes of failure [5]. More than 30% of patients with advanced loco-regional disease eventually died of distant failure [6]. Although meta-analysis showed neoadjuvant chemotherapy (NACT) could significantly reduce distant failures in head and neck squamous cell carcinoma and improve prognosis [7]. The roles of NACT in NPC remain uncertain though a series of phase II clinical trials have recently indicated that patients with 2-3 cycles of NACT before concurrent chemo-radiation had a trend of better survival than those without NACT [8]. It is known that the metastasis risk of NPC correlates with both T and N stage, but N stage is by far the most significant predicting factor [9]. Even after multimodality treatment based on IMRT plus CCT, stage N2-3 disease was proved to be an independent factor predicting a greater risk of distant failure and poor overall survival (5-year distant-metastasis rate, 35.2%) [10,11]. Clinical outcome of these patients might be further improved through eradicating metastases. However, the previous studies on NACT of NPC almost enrolled patients with Stage III-IVB diseases. There was no published study focusing on N2-3 NPC patients, or appropriate cycle number of NACT for them. Therefore, we performed a case-control pilot study to evaluate the impact of NACT of different cycles on survival of patients with N2-3 NPC.

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Materials and Methods

Patient selection

Patients with pathologically diagnosed and previously untreated NPC in our hospital from January 1st 2008 to December 31st 2009 were initially considered. The ones would be included if they had age younger than 70 years old and T1-4N2-3M0 NPC. Stage of all patients was determined through magnetic resonance imaging of head and neck (HN-MRI), whole-body bone scan and thoraco-abdominal computed tomography (or chest radiograph plus abdominal ultrasonography) and according to the Union Internationale Contre le Cancer/American Joint Cancer Committee TNM classification version 2002 [12]. After staging, 593 consecutive patients with N2-3 disease were enrolled into our study.

The exclusion criteria included: (i) Karnofsky performance score <80; (ii)severe dysfunction of heart, lung, liver or kidney; (iii) history of other malignancies; (iv) prior chemotherapy or radiotherapy; (v) distant metastases before or during radiotherapy. 40 patients were excluded for distant metastases before or during radiotherapy. Then a total of 553 patients with N2-3 non-metastatic NPC were eligible for this study. Among these patients, 102 cases received NACT of 3 cycles or more (NACT≥3 group) and were defined as the experimental group. 185 did not receive NACT (NACT=0 group) and 266 received NACT of 2 cycles (NACT=2 group). Through the frequency-matching technique, patients of the NACT≥3 group were then matched in a ratio of 1:2:1 to those of the NACT=2 group and the NACT=0 group, which were defined as the control groups. Patients were matched when they had the same histological subtype (squamous cell carcinoma vs. non-keratinizing carcinoma vs. undifferentiated carcinoma), the same N stage (N2 vs. N3), the same NACT regimen (docetaxel plus cisplatin vs. cisplatin plus 5-fluorouracil) and the closet age. If there were several cases fit for matching to the same patient, selection was made randomly. Investigators were blinded to oncological outcomes during the selection process. The whole procedure of enrollment of the patients was summarized in (Figure 1).

This study was approved by the ethics committee of our hospital. All patients signed informed consent before treatment and had detailed medical records.

Treatment strategy

In patients with NACT, NACT was administrated every 3 weeks with the first-line regimen comprised of docetaxel 75 mg/m^2 d1 plus cisplatin 75 mg/m^2 d1 or cisplatin 80 mg/m^2 d1 plus 5-fluorouracil 1000 mg/m^2 d1-4. If grade 3 to 4 (G3/4) blood, renal or hepatic disorder of Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) appeared, NACT was delayed until the disorder recovered to grade 1 or disappear, and the dose was decreased by 20% in the subsequent cycles. NACT was ceased if delay time reached 2 weeks. After 2 cycles of NACT, each patient in the NACT≥3 group underwent a HN-MRI to evaluate response of metastatic cervical

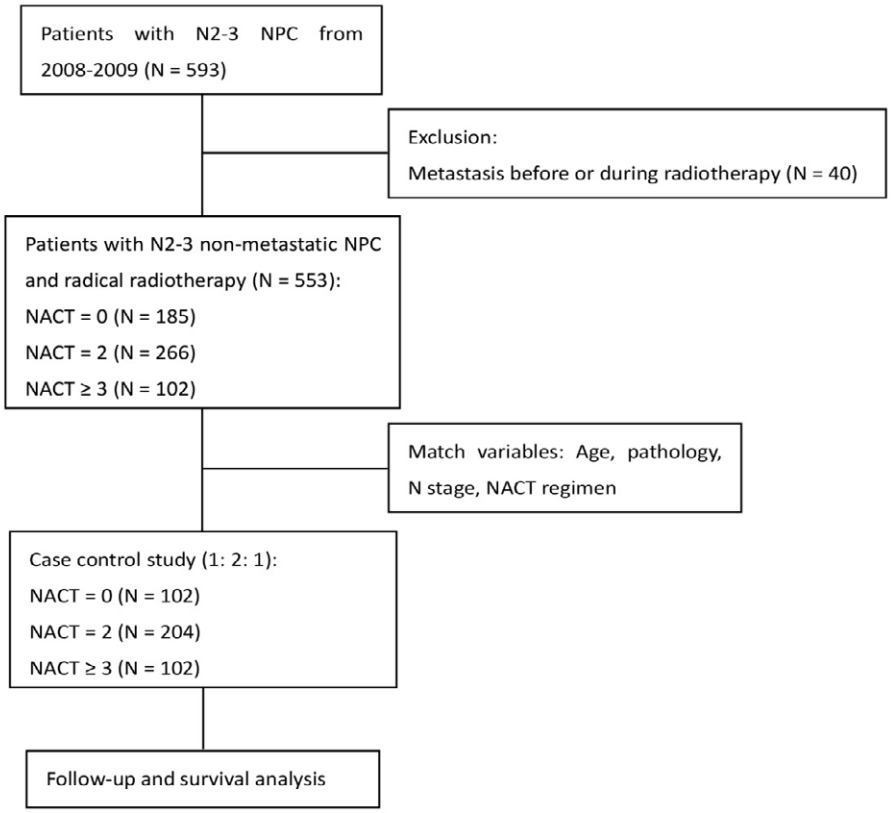

Figure 1: Flow chart of the study: 593 consecutive patients diagnosed with N2-3 nasopharyngeal carcinoma (NPC) in our hospital from Jan. 1st 2008 to Dec. 31st 2009 and age younger than 70-year-old were initially considered in this study. Patients with distant metastases before or during radiotherapy (n=40) were excluded. Finally a total of 553 patients were eligible. Of those, 102 patients with neoadjuvant chemotherapy (NACT) of three cycles or more (NACT≥3 group) were then matched 1:2:1 to 204 patients with NACT of two cycles (NACT=2 group) and 102 patients without NACT (NACT=0 group), according to age, N stage, histological subtype and NACT regimen.

lymph nodes. NACT was continued if a partial remission was attained, or was terminated if stable or progression disease and concurrent chemo-radiation was started instead. NACT was ceased after 3 cycles if lymph nodes became impalpatable. If not, one more cycle of NACT (4 cycles in total) was applied.

Regimen of CCT was single-agent cisplatin 40 mg/m^2 weekly or 80 mg/m^2 every 3 weeks throughout the whole procedure of radiotherapy. No patient in this study received adjuvant chemotherapy or monoclonal antibodies.

All patients underwent radical radiotherapy in the hospital. The target definition, delineation and dosage of radiotherapy were based on the standard of our hospital [13]. Conventional 2-dimensional radiotherapy consisted of two lateral opposing facio-cervical fields to cover nasopharynx and the upper cervical lymphatic drainage region, and a lower anterior cervical field to cover the lower cervical region. After a dose of 36-40Gy irradiated, two opposing lateral preauricular fields were used for the primary region, and anterior split neck fields were used for the cervical region instead. The primary tumor was given a total dose of 60-78Gy, according to the tumor remission rate. In IMRT, a total dose of 66-72Gy was given to the gross tumor of nasopharynx, 60-70Gy to the positive neck lymph nodes, 60Gy to the high-risk region, and 50-54Gy to the prophylactic irradiation region.

Follow-up

Patients were followed up after treatment by telephone, letters or outpatient interview. The intervals were 3 months for the first 3 years, 6 months for the 4th and 5th years, and 1 year for 5 years after. Follow-up was made until death from NPC or December 31st 2014, whichever came first. Causes of deaths were confirmed by death certificates, which were supplemented with medical records if necessary.

The primary endpoint of this study was overall survival. And secondary endpoints included disease-free survival, local-recurrence-free survival and distant-metastasis-free survival.

Statistical analysis

Distribution of the baseline clinical characteristics except matching variables between the NACT≥3 group and the NACT≤2 group (patients with NACT of two cycles or less, including the NACT=2 group and the NACT=0 group) was assessed by the Chi-square test. Calculation of survival was made by a life-table method with the date of diagnosis defined as the starting point. Sex (Male vs. Female), T stage (T1-2 vs. T3-4), CCT (Yes vs. No), IMRT (Yes vs. No) and NACT cycle (0, 2 vs. ≥3) were candidate variables for survival analysis. Each of them was first put into univariate survival analysis by Kaplan-Meier approach to test whether it was a possible risk factor associated with survival. Differences in survival were assessed by a log-rank test. Multiple comparisons were made among the NACT≥3 group, the NACT=2 group and the NACT=0 group. Then all the variables above went through the multivariate analysis based on Cox proportional hazards models. And hazard ratio (HR) and 95% confidence interval (95% CI) of each variable were calculated. The ones which maintained statistical significance were determined to be the independent prognostic factors.

The whole procedure of statistical analysis was made by SPSS Statistics 19.0 (SPSS Inc.). A difference with two-sided P value of less than 0.05 was considered to be statistically significant.

Results

Baseline clinical characteristics

The median follow-up time of the study patients was 65 months (range, 5-84 months). The results of Chi-square test were shown in (Table 1). The NACT≤2 group had more patients who received CCT (69.3% vs. 57.8%, P=0.034), compared with the NACT≥3 group. There was no difference on distribution of sex, T stage and IMRT application between the NACT≥3 group and the NACT≤2 group.

Treatment result and survival analysis

In the 102 patients of the NACT≥3 group, 85 patients received NACT of 3 cycles and 17 patients received NACT of 4 cycles.

A total of 87 patients died, in which 76 cases died of NPC. 27 cancer deaths were from the 102 patients of NACT=0 group (26.5%). 42 were from the 204 patients of NACT=2 group (20.6%). And 7 were from the 102 patients of NACT≥3 group (6.9%). 85 patients showed local recurrence, including 27 cases from the 102 patients of NACT=0 group (26.5%), 48 from the 204 patients of NACT=2 group (23.5%) and 10 from the 102 patients of NACT≥3 group (9.8%). And 99 patients showed distant metastasis, including 35 cases from the 102 patients of NACT=0 group (34.3%), 53 from the 204 patients of NACT=2 group

	NACT≤2			NACT≥3	X^2	P Value
	NACT=0	NACT=2	Total			
Age						
< 50	68	138	206	73		
≥ 50	34	66	100	31		
Sex						
Female	36	55	91	22	0.129	0.808
Male	66	149	215	80		
Pathology						
Squamous cell carcinoma	2	4	6	2		
Non-keratinizing carcinoma	5	10	15	5		
Undifferentiated carcinoma	95	190	285	95		
T Stage						
T1-2	26	47	73	30	1.251	0.263
T3-4	76	157	233	72		
N Stage						
N2	65	130	195	65		
N3	37	74	111	37		
NACT* Regimen						
DP†	0	102	102	51		
PF‡	0	102	102	51		
CCT$						
No	0	94	94	43	4.487	0.034
Yes	102	110	212	59		
IMRT#						
No	48	133	181	53	1.617	0.206
Yes	54	71	125	49		
Grade 3/4 myelosuppression						
No	80	165	245	83	0.083	0.886
Yes	22	39	61	19		
Grade 3/4 mucositis/ matitis						
No	77	188	265	92	0.904	0.391
Yes	25	16	41	10		

*NACT=Neoadjuvant Chemotherapy; † DP=Docetaxel+Cisplatin; ‡ PF=Cisplatin+Flurouracil; $ CCT=Concurrent Chemotherapy; # IMRT=Intensity-modulated Radiotherapy.

Table 1: Baseline clinical characteristics of the study population.

(26.0%) and 11 from the 102 patients of NACT≥3 group (10.8%). Treatment results were shown in (Figure 2).

Survivals calculated by life-table method according to clinical stages and cycle number of NACT were summarized in (Table 2). Through univariate analysis, patients applied NACT of three cycles or more (90.0% vs. 75.6% vs. 68.6%, P=0.001) appeared to have better 5-year overall survival (5y-OS). Female patients (77.9% vs. 67.5%, P=0.043), patients with T1-2 disease (78.6% vs. 67.5%, P=0.034) and patients applied NACT of three cycles or more (82.8% vs. 66.6% vs. 61.2%, P=0.001) had better 5-year disease-free survival (5y-DFS). Patients applied NACT of three cycles or more (87.0% vs. 72.9% vs. 68.7%, P=0.006) had better 5-year local-recurrence-free survival (5y-RFS). Female patients (80.5% vs. 70.2%, P=0.042), patients with T1-2 disease (82.5% vs. 69.8%, P=0.015) and patients applied NACT of three cycles

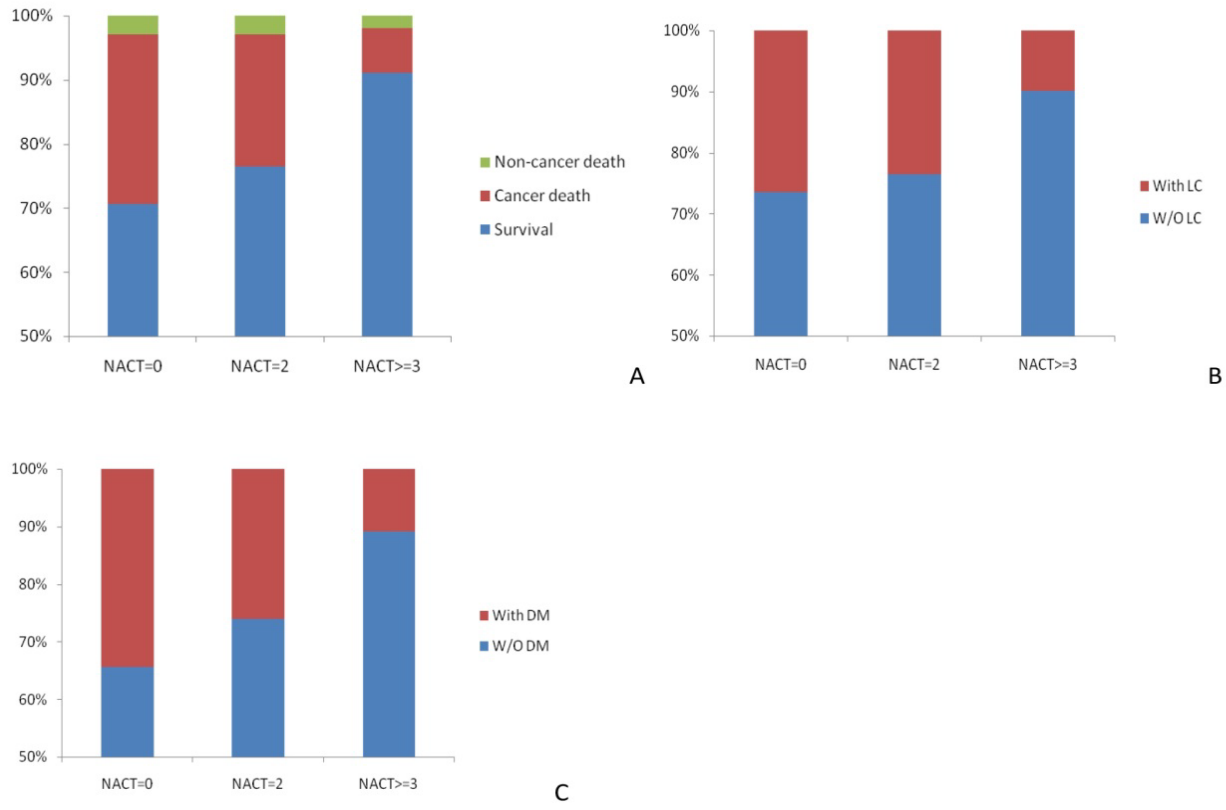

Figure 2: Treatment result according to cycles of neoadjuvant chemotherapy (NACT):
Panel A: 76 patients showed cancer death. 27 cancer deaths were from the 102 patients of NACT=0 group (26.5%). 42 were from the 204 patients of NACT=2 group (20.6%). And 7 were from the 102 patients of NACT≥3 group (6.9%).
Panel B: 85 patients showed local recurrence. 27 local recurrences were from the 102 patients of NACT=0 group (26.5%). 48 were from the 204 patients of NACT=2 group (23.5%). And 10 were from the 102 patients of NACT≥3 group (9.8%).
Panel C: 99 patients showed distant metastasis. 35 distant metastases were from the 102 patients of NACT=0 group (34.3%). 53 were from the 204 patients of NACT=2 group (26.0%). And 11 were from the 102 patients of NACT≥3 group (10.8%).

		5-year survival (%)			
		OS*	DFS†	RFS$	MFS#
All Patients		77.6	69.4	75.4	72.1
T Stage	T1	100	92.0	92.0	100
	T2	81.3	75.5	79.8	78.8
	T3	80.7	72.4	77.9	74.8
	T4	64.9	55.0	62.0	56.9
N Stage	N2	83.3	74.7	79.8	78.7
	N3	67.3	59.9	67.5	60.5
Clinical Stage	III	88.3	79.8	84.6	84.1
	IV	67.8	60.0	67.0	61.3
NACT Cycles	NACT=0	68.6	61.2	68.7	61.1
	NACT=2	75.6	66.6	72.9	70.5
	NACT≥3	90.0	82.8	87.0	85.9

* OS=Overall Survival; † DFS=Disease-free Survival; $ RFS=Local-recurrence-free Survival; # MFS=Distant-metastasis-free Survival.

Table 2: Survival of the patients according to stages and cycles of neoadjuvant chemotherapy (NACT).

or more (85.9% vs. 70.5% vs. 61.1%, P<0.001) had better 5-year distant-metastasis-free survival (5y-MFS). Results of univariate analysis were shown in (Table 3).

Multiple comparisons among the NACT≥3 group, the NACT=2 group and the NACT=0 group were made (Figure 3). The 5y-OS, 5y-DFS, 5y-RFS and 5y-MFS of the NACT≥3 group were all better than those of the NACT=2 group (P values were 0.002, 0.002, 0.005 and 0.002) and the NACT=0 group (P values were <0.001, <0.001,

		5y-OS (%)	*P* Value	5y-DFS (%)	*P* Value	5y-RFS (%)	*P* Value	5y-MFS (%)	*P* Value
Sex	Female	85.0	0.054	77.9	0.043	82.3	0.085	80.5	0.042
	Male	76.3		67.5		74.2		70.2	
T stage	T1-2	85.4	0.057	78.6	0.034	81.6	0.153	82.5	0.015
	T3-4	76.3		67.5		74.8		69.8	
NACT	≥ 3	90.0	0.001	82.8	0.001	87.0	0.006	85.9	<0.001
	2	75.6		66.6		72.9		70.5	
	0	68.6		61.2		68.7		61.1	
CCT	Yes	78.8	0.930	73.7	0.299	76.6	0.960	76.6	0.246
	No	78.6		68.6		76.4		71.2	
IMRT	Yes	80.7	0.518	70.5	0.951	78.0	0.587	73.3	0.880
	No	77.5		70.0		75.6		72.7	

Table 3: Result of univariate analysis on 5-year overall survival (5y-OS), 5-year disease-free survival (5y-DFS), 5-year local-recurrence-free survival (5y-RFS) and 5-year distant-metastases-free survival (5y-MFS).

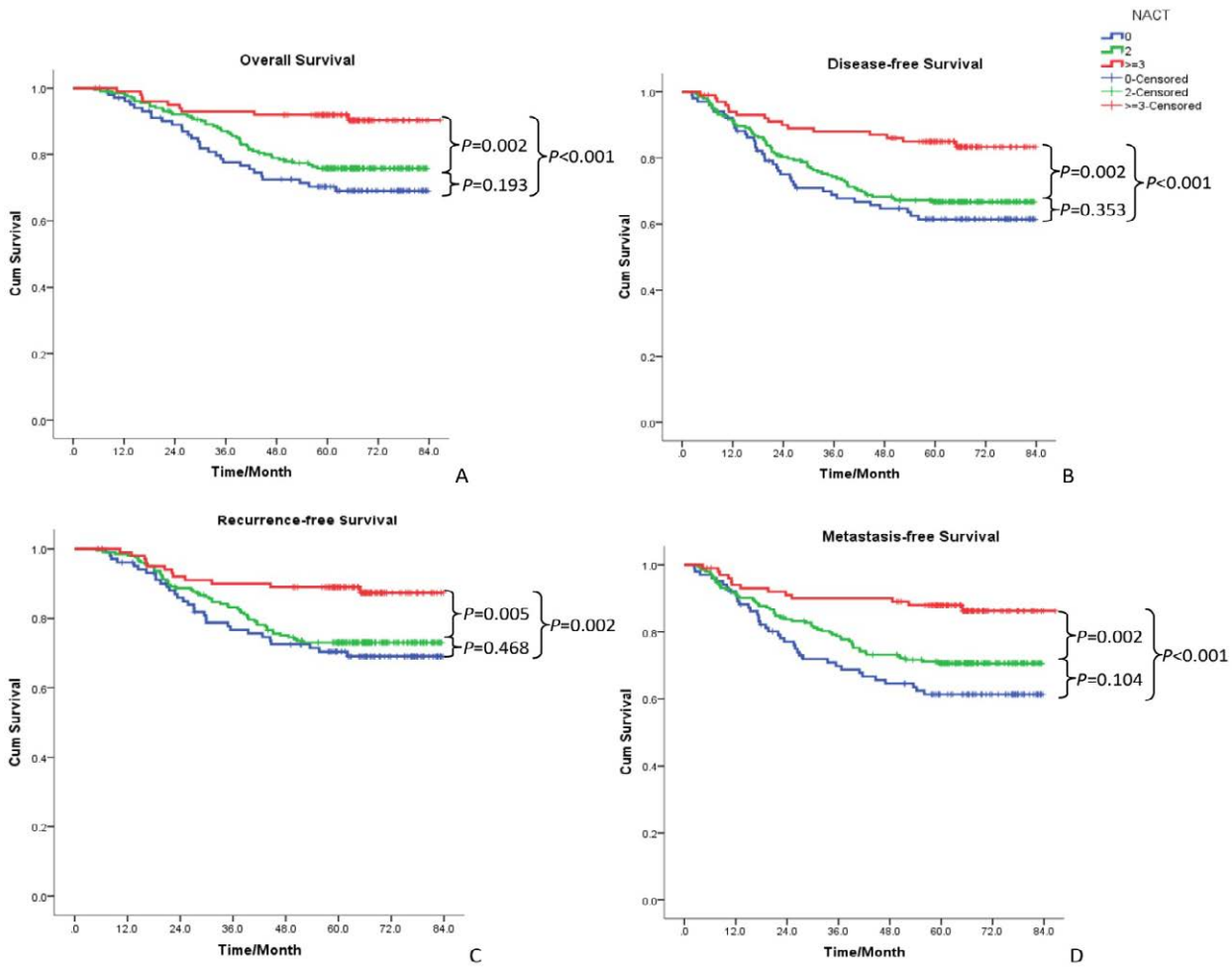

Figure 3: Survival curves of patients without neoadjuvant chemotherapy (NACT), with NACT of 2 cycles and 3 cycles or more:
Panel A: Survival curves of 5-year overall survival (5y-OS).
Panel B: Survival curves of 5-year disease-free survival (5y-DFS).
Panel C: Survival Curves of 5-year local-recurrence-free survival (5y-RFS).
Panel D: Survival curves of 5-year distant-metastasis-free survival (5y-MFS). The 5y-OS, 5y-DFS, 5y-RFS and 5y-MFS of the NACT≥3 group were all better than those of the NACT=2 group (P values were 0.002, 0.002, 0.005 and 0.002) and the NACT=0 group (P values were <0.001, <0.001, 0.002 and <0.001). Significant differences were not seen between the NACT=2 group and the NACT=0 group on 5y-OS, 5y-DFS, 5y-RFS or 5y-MFS.

	Factor	*P* Value	B	HR*	95% CI† for HR
5y-OS	**Sex**	0.029	0.592	1.808	1.061-3.083
	T Stage	<0.001	0.544	1.724	1.274-2.332
	NACT	<0.001	-0.408	0.665	0.536-0.824
	CCT	0.116	-0.448	0.642	0.370-1.116
	IMRT	0.670	-0.104	0.901	0.559-1.453
5y-DFS	**Sex**	0.020	0.528	1.696	1.088-2.644
	T Stage	<0.001	0.479	1.614	1.254-2.078
	NACT	0.002	-0.280	0.756	0.636-0.898
	CCT	0.604	-0.123	0.885	0.557-1.406
	IMRT	0.971	-0.007	0.993	0.669-1.473
5y-RFS	**Sex**	0.048	0.500	1.648	1.003-2.706
	T Stage	0.001	0.485	1.625	1.220-2.164
	NACT	0.002	-0.313	0.731	0.598-0.894
	CCT	0.180	-0.354	0.702	0.419-1.177
	IMRT	0.707	-0.087	0.917	0.584-1.440
5y-MFS	**Sex**	0.017	0.573	1.774	1.107-2.841
	T Stage	<0.001	0.555	1.741	1.332-2.277
	NACT	<0.001	-0.350	0.705	0.587-0.846
	CCT	0.495	-0.172	0.842	0.514-1.379
	IMRT	0.950	-0.013	0.987	0653-1.493
*HR = Hazard Ratio †CI = Confidence Interval					

Table 4: Result of multivariate analysis on 5-year overall survival (5y-OS), 5-year disease-free survival (5y-DFS), 5-year local-recurrence-free survival (5y-RFS) and 5-year distant-metastases-free survival (5y-MFS).

0.002 and <0.001). Significant differences were not seen between the NACT=2 group and the NACT=0 group on 5y-OS, 5y-DFS, 5y-RFS or 5y-MFS.

(Table 4) was a summary of the multivariate analysis by Cox model on 5y-OS, 5y-DFS, 5y-RFS and 5y-MFS. The candidate variables included were the same to univariate analysis. Female, T1-2 and NACT of three cycles or more maintained statistical significance on 5y-OS (P values were 0.029, <0.001 and <0.001), 5y-DFS (P values were 0.020, <0.001 and 0.002), 5y-RFS (P values were 0.048, 0.001 and 0.002).and 5y-MFS (P values were 0.017, <0.001 and <0.001). Thus, NACT of three cycles or more appeared to be an independent factor associated with improvement of 5y-OS (HR 0.665, 95% CI 0.536-0.824), 5y-DFS (HR 0.756, 95% CI 0.636-0.898), 5y-RFS (HR 0.731, 95% CI 0.598-0.894) and 5y-MFS (HR 0.705, 95% CI 0.587-0.846).

Acute toxicity

Evaluation of acute toxicity was made on basis of CTCAE v4.0. There was no grade 5 toxicity during treatment. The most common G3/4 adverse events were myelosuppression, mucositis and mastitis. There was no significant difference between the NACT≥3 group and the NACT≤2 group on number of patients with G3/4 myelosuppression, or mucositis plus mastitis.

Discussion

Distant metastases have emerged as the main obstacles to successful treatment of loco-regionally advanced NPC these days, especially those with N2-3 disease. The 5-year distant-metastasis rate of patients with N2-3 NPC was still as high as 35.2% after IMRT plus CCT and 51.4% of the distant metastases happened within one year [11]. Though circulating tumor cells (CTC) could shed from primary tumor and metastatic lymph nodes before, during or after treatment to form micrometastases. We inferred that subclinical micrometastases were already present before treatment starting in most cases with distant metastases shortly after removal of primary tumor and metastatic lymph nodes. Hence, it was more appropriate to consider N2-3 NPC as a systemic disease instead of a local disease. The intensity of CCT which aimed to enhance radiosensitivity of primary lesion and regional lymph nodes might not be effective enough for control of the pre-existing micrometastases. And more intensive systemic therapy such as NACT might be needed.

Attempts had been made on modifying timing of chemotherapy to neoadjuvant-concurrent sequence. Evidences on necessity of NACT for loco-regionally advanced NPC were increasing. In a recent phase II trial of Hui et al, two cycles of NACT improved the 3-year overall survival (94.1% vs. 67.7%, P=0.012) in patients with Stage III-IV NPC [14]. Nevertheless, improvement of survival was not showed in Lee's trial in patients with Stage III-IVB diseases, or Tan's trial in patients with T3-4NxM0 or TxN2-3M0 diseases [15,16]. There were still many controversies on NACT such as suitable patients and appropriate cycle number. It was demonstrated that in solid tumors there was a positive correlation between classical markers reflecting tumor burden such as N stage and level of CTC, which could form micrometastases [17-20]. Therefore, NPC patients with late N stage (N2-3) were more susceptible to micrometastases and might be more suitable for NACT, especially NACT of more intensity. The main objective of this study was to find out the association between cycle number of NACT and prognosis of N2-3 NPC patients.

Cumulative dose of concurrent chemotherapy was proved to have a prognostic implication in patients with head and neck squamous cell carcinomas [21]. A study of Loong et al also proved that Stage II-IVB NPC patients who received concurrent chemotherapy with cisplatin of cumulative dose more than 200 mg/m^2 had significantly better overall survival [22]. For NACT, prolonged cycles (4-6 cycles) were proved to be effective for controlling distant metastasis and improving clinical outcome of some solid tumors such as gynecologic cancer and breast cancer, which were known as systemic diseases [23,24].

After matching on well-known confounding prognostic factors such as N stage [9], we demonstrated in this study that NACT of three cycles or more was an independent protective factor for overall survival, disease-free survival, local-recurrence-free survival and distant-metastasis-free survival in patients with N2-3 non-metastatic NPC. Even though more patients with NACT of two cycles and without NACT received CCT, which was proved to improve clinical outcome of loco-regionally advanced NPC; 5y-OS, 5y-DFS, 5y-RFS and 5y-MFS were all better in patients with NACT of three cycles or more than those with NACT of two cycles and without NACT. The difference of 5y-MFS was especially great (85.9% vs. 70.5% vs. 61.1%, P<0.001). It strongly suggested that N2-3 NPC was a systemic disease rather than a local disease. Actually, although the differences in 5y-OS, 5y-DFS, 5y-RFS and 5y-MFS between patients with NACT of two cycles and those without NACT did not attain statistical significance, there was a trend of improvement (differences were 7.0%, 5.4%, 4.2%, 9.4%, respectively). The differences in survival might thus be magnified by increasing cycles of NACT. Encouragingly, there was an obvious improvement of 5y-OS, 5y-DFS, 5y-RFS and 5y-MFS in patients with NACT of three cycles or more, compared with those who did not receive NACT (differences were 21.4%, 21.6%, 18.3%, 24.8%, respectively). It confirmed our hypothesis that NACT of three cycles or more could reduce metastasis and further improve survival of those patients.

This study was the first study focusing on NACT in N2-3 NPC patients and impact of the cycle number on survival of those patients. However, it still had several limitations. First, although patients were followed up prospectively collected to avoid missing of data,

retrospective nature of this study might bring selection bias. For example, patients' choice of NACT regimen largely depended on their socioeconomic status, which might also affect prognosis. Matching on NACT regimen could reduce its influence. Second, tumor volume and some functional factors, such as circulating cell-free DNA of Epstein-Barr virus and epidermal growth factor receptor expression, could be important for prediction of distant metastasis and should be considered. These factors were not included in this study largely subject to laboratory conditions at that time. Third, proportion of CCT application was not balanced among the NACT≥3 group, the NACT=2 group and the NACT=0 group, which might be a confounding factor in the process of survival analysis. A randomized controlled clinical trial is now being prepared to validate the conclusion from this study.

In conclusion, NACT of three cycles or more before radical radiotherapy of patients with N2-3 NPC appeared to be an independent factor associated with improvement of clinical outcome in this study. This finding may be informative for clinicians to conduct clinical trials and direct treatment strategies though further validation is needed.

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