Oral Oncology 98 (2019) 62–68

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Construction of a comprehensive nutritional index and its correlation with quality of life and survival in patients with nasopharyngeal carcinoma undergoing IMRT: A prospective study

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ARTICLE INFO

Keywords:
Nasopharyngeal carcinoma
Intensity-modulated radiation therapy
Nutrition
Quality of life
Survival

ABSTRACT

Objectives: The aim of this study was to investigate the relationship between a comprehensive nutritional index (CNI) and QoL in patients with NPC who undergo IMRT and to explore the relationship between CNI and survival.

Methods: 359 patients with newly diagnosed NPC were enrolled. QoL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 and Quality of Life Questionnaire Head and Neck Cancer Module at three time points: before, immediately after, and 3 months after IMRT. The CNI comprised five values including body mass index, usual body weight percentage, hemoglobin, albumin, and total lymphocyte count, and was evaluated before and immediately after IMRT. The correlation between the CNI and QoL and the effect of CNI on prognosis were analysed.

Results: QoL and CNI scores decreased remarkably after IMRT ($P < 0.05$). The CNI was quite low in patients with III–IV clinical tumor stage and those undergoing induction chemotherapy plus concurrent chemotherapy. After IMRT, lower CNI score correlated worse QoL ($P < 0.05$). The Kaplan-Meier curve indicated that patients with lower CNI had significantly poorer survival outcomes ($P = 0.02$). In multivariate analysis, CNI remained an independent prognostic factor of overall survival ($P = 0.046$).

Conclusions: CNI can be recommended as an appropriate indicator reflecting the integrated nutrition status of NPC patients. Low CNI was associated with poor QoL and predicted a poor survival outcome. More interventions should be taken to improve the nutrition status of NPC patients to improve QoL and enhance survival outcomes.

Introduction

Nasopharyngeal carcinoma (NPC) is a common cancer in southern China and Southeast Asia, 129,079 new cases of NPC were diagnosed worldwide in 2018 [1]. NPC is generally sensitive to chemotherapy and radiotherapy, and the enhanced radiation treatment known as intensity-modulated radiation therapy (IMRT) is excellent for locoregional control. Therefore, IMRT with or without chemotherapy is the primary treatment modality for NPC.

However, IMRT inevitably damages normal tissues and can lead to acute mucosal changes in the oral cavity and oropharynx. This causes different degrees of dry mouth, taste changes, hoarseness, pain, and difficulty swallowing, which directly affect patients' appetite and ability to eat [2]. Meanwhile, NPC patients also suffer from anxiety, depression, nausea, vomiting, anorexia, and other complications due to IMRT, which further decrease patients' food intake and worsen their nutritional status [3]. Quality of life (QoL) is a multidimensional issue that encompasses the social and psychological states of patients and their subjective feelings and functional status. According to a previous study, the QoL of head and neck cancer patients deteriorates

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https://doi.org/10.1016/j.oraloncology.2019.09.014
Received 8 August 2019; Accepted 13 September 2019
Available online 18 September 2019
1368-8375/

immediately after treatment [4]. Complications, especially oral problems caused by radiochemotherapy, may influence patients' QoL by affecting nutritional intake.

Malnutrition is associated with overall survival among cancer patients. In a prospective study from southern China, 76% of 92 NPC patients lost more than 10% of their body weight during IMRT [5]. Malnutrition can damage the body's immune function, tissues, and organs; reduce the body's ability to tolerate concurrent chemoradiotherapy; affect the duration of rehabilitation and hospitalization; and lead to suspension or discontinuation of treatment [2,6]. Obviously, nutritional assessment should include various indexes rather than only one or two parameters. Therefore, the authors built a comprehensive nutritional index (CNI) based on previous study to reflect nutrition status in NPC patients [5,7]. It has previously been confirmed that the CNI of NPC patients decreases significantly after treatment [5]. However, few studies have focused on the effect of nutritional index on treatment outcomes.

In the current study, a CNI to assess comprehensive nutritional status was built with principal component analysis. The relationship between CNI and QoL, measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) and Quality of Life Questionnaire Head and Neck Cancer Module (QLQ-H&N35), was investigated. The effect of CNI on treatment outcomes, which has important clinical significance in the management of NPC patients, was also explored.

Methods

Patients and study design

From July 2011 to December 2014, 359 patients with newly diagnosed NPC participated in this study. Inclusion criteria were as follows: (1) primary diagnosis of NPC, (2) age between 16 and 72 years; (3) agreement to fill out study questionnaires, independently or with the help of others; and (4) written informed consent. Research nurses collected the completed questionnaires for subsequent data entry. Exclusion criteria were as follows: (1) previous acceptance of radiation or cervical lymphadenectomy, (2) multiple distant metastases (bone metastasis or lung metastasis), (3) mental illness or intellectual disability. This prospective study was approved by the Research Ethics Committee of Sun Yat-Sen Cancer Center, Guangzhou, China.

A standardized questionnaire was used to collect demographic data on age, gender, marital status, education level, tumor stage (Union for International Cancer Control [UICC] TNM tumor classification), and treatment. The nutrition index, which included body mass index (BMI), usual body weight percentage (UBW%), total lymphocyte count (TLC), hemoglobin level (Hb), and total protein albumin, was evaluated within 48 h after admission (pre-IMRT) and immediately after IMRT (immediately post-IMRT). The QLQ-H&N35 and QLQ-C30 were administered at three time points: before IMRT, immediately after IMRT, and three months after IMRT. The patients' survival outcomes were recorded until March 2019.

Treatments

All patients involved in this study were treated with IMRT. All the target volumes were depicted slice-by-slice on the treatment planning computed tomography scan. The primary nasopharyngeal gross tumor volume (GTVnx) and the involved cervical lymph nodes were determined on the basis of imaging and clinical and endoscopic findings. The enlarged retropharyngeal nodes, together with primary gross tumor volume (GTV), were outlined as the GTVnx on the IMRT plans; clinically-involved cervical lymph nodes was outlined GTVnd. High-risk clinical tumor volume(CTV1) was defined as the area from 0.5 to 1.0 cm outside the GTV, which includes potential sites of local infiltration. Low-risk clinical target volume (CTV2) was defined as the margin from 0.5 to 1.0 cm around CTV1 and the lymph node draining area (levels II, III, IV, and V). The planning target volume (PTV)-nx, PTV-nd, PTV-1, PTV-2, were constructed by expanding the GTVnx, GTVnd, CTV1 and CTV2, respectively, by 3 mm; a 3 mm margin was added to the brainstem and spinal cord to generate planning organ at risk volume (PRV). The IMRT doses in the target region were 69.96 to 73.92 Gy for the PTVnx, 69.96 to 73.92 Gy for the PTVnd, 60 to 66 Gy for the PTV-1, and 54 to 56 Gy for the PTV-2, with varying treatment plans according to the tumor volume and cancer stage. The IMRT dose was 2.0 to 2.2 Gy per fraction per day. Irradiation was performed one time per day, five days per week, and then a two-day rest was taken. The total number of exposures was approximately 30 to 33 times. The total dose of IMRT that the patients received was consistent with Sun Yat Sen University Cancer Center guidelines [8].

Chemotherapy in this study included induction chemotherapy (IC) and concurrent chemotherapy (CCT). One hundred and fifty-five patients received IC plus CCRT, 35 patients received IC alone, 145 patients received CCRT alone, and 24 patients did not receive chemotherapy. The IC generally included the following regimens every three weeks for two or three cycles: fluorouracil (500–750 mg/m^2) and cisplatin (60–90 mg/m^2); paclitaxel (135–175 mg/m^2) and fluorouracil (500–750 mg/m^2); or paclitaxel (135–175 mg/m^2), fluorouracil (500–750 mg/m^2), and cisplatin (60–90 mg/m^2). The CCT regimen comprised cisplatin (70–100 mg/m^2) every three weeks for two or three cycles.

Nutritional measurement

We evaluated the nutritional status of patients with anthropometric, biochemical, and hematological data from their medical records acquired at two time points: within 48 h after admission (pre-IMRT) and immediately after treatment with IMRT (immediately post-IMRT). Nutritional measurements included TLC, Hb, albumin, BMI, and UBW %.

A stadiometer (RGZ-120-RT; Wuxi Weigher Factory) was used to measure patient height, and a digital electronic scale (RGZ-120-RT; Wuxi Weigher Factory) was used to measure body weight. Albumin levels were measured with the Germany Roche Modular P800 system, while TLC and Hb levels were measured with an America Beckman Coulter LH750. BMI was calculated with the following formula: weight (kg)/square of height (meters). The UBW% reflects the change of weight and was defined as the actual body weight divided by the usual body weight (the body weight pre-IMRT was regarded as the usual body weight in this study).

Assessments of QoL

QoL was measured with the QLQ-C30 version 3.0 (Chinese version 3.0) and the QLQ-H&N35. These questionnaires are widely implemented in clinical research, especially in research on head and neck carcinomas, because of their integrated, modular approach [9]. The QLQ-C30 comprises 30 items including one global health status, five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), and six single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [10]. The QLQ-H&N35 is a specific scale covering head and neck issues that consists of 35 questions including 11 single items (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain medication use, nutritional supplementation, feeding tube requirement, weight loss, and weight gain) and seven multi-item scales (pain, swallowing, sensation, speech, eating from a social perspective, social interactions, and sexuality). The two questionnaires were completed by the enrolled patients either independently or with the assistance of others. All single items and scales from the questionnaires were converted to scores ranging from 0 to 100 by transformation. Higher scores in the global health status and five

functional scales of QLQ-C30 represent better QoL, while lower scores of symptom items of QLQ-C30 and lower scores of QLQ-H&N35 indicate better quality of life.

Follow-up

All participants were followed until March 2019 through the follow-up system of the center where the study was conducted, and the end events were either death or loss to follow-up. The primary outcome of the study was overall survival (OS).

Statistical analysis

All statistical analyses were conducted by SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Patients' clinical characteristics were expressed with descriptive statistics. As patients' nutrition index values were normally distributed, the paired-samples *t* test was used to compare patients' nutrition status pre-IMRT and immediately post-IMRT. Overall difference in the QLQ-C30 and QLQ-H&N35 values measured at the three time points (pre-IMRT, immediately post-IMRT, and three months after IMRT) were performed by Friedman analysis because the data were not normally distributed. The Bonferroni method was used in post hoc multiple comparisons of the three time points, and adjusted *P* values were reported.

Principal components analysis aims to reduce excessive variance and establish an equation with unrelated variables that accounts for most of the variance of all tested variables. BMI, UBW%, Hb levels, TLC, and albumin immediately post-IMRT were analyzed by principal components analysis with SPSS 21.0. Principal components were considered significant for eigenvalues > 1 and a cumulative proportion of > 70%. CNI was then calculated according to the weight coefficient of principal components identified above and reflect the comprehensive nutritional status immediately post-IMRT. Comparison of binary or polytomous variables in CNI was assessed by the independent-samples *t* test or analysis of variance. The Spearman correlation coefficient was used to verify the correlations between the CNI and QLQ-C30 and QLQ-H&N35 immediately post treatment and 3 months after IMRT. The cut-off points for continuous variables were chosen on the basis of receiver operating characteristic curve analysis, which showed the best trade-off between sensitivity and specificity. Survival probabilities between patients in different groups were evaluated using the Kaplan-Meier method with the log-rank test. Multivariable Cox regression analyses were used to estimate the hazard ratios and 95% confidence intervals. All statistical tests in our study were 2-tailed. $P < 0.05$ was considered to represent statistical significance.

Results

Patient characteristics

This study included 359 patients with a primary diagnosis of NPC. The ratio of male to female patients was 3.3 to 1, and the mean age of the patients was 44.2 years (range, 16–72 years). Most of the patients had advanced-stage disease: stage III (56.0%, n = 201) and stage IV (33.4%, n = 120) of the UICC staging system. Other characteristics of the 359 patients are summarized in Table 1.

Table 1
Clinical characteristics of patients ($n = 359$).

Characteristic	n (%)
Age	
18–44	181 (50.4)
45–59	156 (43.5)
60–72	22 (6.1)
Gender	
Male	275 (76.6)
Female	84 (23.4)
Marital status	
Married	338 (94.2)
Other	21 (5.8)
Education level	
Primary	73 (20.3)
Middle and high school	192 (53.5)
University	94 (26.2)
Targeted therapy	
No	335 (93.3)
Yes	23 (6.7)
UICC stage	
I	6 (1.7)
II	32 (8.9)
III	201 (56.0)
IV	120 (33.4)
Chemotherapy	
Induction chemotherapy	35 (9.7)
Concurrent chemotherapy radiotherapy	145 (40.4)
Induction plus concurrent chemotherapy	155 (43.2)
None	24 (6.7)
Nutrition therapy	
Parental nutrition	175 (48.7)
Enteral nutrition	7 (1.9)
Parental and enteral nutrition	5 (1.4)
No	172 (47.9)

Changes in single nutrition index

We compared five single nutritional indexes before IMRT and immediately after IMRT. Details of those nutritional indexes are shown in Table 2. The average weight loss of patients was 4.96 ± 4.64 kg from pre-IMRT to immediately post-IMRT. Fifty patients (13.9%) did not lose weight, 185 patients (51.6%) lost 1.0% to 9.9% of their body weight, 111 patients (30.9%) lost 10.0% to 19.9% of their body weight, and 13 patients (3.6%) lost > 20.0% of their body weight. The data showed significant differences in all indexes between pre-IMRT and immediately post-IMRT. Each index clearly decreased after IMRT, which indicates a worse nutrition status immediately after IMRT than before IMRT.

Construction of the CNI and Comparison of the CNI to patient characteristics

Five nutritional indexes (BMI, UBW%, Hb, albumin, and TLC) are used for construction of a CNI to assess the impact of IMRT on the nutritional status of patients with NPC. Principal components analysis was used to extract two principal components. The cumulative eigenvalue of the first two components was greater than one and its cumulative proportion reached 72.65%, while the first component reached 43.11% and the second component reached 29.54%. These two components were as follows:

$$C_1 = 0.913ZX_1 + 0.912ZX_2 + 0.384ZX_3 + 0.477ZX_4 + 0.341ZX_5$$

$$C_2 = -0.402ZX_1 - 0.404ZX_2 + 0.741ZX_3 + 0.682ZX_4 + 0.372ZX_5$$

According to the statistical weight coefficient of the two components, CNI = 0.431*C_1 + 0.295*C_2. Patients' CNI could be calculated from this formula. The CNI scores of the 359 patients ranged from − 2.77 to 3.07. The CNI was not significantly associated with age, gender, marital status, education level, or targeted therapy application ($P > 0.05$). There were significant differences in CNI scores among different treatment plans (IC plus CCRT, −0.24 ± 1.13; CCRT, 0.04 ± 0.8; IC plus IMRT alone, 0.35 ± 0.95; IMRT alone, 0.82 ± 0.80), which suggests that a more complex treatment plan is associated with a worse nutrition status ($P < 0.001$). Patients with stage I or II NPC (2010 UICC) had higher CNI scores than patients with stage III or IV NPC (0.61 ± 0.98 vs −0.07 ± 1.01, $P < 0.001$).

Table 2
Descriptive analyses and comparisons of the single nutrition index before and immediately after intensity-modulated radiation therapy (n = 359).

Variable	Pre-IMRT (T1) mean ± SD	Post-IMRT (T2) mean ± SD	T1 − T2	*t*	*P*
BMI (kg/m^2)	23.05 ± 3.21	21.27 ± 3.11	1.78 ± 1.65	20.39	< 0.001
UBW%	1.07 ± 0.15	0.98 ± 0.14	0.08 ± 0.08	20.43	< 0.001
Albumin (g/L)	43.51 ± 3.42	39.06 ± 4.48	4.45 ± 4.88	17.26	< 0.001
Hb (g/L)	142.24 ± 14.54	114.54 ± 17.84	27.70 ± 18.63	28.16	< 0.001
TLC (10^9/L)	1.75 ± 0.75	0.49 ± 0.48	1.26 ± 0.82	29.05	< 0.001

Abbreviations: BMI, body mass index; Hb, hemoglobin; pre-IMRT, before intensity-modulated radiation therapy; post-IMRT, immediately after intensity-modulated radiation therapy; T1–T2, difference between pre-IMRT and post-IMRT values; TLC, total lymphocyte count; UBW%, usual body weight percentage.

Table 3
Comparison of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) scores of patients with nasopharyngeal carcinoma at three time points (n = 359).

Subscale	Pre-IMRT	Post-IMRT	3 Months	All 3 Times*	Pre vs Post#	Pre vs 3 Months#	Post vs 3 Months#
	Mean ± SD			*P* value			
Physical functioning	93.67 ± 9.63	76.02 ± 17.63	89.64 ± 11.92	< 0.001	< 0.001	< 0.001	< 0.001
Role functioning	94.06 ± 14.10	70.17 ± 27.44	85.77 ± 18.61	< 0.001	< 0.001	< 0.001	< 0.001
Emotional functioning	83.94 ± 16.55	77.39 ± 18.82	88.83 ± 13.75	< 0.001	< 0.001	0.002	< 0.001
Cognitive functioning	88.58 ± 15.64	78.38 ± 20.69	87.73 ± 14.73	< 0.001	< 0.001	1.000	< 0.001
Social functioning	75.91 ± 25.27	65.92 ± 26.01	81.79 ± 20.36	< 0.001	< 0.001	0.080	< 0.001
Global health status	70.22 ± 22.65	52.20 ± 22.77	73.83 ± 19.27	< 0.001	< 0.001	0.205	< 0.001
Fatigue	17.05 ± 16.67	45.04 ± 23.26	20.63 ± 19.03	< 0.001	< 0.001	0.127	< 0.001
Nausea and vomiting	3.67 ± 11.20	30.77 ± 26.74	4.26 ± 11.18	< 0.001	< 0.001	1.000	< 0.001
Pain	12.63 ± 17.75	37.93 ± 27.22	10.63 ± 15.53	< 0.001	< 0.001	0.904	< 0.001
Dyspnea	6.96 ± 15.09	23.39 ± 30.32	10.67 ± 21.85	< 0.001	< 0.001	0.584	< 0.001
Insomnia	15.97 ± 22.67	33.24 ± 28.80	15.54 ± 20.21	< 0.001	< 0.001	1.000	< 0.001
Appetite loss	7.42 ± 16.91	52.19 ± 30.38	16.20 ± 20.85	< 0.001	< 0.001	< 0.001	< 0.001
Constipation	7.61 ± 17.01	31.09 ± 29.79	6.55 ± 15.24	< 0.001	< 0.001	1.000	< 0.001
Diarrhea	10.89 ± 31.20	12.89 ± 33.55	4.49 ± 20.75	< 0.001	1.000	0.582	0.271
Financial difficulties	32.22 ± 31.89	32.96 ± 30.40	21.35 ± 26.48	< 0.001	1.000	< 0.001	< 0.001

Abbreviations: Pre-IMRT, before intensity-modulated radiation therapy (baseline); Post-IMRT, immediately after intensity-modulated radiation therapy; 3 Months, three months after intensity-modulated radiation therapy.
* Related-samples Friedman's two-way analysis of variance by ranks.
\# Bonferroni adjusted.

Comparison of QoL at three time points

All patients (n = 359) completed the QLQ-C30 and QLQ-H&N35 questionnaires before treatment, immediately after treatment, and three months after treatment. The QLQ-C30 scores are shown in Table 3, and the QLQ-H&N35 scores are shown in Table 4. The scores of items related to functioning decreased after IMRT, and the scores of items related to symptoms increased significantly after IMRT ($P < 0.05$), except for diarrhea and financial difficulties in QLQ-C30. Patients' QoL tended to improve 3 months after IMRT. On the other hand, scores on items on the QLQ-H&N35 related to dry mouth and sticky saliva were worse three months after treatment than they were before treatment, which indicates serious oral complications after IMRT. Nevertheless, the items felt ill, use of pain killers, nutrition supplements, and weight gain were better three months after IMRT than they were immediately after IMRT, and that represents improvement of general health.

Correlation of CNI with QLQ-C30 and QLQ-H&N35

The correlation between CNI immediately after IMRT and QLQ-C30 or QLQ-H&N35 is shown in Table 5. At immediately post-IMRT, items of QLQ-C30 and QLQ-H&N35 had significant correlations with CNI. When analyzed three months after IMRT, some items remained the factors that were significantly correlated with CNI, such as social functioning, constipation, swallowing, felt ill, and tube feeding ($P < 0.05$).

Relationship between survival and CNI

The median CNI level for the 359 patients was 0 (range, −2.77 to 3.07). The cut-off value determined by receiver operating characteristic curve analysis was −0.177 for overall survival (sensitivity, 0.519; specificity, 0.600; area under curve, 0.585), which was used for further analysis. Survival at last follow-up data were available for 332 patients. Of these patients, 145 (64.4%) were in the lower CNI group and 187 (35.6%) were in the higher CNI group. As shown in Fig. 1, patients with higher CNI achieved a better overall survival than patients with lower CNI (85.7, 95% CI 79.2%–91.6% versus 95.1, 95% CI 92.0–98.2%; $P = 0.020$). We carried out multivariate analyses that included patient age (≤44 years or > 44), sex (male or female), UICC stage (I–III or IV), and CNI (≤0.177 or > 0.177). As shown in Table 6, higher CNI was a significantly protective factor for overall survival (hazard ratio, 0.544, 95% CI 0.299–0.989; $P = 0.046$).

Discussion

This study investigated the QoL of patients with NPC on the basis of two questionnaires (QLQ-C30 and QLQ-H&N35) and nutrition level. In addition, a CNI was established to reflect patients' integrated nutrition status, and the correlation between QoL and CNI and the effect of CNI on survival time were explored.

IMRT can maximize the radiation dose concentrated within the target area to kill tumor cells [11]. It has been the preferred therapy for NPC in recent decades because it provides better local control of tumor cells than conventional radiation therapy. However, the adverse effects of IMRT cause a remarkable decline in QoL [11]. Our results were

Table 4
Comparison of The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Cancer Module (QLQ-H&N35) scores of patients with nasopharyngeal carcinoma at three time points (n = 359).

Subscale	Pre-IMRT	Post-IMRT	3 Months	All 3 Times*	Pre vs Post#	Pre vs 3 Months#	Post vs 3 Months#
	mean ± SD			*P* value			
Pain	7.24 ± 9.82	46.27 ± 26.03	10.07 ± 13.48	< 0.001	< 0.001	0.510	< 0.001
Swallowing	3.61 ± 8.93	43.77 ± 27.25	11.57 ± 12.45	< 0.001	< 0.001	< 0.001	< 0.001
Senses	5.80 ± 13.34	41.78 ± 23.76	23.74 ± 21.72	< 0.001	< 0.001	< 0.001	< 0.001
Speech	7.06 ± 13.75	28.51 ± 26.36	9.77 ± 13.70	< 0.001	< 0.001	0.076	< 0.001
Social eating	4.02 ± 9.02	36.06 ± 23.61	10.20 ± 13.42	< 0.001	< 0.001	< 0.001	< 0.001
Social contact	4.10 ± 8.64	25.58 ± 22.47	8.05 ± 12.49	< 0.001	< 0.001	0.006	< 0.001
Sexuality	16.85 ± 20.66	45.94 ± 30.13	28.23 ± 26.18	< 0.001	< 0.001	< 0.001	< 0.001
Teeth	14.67 ± 19.81	20.35 ± 23.89	17.60 ± 21.72	< 0.001	0.034	0.343	1.000
Opening mouth	6.22 ± 15.81	26.24 ± 26.31	8.80 ± 18.49	< 0.001	< 0.001	0.565	< 0.001
Dry mouth	17.55 ± 20.96	51.69 ± 28.42	52.81 ± 28.11	< 0.001	< 0.001	< 0.001	1.000
Sticky saliva	12.29 ± 18.78	49.95 ± 32.15	24.63 ± 26.75	< 0.001	< 0.001	< 0.001	< 0.001
Coughing	9.12 ± 16.87	31.65 ± 27.66	8.52 ± 17.67	< 0.001	< 0.001	1.000	< 0.001
Felt ill	26.09 ± 27.35	46.31 ± 30.95	16.01 ± 23.13	< 0.001	< 0.001	< 0.001	< 0.001
Pain killers	18.94 ± 39.24	46.50 ± 49.95	6.18 ± 24.11	< 0.001	< 0.001	0.039	< 0.001
Nutrition supplements	18.94 ± 39.24	50.98 ± 50.06	49.44 ± 50.07	< 0.001	< 0.001	< 0.001	1.000
Feeding tube	0.83 ± 9.12	2.80 ± 16.52	2.52 ± 15.72	0.104	–	–	–
Weight loss	36.49 ± 48.21	90.48 ± 29.40	33.99 ± 47.43	< 0.001	< 0.001	1.000	< 0.001
Weight gain	7.24 ± 25.95	3.92 ± 19.44	32.02 ± 46.72	< 0.001	1.000	< 0.001	< 0.001

Abbreviations: Pre-IMRT, before intensity-modulated radiation therapy (baseline); Immediately Post-IMRT, immediately after intensity-modulated radiation therapy; 3 Months, three months after intensity-modulated radiation therapy.
* Related-samples Friedman's two-way analysis of variance by ranks.
\# Bonferroni adjusted.

Table 5
Correlation of the comprehensive nutritional index (CNI) with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) and Quality of Life Questionnaire Head and Neck Cancer Module (QLQ-H&N35) (n = 359).

QLQ-C30 subscales	CNI		QLQ-H&N35 subscales	CNI	
	r	*P*		*r*	*P*
Physical functioning	0.245	< 0.001	Pain	−0.127	0.016
Role functioning	0.104	0.050	Swallowing	−0.158	0.003
Emotional functioning	0.114	0.032	Senses	−0.169	0.001
Cognitive functioning	0.127	0.017	Speech	−0.153	0.004
Global health status	0.152	0.004	Social eating	−0.123	0.020
Fatigue	−0.114	0.031	Social contact	−0.115	0.029
Pain	−0.105	0.047	Teeth	−0.126	0.017
Insomnia	−0.126	0.017	Opening mouth	−0.150	0.005
Appetite loss	−0.120	0.024	Sticky saliva	−0.125	0.018
Constipation	−0.109	0.040	Feeding tube	0.157	0.003
Financial difficulties	−0.124	0.019	Swallowing (3 Months)	−0.136	0.011
Social functioning (3 Months)	0.125	0.018	Felt ill (3 Months)	−0.125	0.018
Constipation (3 Months)	−0.114	0.032	Feeding tube (3 months)	0.109	0.039

Abbreviations: 3 Months, three months after intensity-modulated radiation therapy.

consistent with a previous study that demonstrated that QoL and nutrition index decreased dramatically in patients treated with IMRT with or without chemotherapy [5].

The CNI assesses immunological and nutrition functions of NPC patients and can help identify patients who require nutritional interventions and patients exhibiting better tolerance to IMRT [12]. Single or double nutrition-related indexes, such as serum albumin, Hb, TLC, and body weight, are unlikely to represent total nutrition status [13–15]. A previous study established the CNI to evaluate the nutrition status of NPC patients. The CNI is calculated with several nutritional parameters (albumin level, TLC, Hb, BMI, and UBW%) [16]. Two principal components were extracted and combined with a weight coefficient. Lower CNI indicate a worse nutrition level. Results showed that patients who had stage III or IV (2010 UICC) NPC and underwent induction plus concurrent chemotherapy, in addition to IMRT, remained in poor nutritional status after IMRT. This might be because these patients were in the long-term consumption phase of the disease, and the complex chemotherapy regimen caused a series of side effects that were detrimental to the patients' nutrition status. Clinicians should pay more attention to these patients and correct their malnutrition.

Few studies combined QLQ-C30 with QLQ-H&N35 to assess QoL of NPC patients. This study utilized two questionnaires to reflect all aspects of functions and symptoms, and the results showed that all items immediately became worse after IMRT. Notably, oral symptoms were a serious problem after IMRT. Mouth dryness and mouth sores are common side effects in NPC patients [17]; salivary gland damage inevitably caused by the repeated radiation directly influenced the patients' ability to eat [18]. Meanwhile, our study showed that pain is statistically related to advanced stages of cancer and directly affected QoL [19]. Patients with serious pain were likely to choose to insert a gastric tube by themselves with the help of nurses. In addition, appetite loss, difficulty swallowing, sense, dry mouth, and sticky saliva continued to negatively impact survivors' QoL three months after IMRT. Patients' sexuality was still lessened three months after IMRT, probably because of body weakness or other side effects of IMRT.

According to previous studies, malnutrition negatively influences QoL in patients with head and neck cancer both before and shortly after treatment [14,20], and head and neck cancer patients treated with radiotherapy had the highest prevalence of malnutrition immediately after and three months after IMRT [21,22]. Therefore, the nutrition status of NPC patients should be evaluated as an important determinant of QoL in NPC patients.

The Spearman rank correlation results indicated that the lower CNI scores related poorer QoL after IMRT. Fatigue is a common and frequently disabling symptom in cancer survivors [23] that can last for a long time after treatment. Fatigue influences patients' daily activities [24], increases anxiety and depression, and lowers QoL. Feeling pain is common among head and neck cancer patients, with a prevalence of 60% at diagnosis and 55% during treatment [25]. Oral complications greatly affect patients' eating habits and nutrition level, and clinicians should take more measures to improve the oral health of NPC patients.

Analysis of survival showed that low CNI scores were associated

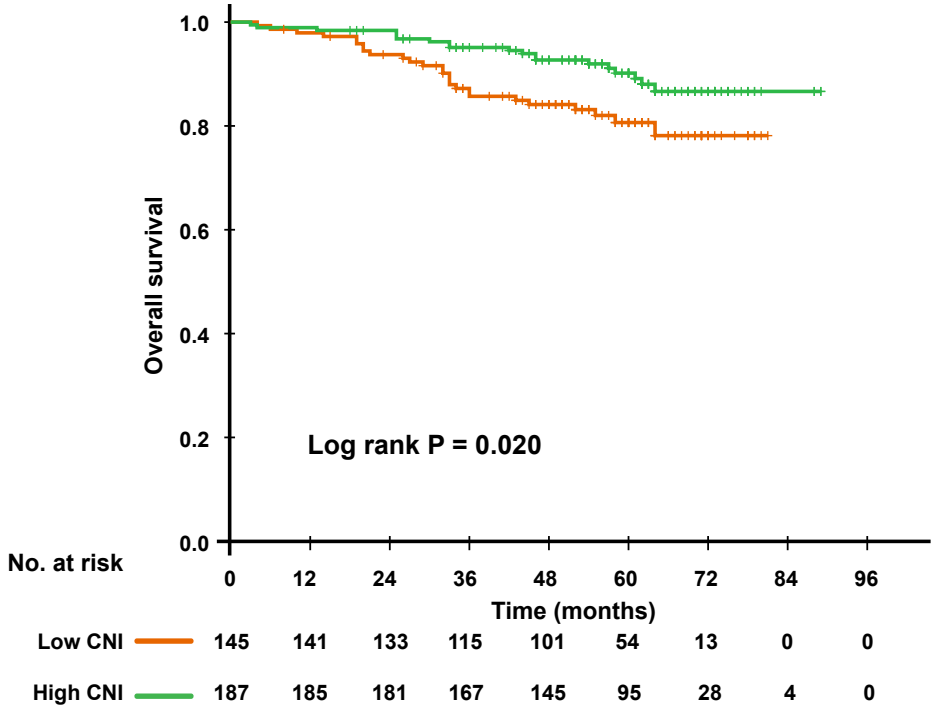

Fig. 1. Kaplan–Meier OS curves of patients with lower or higher comprehensive nutritional index (n = 332).

Table 6
Multivariable analysis of prognostic factors for overall survival (n = 332).

Characteristic	HR	*95% CI*	*P value*
Age	1.307	0.796–2.145	0.290
Sex	0.733	0.337–1.593	0.432
UICC stage	2.114	1.159–3.857	0.015
CNI	0.544	0.299–0.989	0.046

Abbreviations: HR = hazard ratio; CI = confidence interval; UICC = Union for International Cancer Control; CNI = comprehensive nutritional index.
A Cox proportional hazard model was used to perform multivariate analyses. All variables were transformed into categorical variables. HRs were calculated for Age (years) (> 44 vs. ≤ 44); Sex (Female vs. Male); UICC stage (IV vs. I–III); CNI (> 0.177 vs. ≤ 0.177).

with short survival time, while patients with high CNI scores achieved higher overall survival. Several reasons may explain why CNI affected survival outcomes. Firstly, poor nutrition status may have prolonged treatment duration and reduced radiochemotherapy tolerance. Secondly, malnutrition may have weakened defense mechanisms, including cellular and immune systems, further increasing the risk of secondary infection [26].

Psychological problems of NPC patients also needed more attention by clinicians. Depression and anxiety are salient psychological problems in cancer patients; their prevalence ranges from 25% to 54% [27]. Studies indicate that psychological disorders are apparent at the start of radiation therapy and last for a long time after radiation therapy [28,29]. Negative mental states can increase the risk of insomnia and emotional dysfunction, and thus influence patients' nutrition intake. More communication is needed to know the inner thoughts of NPC patients and propose specific methods to overcome psychological problems.

This study has a few limitations. Firstly, the patients were treated with various treatment plans, which may result in confounding effects. Secondly, the effect of psychological problems on CNI was not investigated. Future research should include a qualitative study designed to explore the reasons for patients' psychological disorders in order to provide solutions for NPC patients.

Conclusion

Malnutrition and decreased QoL are common in NPC patients. This study combined two questionnaires to reflect QoL and established a CNI for use in NPC patients. The CNI reflects the integrated nutrition status of NPC patients. Low CNI scores in NPC patients were associated with poor QoL and predicted poor survival outcomes. More interventions should be taken to improve the comprehensive nutrition condition of patients with NPC to enhance survival outcomes.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

We thank for the patients who participated in this study. Our work were also supported by department of Nasopharyngeal Carcinoma and Nursing department, Sun Yat-sen University Cancer Center.

Funding

This research was partly supported by grants from the Medical Research Foundation of Guangdong Province (No: A2014252), the Nurses Fund of Sun Yat-sen University Cancer Center (No: 201301) and the Nursing Youth Talents Foundation of Sun Yat-sen University (No: N2017Y04).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.09.014.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.

[2] Li G, Jiang XY, Qiu B, et al. Vicious circle of acute radiation toxicities and weight loss predicts poor prognosis for nasopharyngeal carcinoma patients receiving intensity modulated radiotherapy. J Cancer 2017;8(5):832–8. https://doi.org/10.7150/jca.17458.
[3] Rhoten BA, Murphy BA, Dietrich MS, et al. Depressive symptoms, social anxiety, and perceived neck function in patients with head and neck cancer. Head Neck 2018;40(7):1443–52. https://doi.org/10.1002/hed.25129.
[4] Hoxbroe MS, Gronhoj C, Hoxbroe MJ, et al. Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. Eur J Cancer 2017;78:91–102. https://doi.org/10.1016/j.ejca.2017.03.006.
[5] He Y, Chen L, Chen L, et al. Relationship between the comprehensive nutritional index and the EORTC QLQ-H&N35 in nasopharyngeal carcinoma patients treated with intensity-modulated radiation therapy. Nutr Cancer 2017;69(3):436–43. https://doi.org/10.1080/01635581.2017.1283422.
[6] Qiu C, Yang N, Tian G, et al. Weight loss during radiotherapy for nasopharyngeal carcinoma: a prospective study from northern China. Nutr Cancer 2011;63(6):873–9. https://doi.org/10.1080/01635581.2011.582223.
[7] Ma L, Wu T, Pan J, et al. The correlation between the comprehensive nutrition index and quality of life of patients with nasopharyngeal carcinoma treated by intensity-modulated radiotherapy. Nutr Cancer 2014;66(1):152–8. https://doi.org/10.1080/01635581.2014.853815.
[8] Zhao C, Han F, Lu LX, et al. Intensity modulated radiotherapy for local-regional advanced nasopharyngeal carcinoma. Ai Zheng 2004;23(11 Suppl):1532–7.
[9] Bian X, Song T, Wu S. Outcomes of xerostomia-related quality of life for nasopharyngeal carcinoma treated by IMRT: based on the EORTC QLQ-C30 and H&N35 questionnaires. Expert Rev Anticancer Ther 2015;15(1):109–19. https://doi.org/10.1586/14737140.2015.961427.
[10] Dinescu FV, Ţiple C, Chirilă M, et al. Evaluation of health-related quality of life with EORTC QLQ-C30 and QLQ-H&N35 in Romanian laryngeal cancer patients. Eur Arch Otorhinolaryngol 2016;273(9):2735–40. https://doi.org/10.1007/s00405-015-3809-0.
[11] Chen J, Liu P, Wang Q, et al. Influence of intensity-modulated radiation therapy on the life quality of patients with nasopharyngeal carcinoma. Cell Biochem Biophys 2015;73(3):731–6. https://doi.org/10.1007/s12013-015-0638-0.
[12] Paccagnella A, Morassutti I, Rosti G. Nutritional intervention for improving treatment tolerance in cancer patients. Curr Opin Oncol 2011;23(4):322–30. https://doi.org/10.1097/CCO.0b013e3283479c66.
[13] Capuano G, Gentile PC, Bianciardi F, et al. Prevalence and influence of malnutrition on quality of life and performance status in patients with locally advanced head and neck cancer before treatment. Support Care Cancer 2010;18(4):433–7. https://doi.org/10.1007/s00520-009-0681-8.
[14] van den Berg MG, Rasmussen-Conrad EL, van Nispen L, et al. A prospective study on malnutrition and quality of life in patients with head and neck cancer. Oral Oncol 2008;44(9):830–7. https://doi.org/10.1016/j.oraloncology.2007.11.002.
[15] Miao J, Xiao W, Wang L, et al. The value of the Prognostic Nutritional Index (PNI) in predicting outcomes and guiding the treatment strategy of nasopharyngeal carcinoma (NPC) patients receiving intensity-modulated radiotherapy (IMRT) with or without chemotherapy. J Cancer Res Clin Oncol 2017;143(7):1263–73. https://doi.org/10.1007/s00432-017-2360-3.
[16] Rapp-Kesek D, Stahle E, Karlsson TT. Body mass index and albumin in the preoperative evaluation of cardiac surgery patients. Clin Nutr 2004;23(6):1398–404. https://doi.org/10.1016/j.clnu.2004.06.006.
[17] Fang FM, Chiu HC, Kuo WR, et al. Health-related quality of life for nasopharyngeal carcinoma patients with cancer-free survival after treatment. Int J Radiat Oncol Biol Phys 2002;53(4):959–68.
[18] Salas S, Deville JL, Giorgi R, et al. Nutritional factors as predictors of response to radio-chemotherapy and survival in unresectable squamous head and neck carcinoma. Radiother Oncol 2008;87(2):195–200. https://doi.org/10.1016/j.radonc.2008.02.011.
[19] Oliveira KG, von Zeidler SV, Podestá JR, et al. Influence of pain severity on the quality of life in patients with head and neck cancer before antineoplastic therapy. BMC cancer 2014;14(1):39. https://doi.org/10.1186/1471-2407-14-39.
[20] Jager-Wittenaar H, Dijkstra PU, Vissink A, et al. Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer. Oral Oncol 2009:61–2. https://doi.org/10.1002/hed.
[21] Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. J Am Diet Assoc 2007;107(3):404–12. https://doi.org/10.1016/j.jada.2006.12.007.
[22] Ravasco P, Monteiro-Grillo I, Marques VP, et al. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head Neck 2005;27(8):659–68. https://doi.org/10.1002/hed.20221.
[23] Hofman M, Ryan JL, Figueroa-Moseley CD, et al. Cancer-related fatigue: the scale of the problem. Oncologist 2007;12(Suppl 1):4–10. https://doi.org/10.1634/theoncologist.12-S1-4.
[24] Diaz N, Menjon S, Rolfo C, et al. Patients' perception of cancer-related fatigue: results of a survey to assess the impact on their everyday life. Clin Transl Oncol 2008;10(11):753–7.
[25] van den Beuken-van EM, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 2007;18(9):1437–49. https://doi.org/10.1093/annonc/mdm056.
[26] Peng H, Chen B, Tang L, et al. Prognostic value of nutritional risk screening 2002 scale in nasopharyngeal carcinoma: a large-scale cohort study. Cancer Sci 2018;109(6):1909–19. https://doi.org/10.1111/cas.13603.
[27] Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. Psychooncology 2001;10(1):19–28.
[28] Tang Y, Luo D, Rong X, et al. Psychological disorders, cognitive dysfunction and quality of life in nasopharyngeal carcinoma patients with radiation-induced brain injury. PLoS ONE 2012;7(6):e36529https://doi.org/10.1371/journal.pone.0036529.
[29] Karasawa K, Horikawa N, Kawase E, et al. Assessment of psychological responses in patients about to receive radiotherapy. Radiat Med 2005;23(7):478–84.