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Research Paper

Decreased Overall and Cancer-Specific Mortality with Neoadjuvant Chemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma Treated by Intensity-modulated Radiotherapy: Multivariate Competing Risk Analysis

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Abstract

Background: Value of neoadjuvant chemotherapy (NACT) is still controversial in locoregionally advanced nasopharyngeal carcinoma (LA-NPC). Based on competing risk analysis model, we aim at evaluating the efficacy of NACT in decreasing cancer-specific mortality for LA-NPC (except T3-4N0) treated by intensity-modulated radiotherapy (IMRT).

Methods: Data on 957 patients with LA-NPC were retrospectively reviewed. The cumulative incidence of cancer-specific and non-cancer-specific (competing) mortality was determined by univariate and multivariate competing risk analysis.

Results: 542 (56.6%) patients received NACT using docetaxel with cisplatin (TP) or fluorouracil with cisplatin (PF) regimens. The median follow-up duration was 57.23 months (range, 1.27-78.53 months). In total, 161/957 (16.8%) patients died, with 140 cancer-specific and 21 non-cancer-specific deaths were observed, respectively. In univariate analysis, the 3- and 5-year cumulative cancer-specific mortality rates for NACT vs. non-NACT group were 8.58% vs. 7.32% and 14.74% vs. 14.52% (P = 0.95), respectively. With regard to competing mortality, the 3- and 5-year cumulative rates (0.93% vs. 1.22% and 1.31% vs. 3.06%; P = 0.196) were comparable between the two groups. Multivariate competing risk analysis established NACT as an independent prognostic factor in decreasing cancer-specific mortality (HR, 0.681; 95% CI, 0.488-0.951; P = 0.016) and overall mortality (HR, 0.654; 95% CI, 0.471-0.909; P = 0.011).

Conclusions: NACT may be a powerful approach in decreasing cancer-specific mortality and overall mortality in LA-NPC treated by IMRT, and our findings would strengthen the role of NACT.

Key words: Nasopharyngeal carcinoma; competing risk analysis; neoadjuvant chemotherapy; cancer-specific mortality; competing mortality; intensity-modulated radiotherapy.

Introduction

As a special kind of head and neck cancer, nasopharyngeal carcinoma (NPC) has an extremely unbalanced geographic distribution. Worldwide, 86,500 cases of NPC were reported in 2012 and 71% of new cases were in east and southeast parts of Asia including south China [1]. Due to the anatomic constrains, surgery is not readily accessible for NPC. Therefore, radiotherapy (RT) has been the unique and curative treatment for NPC as a result of radiation sensitivity. NPC is also sensitive to chemotherapy, and incorporation of standard RT with chemotherapy could achieve better therapeutic outcomes for patients with advanced NPC compared with RT alone [2-6]. With the advent of intensity-modulated radiotherapy (IMRT), distant metastasis has emerged as the predominant treatment failure for patients with advanced NPC [7-9]. Thus, there has been a renewed interest in the re-exploration of neoadjuvant chemotherapy (NACT) [10-16] as it may reduce distant metastasis and improve overall survival. Regretfully, no phase III trial has achieved an overall survival benefit except our recent study using neoadjuvant docetaxel plus cisplatin with fluorouracil (TPF) [17]. Therefore, value of other regimens in advanced NPC still needs to be characterized.

There may be four kinds of final clinical outcomes for patients with malignant tumor after treatment: cancer-specific mortality, non-cancer-specific mortality, survival or lost to follow-up. This could also apply to NPC. In practice, medical researches may find interest in nature and time of a particular event, cancer-specific mortality for example, and the other events are considered in competition with the event of interest. In this case, Kaplan-Meier method may be inappropriate because it treats competing events as independent censorings and overestimates the proportion of cancer-specific death. Therefore, the cumulative incidence function (CIF) [18] could be used since it takes into account the informative nature of the censoring and corresponds to the probability of occurrence of a particular event without the assumption of independence between event types.

The competing risk analysis has been widely used in cancer research like breast cancer [19], ovarian cancer [20], brain metastasis cancer [21] and kidney cancer [22]. However, to the best of our knowledge, no relative study about NPC has been reported. Given the truth that we still lack strong evidence of NACT in prolonging overall survival, we conducted this study to elucidate whether NACT using less effective regimens could decrease cancer-specific mortality or not based on competing risk analysis in locoregionally advanced NPC (LA-NPC).

Materials and Methods

Patient Selection

We retrospectively reviewed data on patients with newly diagnosed stage I-IVB NPC who were treated at Sun Yat-sen university cancer center between November 2009 and March 2012. The including criteria for this study were as follows: (1) World Health Organization (WHO) pathology type II/III; (2) stage III-IVB NPC (except T3-4N0); (3) with the data of pre-treatment Epstein-Barr virus (EBV) DNA (pre-DNA); (4) age 18 years or older. This study was approved by the Research Ethics Committee of Sun Yat-sen university cancer center. Informed consent was obtained from all the patients before treatment.

Clinical Staging workup

Prior to treatment, the medial history of patients were completed. Clinical examinations of the head and neck region, direct fibre-optic nasopharyngoscopy, magnetic resonance imaging (MRI), chest radiography, whole-body bone scan and abdominal sonography were conventionally performed. Positron emission tomography (PET)-CT was also carried out if clinically indicated. Tumour-related markers like pre-DNA were quantified. All patients received a dental evaluation before RT.

All patients were staged according to the 7th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) system [23]. All radiographic materials and clinical records were reviewed to minimize heterogeneity in restaging. Two radiologists (L.Z.L. and L.T.) employed at our hospital separately evaluated all of the scans and disagreements were resolved by consensus.

Real-time quantitative EBV DNA PCR

Plasma EBV DNA load was measured before treatment and plasma DNA was extracted and assayed using real-time quantitative PCR which was described previously [24]. Briefly, the real-time quantitative PCR system targeted the *BamH*I-W region of the EBV genome using primers 5′-GCCAGAGGTAAGTGGACTTT-3′ and 5′-TACC ACCTCCTCTTCTTGCT-3′. The dual fluorescence-labelled oligomer 5′-(FAM) CACACCCAGGCA CACACTACACAT (TAMRA)-3′ served as a probe.

Sequence data for the EBV genome were obtained from the GeneBank sequence database.

Treatment

All the patients received IMRT at Sun Yat-sen university cancer center. The prescribed doses were 66-72Gy at 2.12-2.43 Gy/fraction to the planning target volume (PTV) of the primary gross tumour volume (GTVnx), 66-70Gy to the PTV of the GTV of the positive lymph nodes (GTVnd), 60-63Gy to the PTV of the high-risk clinical target volume (CTV1), and 54–56Gy to the PTV of the low-risk clinical target volume (CTV2). All targets were treated simultaneously using the simultaneous integrated boost technique. NACT was mainly performed for patients with advanced N (N2-3) or T4 category disease to reduce micrometastasis and shrink tumor volume, and consisted of cisplatin (80 mg/m^2) with 5-fluorouracil (750-1000 mg/m^2) (PF), docetaxel (75 mg/m^2) with cisplatin (75 mg/m^2) (TP) every three weeks for two or more cycles. However, NACT would also be considered if patients had to wait a long interval before radiotherapy. Concurrent chemotherapy was cisplatin weekly (40 mg/m^2) for at least 4-7 cycles or on weeks 1, 4 and 7 (80-100 mg/m^2) of radiotherapy. Treatment was reduced or stopped in cases of unacceptable toxicity or at the patient's request.

Follow-Up and Statistical Analysis

Follow-up was measured from first day of therapy to last examination or death. Patients were followed by MRI and plasma EBV DNA at least every 3 months during first 2 years, then every 6 months thereafter (or until death). The only end point (time to first defining event) was overall survival (OS), including cancer-specific death, non-cancer-specific death, survival or lost to follow-up. We treated survival and lost to follow-up patients as censored data. Therefore, there were three kind of survival status in analysis: cancer-specific mortality, non-cancer-specific mortality (i.e. competing mortality) and censored data.

The Chi-square or non-parametric test was used to compare clinical characteristics between NACT and non-NACT groups. Factors entered into analysis included age (continuous variable), gender, lactate dehydrogenase (LDH) (continuous variable), NACT, T category, N category, overall stage, smoking, drinking and pre-DNA (continuous variable). The cumulative incidence of cancer-specific mortality and competing mortality was determined by univariate and multivariate competing risk analysis. Cox proportional hazards models for competing risks according to Fine and Gray [25] were used to study combined effects of the variables on overall mortality, cancer-specific mortality and competing mortality. The analysis was performed under the R 3.3.0 software. Significance was set at $P < 0.05$ (2-sided).

Results

Patient Characteristics

In total, 957/1811 (52.8%) consecutive patients meeting the criteria were recruited for this study. Of the whole cohort, the male (721)-to-female (236) ratio was 3.1, and the median age was 45 years (range, 18-78 years). NACT was delivered to 542 (56.6%) patients, with 444 (82.0%) patients receiving TP regimen and 98 (18%) patients receiving PF regimen. Additionally, 159/957 (16.6%) patients did not receive concurrent chemotherapy (CRT), of whom 113/159 (71.1%) received NACT. The median cumulative cisplatin dose during CCRT for non-NACT and NACT groups were 200 mg/m^2 (range, 0-320) and 200 mg/m^2 (range, 0-300), respectively (P = 0.152). The omitting of chemotherapy for the other 46/159 (28.9%) patients in non-NACT group was mainly attributed to the comorbidities like liver or kidney disease (32 of 46, 69.6%). Moreover, 14/46 (30.4%) patients with age more than 65 years were given RT alone according to clinicians' decision. The baseline characteristics were summarized in Table 1. Obviously, patients receiving NACT had higher percentages of advanced disease (T3-4, N3 and stage IV) and higher pre-DNA level than that of patients not receiving NACT.

Survival data

Up to the last follow-up (April 2, 2016), 77/957 (8.0%) patients were lost to follow-up. The median follow-up duration was 57.23 months (range, 1.27-78.53 months) for the entire cohort and 59.26 months (range, 28.4-78.53 months) for the survival patients. In total, 161/957 (16.8%) patients died, with 140 cancer-specific deaths and 21 non-cancer-specific deaths were observed, respectively. With regard to non-cancer-specific death, 8/21 (38.1%) patients died from treatment-related comorbidities, 3/21 (14.3%) patients died from cardiovascular disease, 4/21 (19.0%) patients died from accident and the cause of death for the other 6/21 (28.6%) patients remained unknown. Notably, among the survival patients, 40/719 (5.6%) patients experienced locoregional failure, 24/719 (3.3%) patients developed distant metastasis and 9/719 (1.3%) patients suffered both locoregional and distant failure.

Table 1. Baseline Characteristics of 957 patients with LA-NPC (except T3-4N0).

Characteristics	NACT	Non-NACT	*P*
	No. (%)	No. (%)	
Age (y, median)	45 (18-78)	46 (18-78)	0.092[a]
Gender			0.723[b]
Male	406 (74.9)	315 (75.9)	
Female	136 (25.1)	100 (24.1)	
LDH (U/L, median)	175 (100-1632)	171 (84-564)	0.007[a]
T category [c]			< 0.001[b]
T1	22 (4.0)	22 (5.3)	
T2	41 (7.6)	19 (4.6)	
T3	299 (55.2)	309 (74.4)	
T4	180 (33.2)	65 (15.7)	
N category [c]			< 0.001[b]
N1	314 (57.9)	280 (67.5)	
N2	123 (22.7)	103 (24.8)	
N3	105 (19.4)	32 (7.7)	
Overall stage [c]			< 0.001[b]
Ⅲ	279 (51.5)	322 (77.6)	
Ⅳ	263 (48.5)	93 (22.4)	
CRT			< 0.001[b]
Yes	429 (79.2)	369 (88.9)	
No	113 (20.8)	46 (11.1)	
Smoking			0.477[b]
Yes	216 (39.9)	156 (37.6)	
No	326 (60.1)	259 (62.4)	
Drinking			0.682[b]
Yes	67 (12.4)	55 (13.3)	
No	475 (87.6)	360 (86.7)	
Pre-DNA (copies/ml, median)	9450 (0-3710000)	1830 (0-6710000)	< 0.001[a]
Mortality			0.244[b]
Cancer-specific	79 (89.8)	61 (83.6)	
Non-cancer-specific	9 (10.2)	12 (16.4)	

Abbreviations: LA-NPC = locoregionally advanced nasopharyngeal carcinoma; NACT = neoadjuvant chemotherapy; LDH = lactate dehydrogenase; CRT = concurrent chemotherapy; Pre-DNA = pre-treatment Epstein-Barr virus DNA.

[a] *P*-values were calculated by Non-parametric test.

[b] *P*-values were calculated by Chi-square test or Fisher exact test if indicated.

[c] According to the 7th AJCC/UICC staging system.

Univariate competing risk analysis

In this univariate analysis, the 3- and 5-year cumulative cancer-specific mortality rates for NACT group vs. non-NACT group were 8.58% vs. 7.32% and 14.74% vs. 14.52% (P = 0.95; Figure 1), respectively. With regard to competing mortality, the 3- and 5-year cumulative rates (0.93% vs. 1.22% and 1.31% vs. 3.06%; P = 0.196; Figure 1) were comparable between the NACT and non-NACT groups. Therefore, compared with non-NACT group, the NACT group was not associated with significantly decreased 3- and 5-year cumulative overall mortality rates (9.51% vs. 8.53% and 16.05% vs. 17.58%; P = 0.86). Obviously, N category (P < 0.001) and overall stage (P < 0.001) correlates with cancer-specific mortality, but both were not associated with competing mortality (P = 0.861 and 0.066, respectively; Figure 2 and Figure 3).

Multivariate competing risk analysis

Given the truth that many prognostic factors were not balanced between these two groups, a multivariate Cox proportional hazards model was performed with considering death as a competing and adjusting for host, tumor and treatment factors. After adjusting for various factors, NACT was found to be an independent prognostic factor in decreasing cancer-specific mortality (HR, 0.681; 95% CI, 0.488-0.951; P = 0.016) and overall mortality (HR, 0.654; 95% CI, 0.471-0.909; P = 0.011, Table 2). Intriguingly, overall stage was found to be associated with competing mortality (HR, 2.932; 95% CI, 1.114-7.720; P = 0.029).

Discussion

To the best of our knowledge, our study was the first one to apply competing risk analysis model in investigating the prognostic value of NACT in LA-NPC treated by IMRT. Based on this model, we clarified that patients with LA-NPC could benefit from neoadjuvant TP or PF regimens, and this benefit mainly originated from decreased cancer-specific mortality which would result in a decreased overall mortality. Our findings were similar to the results of a pooled data analysis of two randomized trials carried out by Chua *et al.* [26]. No substantial relationship between this treatment modality and competing mortality was observed. Consequently, our findings provided a new insight into understanding the value of NACT in stage III-IVB (except T3-4N0) NPC, and this may strengthen the role of NACT in clinical practice.

The outcome of univariate analysis revealed the NACT group had similar cancer-specific mortality and overall mortality rate as the non-NACT group. However, multivariate analysis showed a significant difference of both cancer-specific and overall mortality between the two groups. This was mainly attributed to that the NACT group had a higher percentage of advanced stage and higher pre-DNA load. The unbalanced distribution of tumor-related factors should have diluted any benefit of NACT for decreasing cancer-specific and overall mortality. Furthermore, overall stage was found to be an independent prognostic factor for competing mortality. One explanation is that patients with stage IV disease received more intensive treatment regimen which would result in a higher rate of treatment-related mortality.

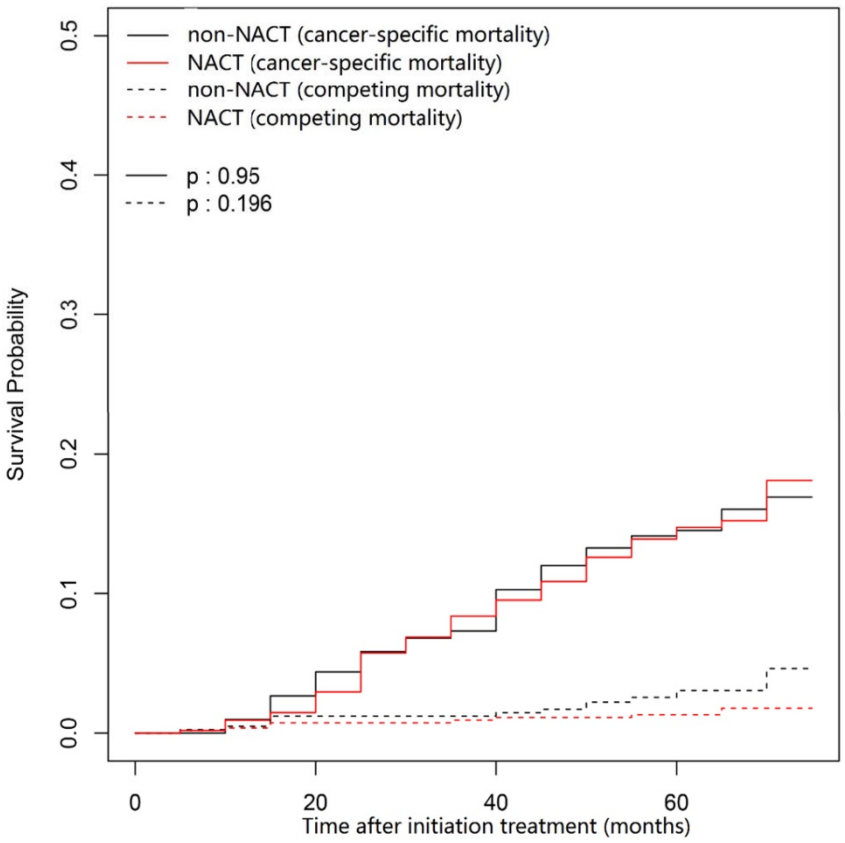

Figure 1. Cumulative cancer-specific and competing mortality curves stratified by application of NACT for the 957 patients with LA-NPC (univariate competing risk analysis). Abbreviations: NACT = neoadjuvant chemotherapy; LA-NPC = locoregionally advanced nasopharyngeal carcinoma (except T3-4N0).

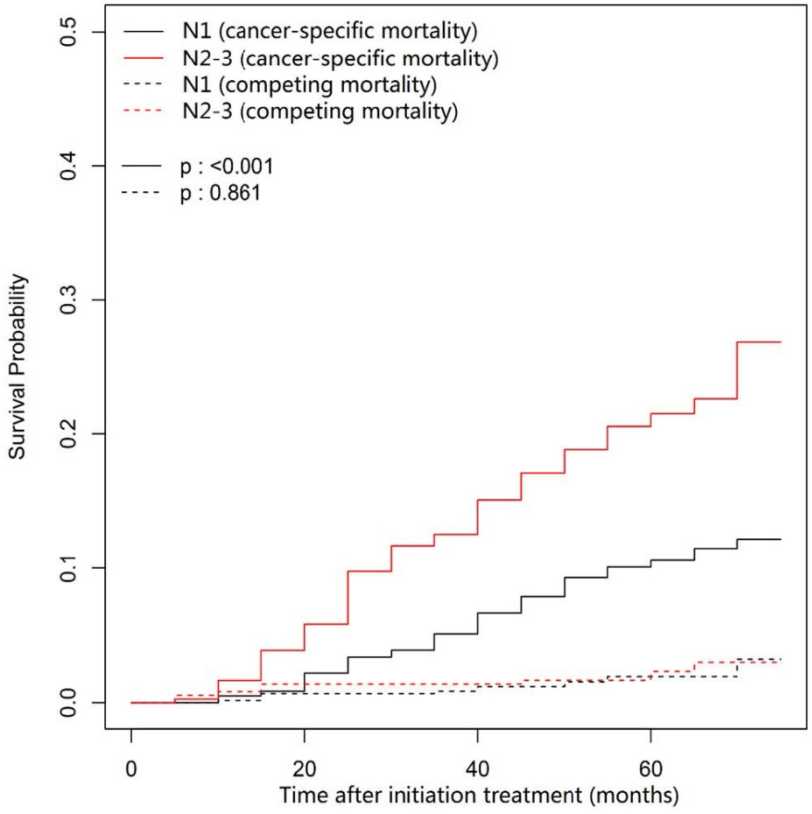

Figure 2. Cumulative cancer-specific and competing mortality curves stratified by N category (N2-3 vs. N1) for the 957 patients with LA-NPC (univariate competing risk analysis). Abbreviations: LA-NPC = locoregionally advanced nasopharyngeal carcinoma (except T3-4N0).

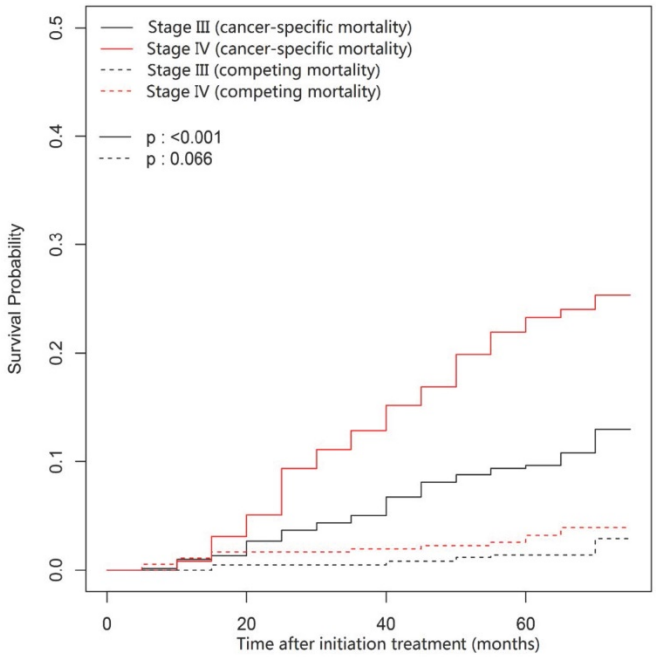

Figure 3. Cumulative cancer-specific and competing mortality curves stratified by overall stage (IV vs. III) for the 957 patients with LA-NPC (univariate competing risk analysis). Abbreviations: LA-NPC = locoregionally advanced nasopharyngeal carcinoma (except T3-4N0).

Table 2. Multivariate competing risk analysis outcomes for overall, cancer-specific and competing mortality of 957 patients with LA-NPC (except T3-4N0).

Category	HR	95% CI	*P*[a]
Endpoint: overall mortality			
Age (continuous variable, per-year increase)	1.022	1.008-1.036	0.0017
Gender (male vs. female)	0.824	0.532-1.276	0.39
LDH (continuous variable, per-U/L increase)	1.001	1.000-1.003	0.064
NACT (Yes vs. No)	0.654	0.471-0.909	0.011
T category (T3-4 vs. T1-2)	1.010	0.606-1.682	0.97
N category (N2-3 vs. N1)	1.622	1.131-2.328	0.0086
Overall stage (IV vs. III)	2.373	1.679-3.354	< 0.001
Smoking (Yes vs. No)	1.026	0.715-1.472	0.89
Drinking (Yes vs. No)	0.984	0.602-1.607	0.95
Pre-DNA (continuous variable, per-copy/ml increase)	1.000	1.000-1.001	0.0015
Endpoint: cancer-specific mortality			
Age (continuous variable, per-year increase)	1.016	1.001-1.03	0.032
Gender (male vs. female)	0.820	0.514-1.310	0.41
LDH (continuous variable, per-U/L increase)	1.002	1.000-1.003	0.044
NACT (Yes vs. No)	0.681	0.488-0.951	0.016
T category (T3-4 vs. T1-2)	1.143	0.663-1.970	0.63
N category (N2-3 vs. N1)	1.871	1.274-2.750	0.0014
Overall stage (IV vs. III)	2.246	1.554-3.250	< 0.001
Smoking (Yes vs. No)	1.101	0.749-1.620	0.62
Drinking (Yes vs. No)	0.899	0.528-1.530	0.70
Pre-DNA (continuous variable, per-copy/ml increase)	1.000	1.000-1.000	0.0061
Endpoint: competing mortality			
Age (continuous variable, per-year increase)	1.058	1.018-1.100	0.0042
Gender (male vs. female)	0.708	0.208-2.410	0.58
LDH (continuous variable, per-U/L increase)	1.001	0.999-1.001	0.53
NACT (Yes vs. No)	0.476	0.188-1.200	0.12
T category (T3-4 vs. T1-2)	0.450	0.095-2.140	0.32
N category (N2-3 vs. N1)	0.679	0.216-2.140	0.51
Overall stage (IV vs. III)	2.932	1.114-7.720	0.029
Smoking (Yes vs. No)	0.649	0.226-1.870	0.42
Drinking (Yes vs. No)	1.362	0.433-4.280	0.60
Pre-DNA (continuous variable, per-copy/ml increase)	0.998	0.992-1.002	0.55

Abbreviations: LA-NPC = locoregionally advanced nasopharyngeal carcinoma; LDH = lactate dehydrogenase; NACT = neoadjuvant chemotherapy; Pre-DNA = pre-treatment Epstein-Barr virus DNA. [a] Multivariate competing *P*-values were calculated using a Cox proportional hazards model with the following parameters: age (continuous variable, per-year increase), gender (male vs. female), LDH (continuous variable, per-U/L increase), NACT (yes vs. no), T category (T3-4 or T1-2), N category (N2-3 or N1), overall stage (IV vs. III), smoking (yes vs. no), drinking (yes vs. no) and pre-DNA (continuous variable, per-copy/ml increase).

Distant metastasis has been the main failure pattern after initial concurrent chemoradiotherapy (CCRT) especially when IMRT technique was applied [7-9]. Therefore, additional cycles of chemotherapy, such as adding adjuvant/neoadjuvant chemotherapy to CCRT, may improve prognosis. However, our previous study characterized that the value of adjuvant chemotherapy using PF regimen might be limited [27]. Moreover, the low rates of compliance (52-62%) [2, 3, 27-29] to adjuvant chemotherapy also would constrain the utility. Thus, NACT prior to CCRT could be a promising treatment modality. Regretfully, almost all the previous randomized phase III trials focusing on NACT failed to obtain a positive result on OS except our recent study using TPF regimen [17]. The negative outcomes may be attributed to following two reasonable explanations. Firstly, most trials included LA-NPC without excluding T3-4N0 disease, and this part of patients may not have higher distant tumor burden and would not really benefit from NACT. Hence, the recruitment of these patients could narrow the benefit of NACT and therefore resulted in insignificant outcomes. Furthermore, a truly effective neoadjuvant regimen has not yet been identified. Three randomized phase trials [30-32] and a meta-analysis [33] revealed TPF was superior to PF in head and neck cancers. Most recently, our randomized trial using TPF regimen also achieved positive results in advanced NPC. These results indicated that neoadjuvant TPF regimen may be more effective. However, the value of less effective regimens (PF or TP) remains unknown if appropriate subpopulation is selected. In our current study, we clarified that less effective regimens could also achieved a significantly decreased cancer-specific and overall mortality when patients with high-risk of distant metastasis (stage III-IV except T3-4N0) were selected. Besides, a meta-analysis carried out by Ouyang *et al.* [34] also supported our findings. Therefore, NACT still remains a promising treatment strategy irrespective of the regimen, but the key is to select appropriate patients who could benefit from it. Another of our ongoing trials (NCT01872962) is awaiting to be reported to further confirm the value of NACT.

The main strength of this study is that pre-DNA was included in analysis. In addition to tumor stage serving as an indicating factor for performing NACT, pre-DNA also has been proven to be a reliable biomarker [35-38] in predicting prognosis. Actually, pre-DNA was also associated with significantly increased cancer-specific and overall mortality in this current study. Our previous studies [39, 40] have demonstrated that pre-DNA could define high- or low-risk patients with advanced NPC who may benefit from NACT or not. Therefore, combination of these multiple prognostic factors is a powerful method for helping delivering individualized NACT.

In conclusion, our findings suggested that NACT using TP or PF regimens could still provide significant benefit for patients with LA-NPC (except T3-4N0) in decreasing cancer-specific and overall mortality. Therefore, it is a feasible approach that leads to better prognosis in the era of IMRT. Apparently, the shortcomings of this study should also be acknowledged: this analysis was performed retrospectively at a single center. Furthermore, the NACT regimens used in this study were non-uniform. However, this may not affect the conclusions because there is no evidence showing the efficacy difference of these two regimens. Also, longer follow-up time may be needed to observe more endpoints since many patients in this study still survival with recurrent disease. Further randomized trials should be warranted to confirm the results of this study.

Conclusions

Based on this competing risk analysis model, we clarified that neoadjuvant chemotherapy using TP or PF regimens could decrease cancer-specific mortality and overall mortality for patients with LA-NPC (except T3-4N0) receiving IMRT. Our findings may further strengthen the role of NACT in LA-NPC treated by IMRT.

Abbreviations

NPC: nasopharyngeal carcinoma; RT: radiotherapy; IMRT: intensity-modulated radiotherapy; NACT: neoadjuvant chemotherapy; TPF: docetaxel plus cisplatin with fluorouracil; CIF: cumulative incidence function; LA-NPC: locoregionally advanced nasopharyngeal carcinoma; WHO: World Health Organization; EBV: Epstein-Barr virus; pre-DNA: pre-treatment Epstein-Barr virus DNA; MRI: magnetic resonance imaging; PET: Positron emission tomography; UICC/AJCC: International Union against Cancer/American Joint Committee on Cancer; PTV: planning target volume; GTVnx: primary gross tumour volume; GTVnd: gross tumour volume of the positive lymph nodes; CTV1: high-risk clinical target volume; CTV2: low-risk clinical target volume; PF: cisplatin with fluorouracil; TP: docetaxel with cisplatin; OS: overall survival; LDH: lactate dehydrogenase; CRT: concurrent chemotherapy.

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Competing Interests

The authors have declared that no competing interest exists.

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