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Joint modeling of longitudinal health-related quality of life during concurrent chemoradiotherapy period and long-term survival among patients with advanced nasopharyngeal carcinoma

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Abstract

Background To investigate the prognosis of longitudinal health-related quality of life (HRQOL) during concurrent chemoradiotherapy (CCRT) on survival outcomes in patients with advanced nasopharyngeal carcinoma (NPC).

Methods During 2012–2014, 145 adult NPC patients with stage II-IVb NPC were investigated weekly using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (EORCT QLQ-C30) during their CCRT period. The effects of longitudinal trends of HRQOL on survival outcomes were estimated using joint modeling, and hazard ratios (HRs) with 95% confidence intervals (95% CIs) were reported as a 10-point increase in HRQOL scores.

Results After a median follow-up of 83.4 months, the multivariable models showed significant associations of longitudinal increasing scores in fatigue and appetite loss during the CCRT period with distant metastasis-free survival: 10-point increases in scores of fatigue and appetite loss domains during CCRT period were significantly associated with 75% (HR: 1.75, 95% CI: 1.01, 3.02; $p=0.047$) and 59% (HR: 1.59, 95% CI: 1.09, 2.59; $p=0.018$) increase in the risk of distant metastasis, respectively. The prognostic effects of the longitudinal HRQOL trend on overall survival and progress-free survival were statistically non-significant.

Conclusion Increases in fatigue and appetite loss of HRQOL during the CCRT period are significantly associated with high risks of distant metastasis in advanced NPC patients. Nutritional support and psychological intervention are warranted for NPC patients during the treatment period.

Keywords Nasopharyngeal carcinoma, Quality of life, Joint model, Survival

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Background

Nasopharyngeal carcinoma (NPC) is endemic in Southeastern Asia, especially in China [1]. Different from other head and neck cancers, NPC is significantly associated with Epstein-Barr virus infection and its major pathological type is non-keratinizing. Most NPC patients present at locally advanced stage at their initial diagnosis due to the conceal tumor-related symptoms on anatomical structure. Radical radiotherapy, such as intensity modulated radiotherapy (IMRT), is the current recommended treatment for NPC patients, and IMRT combined with chemotherapy is the primary treatment modality for locally advanced NPC patients [2]. Along with the improvements in early diagnosis and multimodality therapy, the prognosis of NPC has been largely improved in recent decades. The 5-year overall survival (OS) is over 90% for early-stage NPC patients and around 68–90% for locally advanced NPC patients [3, 4]. However, the treatment-related late side effects and sequela considerably reduce NPC survivors' health-related quality of life (HRQOL) [5]. Our previous study has proved a substantially deteriorated trend of HRQOL during the concurrent chemoradiotherapy (CCRT) period among advanced NPC patients [6].

Previous studies have reported positive associations between pretreatment HRQOL and survival outcomes among patients with advanced lung carcinoma, breast carcinoma, multiple myeloma, melanoma, esophageal carcinoma, and head and neck carcinoma [7–14]. A few of studies reported that scores of some domains/items of HRQOL could predict distant metastasis and tumor recurrence in NPC and other head and neck cancers [15, 16]. One limitation of these studies is that HRQOL was measured at one time point (i.e., pretreatment) without considering its dynamic fluctuation during and after treatment. The longitudinal trend rather than only one measure of HRQOL might provide a more accuracy prediction of NPC prognosis. It has been reported that every 10-point increase of appetite loss during treatment and survival period resulted in a 13% increased risk of death in anaplastic oligodendrogliomas patients [17]. However, how the longitudinally deteriorated HRQOL could affect the long-term survival of NPC patients is still unclear. It is therefore necessary to investigate the effect of longitudinal HRQOL on long-term survival of NPC patients.

HRQOL is dynamically changing during the treatment and survival period of NPC patients, and often correlated with the length of survival period. Treatment and treatment-related impairment of HRQOL might affect survival. Separate analysis of longitudinal and survival data would lead to biased estimations [18]. Joint modeling, which brings both longitudinal measures and time-to-event outcomes together (simultaneously) into a single model, could provide unbiased estimations for longitudinal HRQOL, survival processes, and their association [18] [19]. Therefore, it could be a promising approach to better characterize the effect of longitudinal HRQOL on long-term survival outcomes [20]. Using the updated follow-up data from a multicenter clinical trial conducted in China, this study is objectively to investigate the impact of longitudinal HRQOL during treatment period on the long-term survival outcomes among advanced NPC patients using joint modeling approach.

Methods

Study design and participants

This study was based on an open-label, noninferiority, multicenter randomized clinical trial during 2012–2014 in China [21]. In the trial, patients, who were aged 18–65 years with non-keratinizing clinical stage of II-IVB ($T_{1-4}N_{1-3}$ or $T_{3-4}N_0$) NPC, no evidence of distant metastasis, a Karnofsky score ≥ 70, and adequate hematological, renal, hepatic functions, were randomly allocated (1:1) to cisplatin-based or nedaplatin-based concurrent chemoradiotherapy groups. The exclusion criteria include prior or synchronous malignant disease, primary relapse/distant metastasis, previously received radiotherapy or chemotherapy, pregnancy and lactating mothers, the presence of uncontrolled life-threatening illness, or with any mental disorder or somatic comorbidities of clinical concerns. In this study, a subsample of 145 patients who completed European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (EORCT QLQ-C30) at baseline were involved, and their survival outcomes were updated from 31 June 2017 to 31 December 2020. Details of participants in this study has been reported previously [6].

Measures of health-related quality of life

HRQOL was measured at baseline (i.e., before treatment initiation) and repeatedly evaluated weekly to week 6 (around the end of CCRT) during the CCRT period, using the Chinese version of the EORCT QLQ-C30 (version 3.0). The EORCT QLQ-C30 has been widely used in several international cancer clinical trials [22, 23]. All assessments were carried out by a well-trained clinical research coordinator at the clinic. The fifteen domains of HRQOL, including a global quality of life, five multi-item functioning scales (i.e., physical, role, emotional, cognitive, and social functioning), three multi-item symptom scales (fatigue, pain, and nausea/vomiting), and six single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), were measured by 30 items. All domain scores were normalized into the range from 0 to 100, with higher scores indicating a

better global health status, better performance of functioning, or higher levels of symptoms.

Survival outcomes

This study focused on three survival outcomes, including OS, progression-free survival (PFS), and distant metastasis-free survival (DMFS). OS was defined as the time interval from the date of random assignment to the date of death from any cause or censored at the date of last follow-up. PFS was defined as the time interval from the date of random assignment to the date of local or regional relapse, distant metastasis, or death from any cause, whichever occurred first. DMFS was defined as the time interval from the date of random assignment to the date of distant metastasis, or death from any cause.

Statistical analysis

Descriptive statistics (e.g., means and standard deviation (SD), frequency and percentage) were presented when appropriate. We firstly assessed the associations between baseline HRQOL domains and survival outcomes by cox regression models. Secondly, the associations between longitudinal assessments of HRQOL during the CCRT period and subsequently long-term survival outcomes were estimated using joint modeling method [18]. Joint modeling could simultaneously analyze the longitudinal data of the covariates and time-to-event data, which consists of a longitudinal component to model longitudinal trend of HRQOL and a survival component to model time-to-event outcomes. A linear mixed-effect model that expands the time effect into a B-spline basis matrix was used for longitudinal trend of HRQOL, and an exponential hazard model was used for time-to-event outcomes. The longitudinal and survival components were jointed through a random slope effect as shared parameter with a time lag of 12 months, to associate the true levels of longitudinal trend of HRQOL domains with the risk of a survival outcome (i.e., OS, PFS, or DMFS) [24]. The hazard ratios (HRs) with 95% confidence intervals (95% CIs) were reported as the 10-point increase of HRQOL domain scores, which is the minimal clinically important difference of the scales [25]. The SAS macro JM was applied for the joint modeling analyses [26].

All models were adjusted for age, sex, percentage of weight loss during CCRT period, AJCC stage, EBV-DNA copies before treatment, and treatment group. All data analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA), and a two-sided p value < 0.05 was considered as statistically significant.

Ethical approval

This study was approved by the institutional review board of Sun Yat-sen University Cancer center. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit (www.researchdata.org.cn), with the approval RDD number as RDDA2022748620.

Results

Patients' characteristics

Among 145 patients, the mean age was 44.7 years (SD: 9.3) in the cisplatin group and 43.8 years (SD: 10.3) in the nedaplatin group. Most patients were female, 74.7% in the cisplatin group and 74.3% in the nedaplatin group, 30.7% in cisplatin group and 27.1% in nedaplatin group reported more than 10% of weight loss during CCRT period. (Table 1).

Updated long-term survival rate

After a median follow-up of 83.4 months (range: 5.0, 100.7 months), 20 dead cases, 30 progressed cases, and 16 distant metastasis cases were observed. The 5-year and 8-year overall survival rates were 90.8% (95% CI: 84.7, 94.5) and 82.9% (95% CI: 73.2, 89.3), respectively. The 5-year and 8-year PFS rates were 82.5% (95% CI: 75.2, 87.8) and 75.9% (95% CI: 66.0, 83.3), while the 5-year and 8-year DMFS rates were 90.2% (95% CI: 84.0, 94.1), and 88.5% (95% CI: 81.9, 92.8), respectively. (Fig. 1).

Table 1 Descriptions of sample characteristics

	Cisplatin group ($n=75$)	Nedaplatin group ($n=70$)
Age, years		
Mean ± SD	44.7 ± 9.3	43.8 ± 10.3
Rang	20–64	22–65
≤ 45	39 (52.0)	41 (58.6)
> 45	36 (48.0)	29 (41.4)
Sex		
Male	19 (25.3)	18 (25.7)
Female	56 (74.7)	52 (74.3)
Percentage of weight loss during CCRT period		
No change or increase	9 (12.0)	16 (22.9)
< 5%	20 (26.7)	17 (25.7)
5–10%	23 (30.7)	18 (25.7)
> 10%	23 (30.7)	19 (27.1)
AJCC stage		
II	7 (9.3)	8 (11.4)
III	48 (64.0)	47 (67.1)
IV	20 (26.7)	15 (21.4)
Epstein-Barr virus DNA test		
DNA < 1500 copies per mL	44 (58.7)	35 (50.0)
DNA ≥ 1500 copies per mL	31 (41.3)	35 (50.0)

CCRT, concurrent chemoradiotherapy; AJCC, American joint committee on cancer; SD, standard deviation

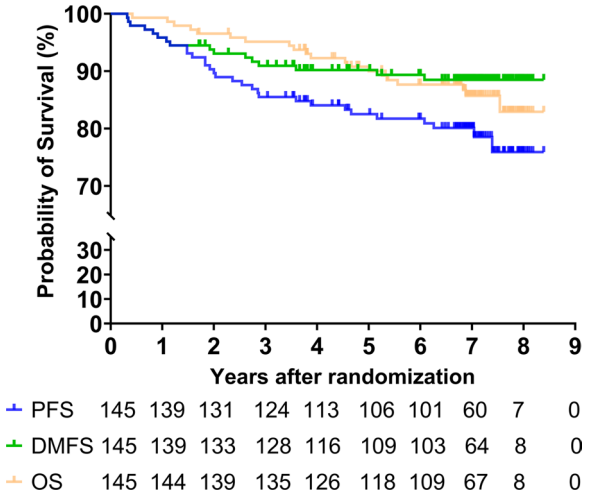

Fig. 1 Kaplan–Meier survival curve of progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS)

Joint modeling of longitudinal scores of HRQOL with survival outcomes

After adjustment of potential covariates, the results in Table 2 showed significant effects of longitudinal trend in fatigue and appetite loss during CCRT period on DMFS: a 10-point increase in scores of fatigue and appetite loss domains over time was associated with 75% (HR: 1.75, 95%CI: 1.01, 3.02; $p=0.047$) and 59% (HR: 1.59, 95%CI: 1.09, 2.59; $p=0.018$) increase in the risk of distant metastasis, respectively. The associations of other domains of HRQOL with DMFS were not statistically significant. The scores of HRQOL domains, neither at baseline nor longitudinal trend, showed statistical significance with OS and PFS (Table S1 and Table S2).

Discussion

To the best of our knowledge, this is the first study to investigate the prognostic effects of longitudinal HRQOL on the long-term survival outcomes in advanced NPC patients, showing that the deteriorated trends of fatigue and appetite loss during CCRT period were significantly associated with lower rates of DMFS.

Fatigue is one of the most prevalent cancer-related symptoms, especially for locally advanced NPC patients [6, 27], and few studies explored its associations with long-term survival in cancer patients. Antolín et al. reported that intensity of fatigue was associated with decreased quality of life but not with metastasis status among prostate cancer [28]. One possible mechanisms of our findings could be the inflammatory changes. Fatigue was found to be significantly associated with the increases of inflammation markers (e.g.,

Table 2 Associations between health-related quality of life and distant metastasis-free survival among advance nasopharyngeal carcinoma

	Univariate		Adjusted †	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Global quality of life				
Baseline	0.94 (0.76, 1.16)	0.56	0.98 (0.79, 1.23)	0.876
Longitudinal	0.72 (0.48,1.07)	0.10	0.71 (0.48,1.04)	0.081
Psychical function				
Baseline	0.81 (0.59, 1.12)	0.205	0.82 (0.57, 1.17)	0.262
Longitudinal	**0.60 (0.36,0.99)**	**0.046**	0.65 (0.39,1.09)	0.102
Role function				
Baseline	1.15 (0.88, 1.49)	0.303	1.15 (0.88, 1.52)	0.309
Longitudinal	0.72 (0.51,1.01)	0.06	0.71 (0.50,1.00)	0.053
Emotional function				
Baseline	0.93 (0.71, 1.22)	0.614	0.97 (0.73, 1.29)	0.841
Longitudinal	0.60 (0.32,1.11)	0.104	0.61 (0.32,1.15)	0.125
Cognitive function				
Baseline	0.84 (0.65, 1.11)	0.217	0.90 (0.68, 1.19)	0.456
Longitudinal	0.63 (0.36,1.10)	0.103	0.68 (0.38,1.22)	0.196
Social function				
Baseline	1.07 (0.88, 1.31)	0.482	1.09 (0.90, 1.33)	0.391
Longitudinal	0.65 (0.38,1.12)	0.121	0.66 (0.37,1.16)	0.143
Fatigue				
Baseline	0.94 (0.74, 1.21)	0.632	0.91 (0.70, 1.17)	0.453
Longitudinal	**1.78 (1.04, 3.06)**	**0.036**	**1.75 (1.01, 3.02)**	**0.047**
Nausea and vomiting				
Baseline	0.93 (0.77, 1.12)	0.438	0.92 (0.76, 1.11)	0.385
Longitudinal	1.76 (0.89, 3.50)	0.105	1.68 (0.86, 3.30)	0.13
Pain				
Baseline	1.05 (0.83, 1.34)	0.675	1.01 (0.78, 1.33)	0.92
Longitudinal	1.31 (0.95, 1.81)	0.096	1.30 (0.94, 1.80)	0.119
Dyspnea				
Baseline	0.87 (0.64, 1.18)	0.377	0.87 (0.64, 1.18)	0.369
Longitudinal	**4.59 (1.10, 19.09)**	**0.037**	3.97 (0.96,16.44)	0.058
Sleep disturbance				
Baseline	1.12 (0.94, 1.32)	0.199	1.20 (0.99, 1.46)	0.068
Longitudinal	1.80 (0.83,2.16)	0.235	1.30 (0.80,2.11)	0.288
Appetite loss				
Baseline	0.95 (0.81, 1.12)	0.546	0.92 (0.77, 1.09)	0.326
Longitudinal	**1.59 (1.09, 2.33)**	**0.018**	**1.59 (1.09, 2.59)**	**0.018**
Constipation				
Baseline	0.94 (0.77, 1.15)	0.551	0.98 (0.79, 1.23)	0.88
Longitudinal	1.28 (0.95,1.74)	0.107	1.30 (0.95,1.78)	0.105
Diarrhea				
Baseline	–		–	
Longitudinal	1.44 (0.07,31.60)	0.815	1.62 (0.16,16.12)	0.68
Financial difficulties				
Baseline	0.97 (0.84, 1.12)	0.654	0.90 (0.76, 1.06)	0.203
Longitudinal	1.47 (0.52, 4.17)	0.465	1.33 (0.40, 4.38)	0.637

The bold values indicate statistically significant

95% CI: 95% confidence interval

Table 2 (continued)

[†] Models were adjusted of age, sex, weight loss during CCRT period, AJCC stage, EBV-DNA copies before treatment, and treatment group

IL6, sTNFR2) in head and neck cancer patients during treatment [29].These inflammatory changes could suppress the immune system [30, 31], and increase the risk of distant metastasis. Another possible mechanism might be hyponatremia. Fatigue is associated with hyponatremia, which was reported to be linked with lower survival rate in patients with lung cancer [32, 33], epithelial ovarian cancer [34], gastric cancer [35], and colorectal cancer [36]. Besides, Workeneh et al. indicated that hyponatremia can reduce the likelihood of survival [37], it is therefore necessary to take care of hyponatremia during anti-cancer treatment.

We also found that longitudinal trend of appetite loss during treatment period was significantly associated with lower DMFS in advanced NPC patients, which highlighted the importance of appetite and nutritional support for advanced NPC patients during treatment period. One possible reason could be that appetite loss could directly reduce patients' nutrition intake and could cause clinically significant weight loss [38, 39], which was associated with a lower rate of DMFS among head and neck patients [40, 41]. Such weight loss, or even malnutrition, could downregulate the immune system, which might lead to unidentified micro-metastasis of metastatic cancer cells. Specifically, tumor immune escape and the initiation of metastasis are critical steps in the malignant progression of tumors [42]. Recruitment of immunosuppressive cells to tumors could protect metastatic cancer cells from surveillance by killer cells, which nullifies the effects of immunotherapy and thus establishes metastasis [43].

The main advantage of our study is that the dynamic effects of longitudinal measures of HRQOL on survival outcomes were estimated by joint modeling, which should have less bias than using only one single measure of HRQOL without considering its dynamic changes. However, there are several limitations in our study. First, the sample is small, especially for limited events of disease progress, distant metastasis, and death. Future studies with large sample size are warranted to confirm our findings. Second, HRQOL in our study was only weekly measured during treatment period, which could not reflect their long-term dynamic profiles after the treatment, and the impact of their dynamic changes during long-term survival period on prognosis of NPC patients is still unclear, and warranted in further research. Third, the generalizability of our finding might be limited by the representativeness of the sample, considering that patients only from one cancer center of epidemic region.

In conclusion, our findings indicate that the longitudinal deteriorated trends in fatigue and appetite loss during treatment period were significantly associated with higher risks of distant metastasis among advanced NPC patients. Proper psychological supportive care nutritional support during treatment period could potentially benefit treatment effects and long-term prognosis of NPC patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02473-y.

Additional file 1.

Additional file 2.

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Author contributions
QY Chen, JB Li, and SS Guo conceived and designed the study; JB Li, SS Guo, T Liu, and LQ Tang acquired the data; JB Li, and ZC Lin conducted the statistical analyses; JB Li, and SS Guo drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript.

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Availability of data and materials
The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit (www.researchdata.org.cn), with the approval RDD number as RDDA2022748620.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of Sun Yat-sen University Cancer center and all the participates approved the inform consent.

Consent for publication
All the authors approved the consent for publication.

Competing interests
All authors declare no conflict of interest.

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