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Original Article

The quality of life in nasopharyngeal carcinoma radiotherapy: A longitudinal study

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ABSTRACT

Objective: This article aims to longitudinally compare nasopharyngeal carcinoma (NPC) patients' quality of life (QoL) during radiotherapy (RT) and identify QoL correlates.
Methods: This study included 98 patients, with 85 completing full follow-up. Data were collected at baseline (T_1), midpoint of RT (T_2), and RT completion (T_3), between October 2021 and November 2022. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). RIOM severity was evaluated by the toxicity criteria of Radiation Therapy Oncology Group (RTOG). The nutritional status was evaluated using the Nutritional Risk Screening 2002 (NRS 2002), body mass index (BMI), and the Patient-Generated Subjective Global Assessment (PG-SGA). The generalized estimating equation described the QoL evolution and correlated it with RIOM, nutritional status, and other influential factors.
Results: Significant deterioration was observed in various subscales of EORTC QLQ-C30 during RT, including global health status (GHS), physical function, role function, emotional function, fatigue, nausea/vomiting, pain, insomnia, appetite loss, and constipation (all $P < 0.05$). Substantial deterioration was also observed in RIOM, nutritional status, and part of hematological indexes (all $P < 0.05$). The decline of QoL was associated with gender, age, education level, chemotherapy regimen, Karnofsky performance status (KPS) score, RIOM severity, NRS 2002 score, PG-SGA score, and lymphocyte level (all $P < 0.05$).
Conclusions: QoL declined during RT and were associated with certain factors. Healthcare professionals should focus on alleviating treatment-related complications and identifying individuals at high risk of malnutrition early to improve outcomes for patients with NPC.

Introduction

Nasopharyngeal carcinoma (NPC) arises from the nasopharyngeal epithelium and is characterized by a distinct geographical distribution, with a higher prevalence in East and Southeast Asia.[1,2] In 2020, there were approximately 133,400 new cases of NPC globally with China accounting for approximately 62,400 new cases (46.78% of all new cases.)[3,4] The nonkeratinizing subtype of NPC is predominant in endemic areas (95%) and exhibits high radiosensitivity.[1] NPC with stage II–IV is usually treated with radiotherapy (RT) to achieve disease control and radical treatment.[2,5,6]

RT aims to cure cancers; however, it also causes damage to normal tissues. On account of the particular location of the NPC, patients who receive RT nearly always experience various adverse reactions, including taste changes, xerostomia, oral and pharyngeal mucositis, dysphagia, and psychological issues,[7,8] in which radiation-induced oral mucositis (RIOM) is one of the most common and serious adverse reactions. These adverse reactions can significantly hinder the patient from eating, resulting in a decline of nutritional status, and impair functioning and well-being, leading to a decline in quality of life (QoL).[9]

QoL is now increasingly recognized as an important secondary or coprimary endpoint for evaluating the clinical benefits of treatment for

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patients with cancer.[10,11] Husson et al.[12] demonstrated that QoL assessment in yielded valuable prognostic information surpassing traditional sociodemographic and clinical measures, highlighting its relevance in clinical practice. Liao et al.[13] identified that long-term high mortality was partially mediated by QoL at pre-RT and 2 years post-RT in patients with NPC. A longitudinal study for patients with NPC with stage II–IV found that the QoL of patients was poor and substantially deteriorated over the concurrent chemoradiotherapy (CCRT) period.[14]

Therefore, a more holistic understanding of the evolution of QoL is crucial for effectively preserving it during RT. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) is one of the most widely used and validated cancer-specific patient-reported outcome (PRO) instruments.[15,16] In this prospective observational study, we longitudinally analyzed the QoL in patients with NPC during RT. Moreover, we identified the RIOM, nutritional status, hematological indexes, and other factors that may significantly influence QoL, enabling healthcare professionals to prioritize the most critical elements for improving the outcomes of patients.

Methods

Participants

This is a longitudinal prospective observational study involved hospitalized patients from Tianjin Medical University Cancer Institute and Hospital between October 2021 and November 2022, utilizing consecutive fixed-point sampling. All patients were treated with intensity-modulated radiotherapy (IMRT) with thermoplastic mask fixation and planned computed tomography. The single RT dose was 2.00/2.12 Gy, 5 times per week, and the duration of RT was approximately 6–7 weeks. Patients were treated with either RT alone or CCRT. The chemotherapy regimen involved weekly or triweekly administration of cisplatin or nedaplatin. All patients received standardized oral care before RT: (1) cleaning teeth in the dental clinic; (2) removing caries; and (3) treating periodontitis and gingivitis.

Inclusion criteria: (1) age $\geq$ 18 years old, (2) pathological diagnosis with NPC of non-keratinizing subtype, (3) receiving RT for the first time with a planned dose of 60–70 Gy in 30–35 fractions, (4) Karnofsky performance status (KPS) score $\geq$ 70, and (5) voluntarily participated in the study.

Exclusion criteria included: (1) presence of oral mucositis before RT, (2) receiving tube feeding or total parenteral nutrition, (3) distant metastasis or combined with other malignant tumors, and (4) having cognitive or mental disorders previously diagnosed by a psychiatrist. Screening was based on medical records.

In addition, patients who failed to complete the three follow-up visits on time due to various reasons, such as an interruption of RT, death, withdrawal from the study, and loss of contact were determined to be lost to follow-up.

Instrument

Sociodemographic and medical data

Sociodemographic data included gender, age, education level, smoking status, and alcohol consumption. Medical data included RT dose, RT sessions, diabetes history, KPS score, tumor stage, chemotherapy regimen, and hematological indexes [prealbumin, hemoglobin, white blood cell (WBC), neutrophil, and lymphocyte].

EORTC QLQ-C30

The EORTC QLQ-C30 V.3.0 was utilized to evaluate the QoL of participants. This scale with 30-items is composed of five functional scales (physical function, role function, cognitive function, emotional function, and social function), nine symptom scales (fatigue, nausea/vomiting, pain, appetite loss, diarrhea, dyspnea, constipation, insomnia, and financial difficulties), along with a global health status (GHS) scale.[15] Respondents were required to select from a four-point response format, ranging from "not at all" to "very much", except for the GHS scale, which employed a seven-point response format. The scores obtained were linearly transformed to a range of 0–100.[17] A higher score on the scales of function and GHS indicates better health, while a higher score on the symptom scales reflects a greater symptom burden.[18]

RTOG

The Radiation Therapy Oncology Group (RTOG) toxicity criteria were utilized to assess RIOM, which is categorized into four levels of severity.[19] Grade 1 of RIOM is associated with mucosal erythema or hyperemia. Grade 2 is characterized by the presence of spot-like ulcers. Grade 3 is identified by the presence of confluent fibrous mucositis. Grade 4 is manifested as hemorrhage or necrosis. Grades 1 and 2 are considered mild, while grades 3 and 4 are classified as severe.

NRS 2002

The nutritional risk of the participants was assessed using the Nutritional Risk Screening 2002 (NRS 2002). The NRS 2002 takes into account the severity of the patient's nutritional impairment [body mass index (BMI), weight loss, and change in dietary intake], the severity of the disease (the degree of increase in nutritional needs), and an additional adjustment for individuals aged $\geq$ 70 years. The NRS 2002 score ranges from 0 to 7, and a score of $\geq$ 3 indicates nutritional risk.[20]

PG-SGA

The Patient-Generated Subjective Global Assessment (PG-SGA) was used to assess the nutritional status of the patients. The PG-SGA is a comprehensive tool that comprises the patient's self-report and the medical practitioners' evaluation.[21,22] The former assesses body weight change, food intake, related symptoms, and physical function, while the latter considers disease, metabolic demand, and physical examination. The total score is the sum of the two components, with higher scores indicating higher levels of malnutrition. In a previous study,[23] the nutritional status was categorized into four levels based on the total score: "0–1" (well nourished), "2–3" (suspected malnutrition), "4–8" (mild malnutrition), and "$\geq$ 9" (severe malnutrition). A score of $\geq$ 9 indicates a critical need for nutrition intervention.[23]

Measures

Patient screening and data collection were performed by two researchers (YK and XW). The day before RT, researchers collected the sociodemographic data through a questionnaire and obtained medical data from the medical information system. During face-to-face assessments of the patients, the severity of RIOM was evaluated using the RTOG criteria. Additionally, the nutritional status was assessed using the NRS 2002 and the PG-SGA, while the EORTC QLQ-C30 was used to assess the QoL. The severity of RIOM, nutritional status, QoL, and hematological indexes were evaluated and collected at three time points: (1) T_1: baseline, (2) T_2: midpoint of RT (the day on which half of the total number of RT sessions was performed), and (3) T_3: completion of RT.

Sample size

The one-way repeated measures analysis was performed using the Power Analysis and Sample Size (PASS) V.2021 software to determine the required sample size. The sample size calculation was based on several parameters, including a desired power of 0.9, a significance level of 0.05, effect multipliers of 0.5, number of measurements of 3, a standard deviation of 10, an autocorrelation coefficient of 0.1, and means of GHS for patients with NPC in previous studies.[14] Based on the analysis, the software determined a required sample size of 74. To account for potential dropouts, the dropout rates were determined based on previous experience and panel discussion in our research center. Assuming a potential dropout rate of 20%, a total of 93 patients were deemed necessary for baseline assessment in this study.

Data analysis

The data were analyzed using SPSS V.26.0. Categorical variables were described as counts and percentages. Continuous variables with normal distribution were described by mean and standard deviation while non-normal distribution were described by median and interquartile range. The trend Chi-square test and generalized estimating equation (GEE) were used to describe the change of repeated measures of categorical variables and continuous variables over time, respectively. In addition, age, BMI, and the PG-SGA score were described as categorical and continuous variables, respectively. KPS score and RIOM severity were described as categorical variables and statistically analyzed as continuous independent variables. The linear GEE for continuous variables was operated with a robust estimator covariance matrix and an independent working correlation matrix to identify influential factors of QoL over RT. An independent variable with a $P < 0.1$ in the univariate model was entered into the multivariate model. Two-sided $P < 0.05$ was considered statistically significant in the multivariate model. To correct the risk of type 1 errors, Bonferroni correction was applied in the GEE model in which a Bonferroni-adjusted $P < 0.05$ indicated a statistically significant difference.

Ethical considerations

This study was conducted after obtaining approval from the Research Ethics Review Committee (IRB) of the Tianjin Medical University Cancer Institute and Hospital (IRB No. bc2021149). The hospital IRB approved both collection and the consent process. Furthermore, the participants were informed of confidentiality and their right to leave the study at will without penalty.

Results

Patient characteristics

A total of 134 patients with NPC underwent RT during this study; however, due to various reasons, 98 patients were included at baseline. Of those, five patients refused follow-up investigation due to inappropriate time or poor physical condition, and eight patients discontinued treatment due to severe RT toxicities, poor nutritional status, or other reasons. Ultimately, 90 and 85 patients underwent assessment at T_2 and T_3, respectively, resulting in a loss rate of 13.3% (13/98). The flowchart of patients is displayed in Fig. 1, and complete data from 85 patients were analyzed, with characteristics shown in Table 1. Patients received 30–35 (33.00 ± 0.60) sessions of RT with a total dose of 60–70 (69.73 ± 1.52) Gy.

Nutritional status, RIOM outcome, and hematological indexes over RT

The result of nutritional status, RIOM outcome, and hematological indexes of patients with NPC during RT are shown in Table 2. From T_1 to T_3, patients lost an average of 4.2 kg (−1.5 kg–14.0 kg), accounting for 5.9% (−2.0%–13.9%) of baseline weight. Furthermore, 47.1% of patients lost 5%–10% weight, and 12.9% of patients experienced a weight loss of > 10% over RT. BMI of patients was 24.70 ± 3.38 kg/m^2, 23.98 ± 3.26 kg/m^2, and 23.24 ± 3.21 kg/m^2 at T_1, T_2, and T_3, respectively. BMI significantly declined during RT (Wald $\chi^2 = 6.786$, $P = 0.009$). In terms of the NRS 2002 results, from T_1 to T_3, 3.5%, 32.9%, and 64.7% of patients scored ≥ 3. These results indicated that the ratio of nutritional risk increased substantially over RT (Wald $\chi^2 = 56.108$, $P < 0.001$). Moreover, the PG-SGA score was 2.81 ± 2.63, 12.07 ± 4.24, and 15.62 ± 4.82 at T_1, T_2, and T_3. In terms of malnutrition, 4.7% of patients were rated as severely malnourished at T_1, which increased to 78.8% at T_2, and further rose to 92.9% at T_3. The analysis revealed a progressive deterioration in nutritional status throughout the course of RT ($\chi^2 = 97.414$, $P < 0.001$).

According to the toxicity criteria of RTOG, the prevalence of RIOM was 0% (0/85), 94.1% (80/85), and 95.3% (81/85) at T_1, T_2, and T_3, respectively. Moreover, its severity increased substantially over RT ($\chi^2 = 154.502$, $P < 0.001$). Additionally, several hematological indexes declined during RT from T_1 to T_3. Specifically, prealbumin levels ($\chi^2 = 97.444$, $P < 0.001$), hemoglobin levels ($\chi^2 = 14.825$, $P < 0.001$), WBC counts ($\chi^2 = 18.050$, $P < 0.001$), and lymphocyte counts ($\chi^2 = 314.485$, $P < 0.001$) decreased during this period. In contrast, the variation of neutrophil counts ($\chi^2 = 1.530$, $P = 0.465$) was insignificant.

The QoL over RT

The result of QoL for patients during RT is presented in Table 3. The downward trend was significant in physical function (Wald $\chi^2 = 73.108$, $P < 0.001$), role function (Wald $\chi^2 = 26.641$, $P < 0.001$), and emotional

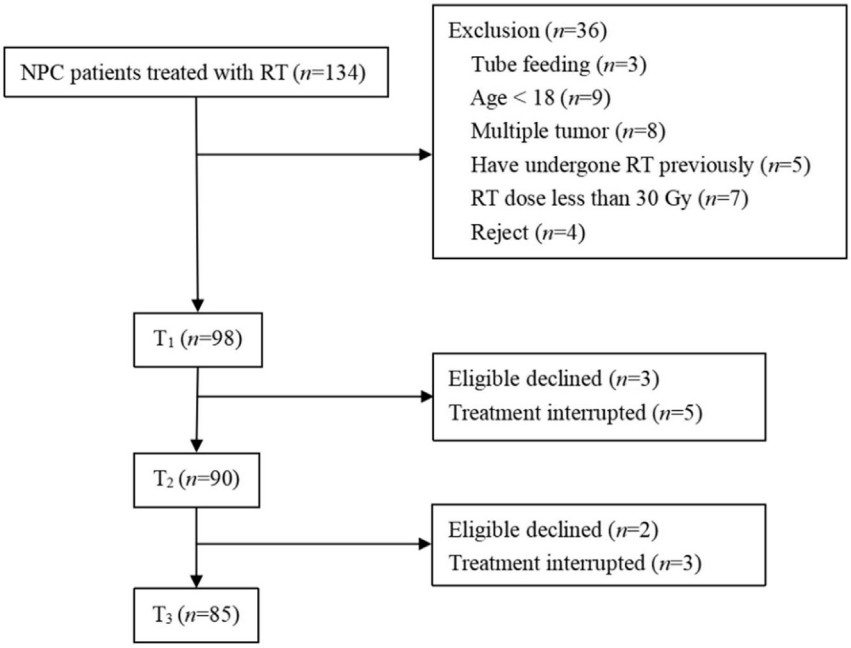

Fig. 1. Patient eligibility within the study. T_1, baseline; T_2, the midpoint of RT; T_3, the completion of RT. NPC, nasopharyngeal carcinoma; RT, radiation therapy.

Table 1
Comparison of sociodemographic and medical characteristics of patients ($n = 85$).

Variable	Category	(Mean ± SD)/*n* (%)	Variable	Category	(Mean ± SD)/*n* (%)
Age (years)[a,b]		49.41 ± 12.33	Diabetes history[b]	No	76 (89.4)
	< 60	67 (78.8)		Yes	9 (10.6)
	≥ 60	18 (21.2)	KPS score[b]	80	9 (10.6)
Gender[b]	Male	65 (76.5)		90	57 (67.1)
	Female	20 (23.5)		100	19 (22.4)
RT dose (Gy)[a]		69.73 ± 1.52	Tumor stage[b]	I	1 (1.2)
RT sessions[a]		33.00 ± 0.60		II	11 (12.9)
Education level[b]	Less than compulsory education	44 (51.8)		III	42 (49.4)
	Senior high school, vocational school, or junior college	25 (29.4)		IV	31 (36.5)
	Bachelor or above	16 (18.8)	Chemotherapy regimen[b]	RT	13 (15.3)
Smoking status[b]	Non-smoker	40 (47.1)		CCRT (cisplatin)	45 (52.9)
	Ever/current	45 (52.9)		CCRT (nedaplatin)	27 (31.8)
Alcohol consumption[b]	Non-drinker	46 (54.1)			
	Ever/current	39 (45.9)			

RT, radiation therapy; KPS, Karnofsky performance status; CCRT, concurrent chemoradiotherapy.
[a] (Mean ± SD).
[b] *n* (%).

function (Wald $\chi^2 = 7.861$, $P = 0.020$), from T_1 to T_3. Social function was the worst among the five functional domains. The symptom subscales, including fatigue (Wald $\chi^2 = 145.327$, $P < 0.001$), nausea/vomiting (Wald $\chi^2 = 29.134$, $P < 0.001$), pain (Wald $\chi^2 = 511.949$, $P < 0.001$), insomnia (Wald $\chi^2 = 45.934$, $P < 0.001$), appetite loss (Wald $\chi^2 = 116.650$, $P < 0.001$), and constipation (Wald $\chi^2 = 28.187$, $P < 0.001$), deteriorated significantly from T_1 to T_3. Furthermore, the decreasing score correlated with the ongoing decline of GHS from T_1 to T_3 (Wald $\chi^2 = 91.410$, $P < 0.001$), with 38.8% of patients experiencing a drop of more than 50% upon completion of RT.

Influential factors of the QoL outcome

In the univariable model using GEE, the EORTC QLQ-C30 subscale scores were set as the dependent variables, while the independent variables included sociodemographic data, medical data, nutritional status, and RIOM severity (Table 4 and Supplementary Material 1). Afterward, the time points and significant independent variables ($P < 0.1$) from the univariable model were entered into the multivariable model (Table 5 and Supplementary Material 2).

The results of the multivariable model of EORTC QLQ-C30 using GEE are as follows: (1) Sociodemographic factors: Worse physical function (Wald $\chi^2 = 4.462$, $P = 0.035$), emotional function (Wald $\chi^2 = 11.394$, $P = 0.001$), and constipation outcome (Wald $\chi^2 = 7.748$, $P = 0.005$) were observed in female patients. Besides, elderly patients were more vulnerable to experiencing poorer role function (Wald $\chi^2 = 12.155$, $P = 0.002$). Moreover, patients with less education had worse emotional function (Wald $\chi^2 = 11.515$, $P = 0.003$) and GHS (Wald $\chi^2 = 7.400$, $P = 0.025$). (2) Medical factors: Patients taking cisplatin for CCRT were more likely to have worse GHS, compared to RT alone. Besides, a lower KPS score was correlated with inferior physical function (Wald $\chi^2 = 6.950$, $P = 0.008$). Moreover, lymphocyte levels were positively

Table 2
Nutritional status, RIOM, and hematological indexes across three time points ($n = 85$).

Items	Grade	T_1 (Mean ± SD)/*n* (%)	T_2 (Mean ± SD)/*n* (%)	T_3 (Mean ± SD)/*n* (%)	Trend χ^2/Wald χ^2	*P* value
BMI, kg/m^2		24.70 ± 3.38[d,e]	23.98 ± 3.26[c,e]	23.24 ± 3.21[c,d]	221.471[b]	< 0.001**
	< 24	36 (42.4)	44 (51.8)	53 (62.4)	6.786[a]	0.009*
	≥ 24	49 (57.6)	41 (48.2)	32 (37.6)		
NRS 2002	< 3	82 (96.5)	57 (67.1)	30 (35.3)	56.108[a]	< 0.001**
	≥ 3	3 (3.5)	28 (32.9)	55 (64.7)		
PG-SGA		2.81 ± 2.63[d,e]	12.07 ± 4.24[c,e]	15.62 ± 4.82[c,d]	549.548[b]	< 0.001**
	≤ 1	39 (45.9)	0 (0)	0 (0)	97.414[a]	< 0.001**
	2–3	23 (27.1)	0 (0)	0 (0)		
	4–8	19 (22.4)	18 (21.2)	6 (7.1)		
	≥ 9	4 (4.7)	67 (78.8)	79 (92.9)		
RIOM	0	85 (100.0)	5 (5.9)	4 (4.7)	154.502[a]	< 0.001**
	1	0 (0)	15 (17.6)	9 (10.6)		
	2	0 (0)	59 (69.4)	51 (60.0)		
	3	0 (0)	6 (7.1)	21 (24.7)		
Prealbumin, g/L		0.27 ± 0.06[d,e]	0.23 ± 0.06[c,e]	0.22 ± 0.05[c,d]	97.444[b]	< 0.001**
Hemoglobin, g/L		129.02 ± 18.76[e]	126.38 ± 16.25[e]	122.83 ± 15.81[c,d]	14.825[b]	< 0.001**
WBC count, ×10^9/L		5.62 ± 1.95[e]	5.03 ± 2.84	4.52 ± 1.87[c]	18.050[b]	< 0.001**
Neutrophil count, ×10^9/L		3.48 ± 1.65	3.83 ± 2.65	3.49 ± 1.63	1.530[b]	0.465
Lymphocyte count, × 10^9/L		1.55 ± 0.63[d,e]	0.58 ± 0.24[c,e]	0.41 ± 0.29[c,d]	314.485[b]	< 0.001**

T_1, baseline; T_2, the midpoint of RT; T_3, the completion of RT.
*$P < 0.05$, **$P < 0.001$.
BMI, body mass index; NRS 2002, the Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; RIOM, radiation-induced oral mucositis; WBC, white blood cell.
[a] Trend χ^2.
[b] Wald χ^2.
[c] Compare with 'T_1' time point, $P < 0.05$.
[d] Compare with 'T_2' time point, $P < 0.05$.
[e] Compare with 'T_3' time point, $P < 0.05$.

Table 3
The standard score of EORTC QLQ-C30 across three time points ($n = 85$).

Items	T_1(Mean ± SD)/(*M*, *IQR*)	T_2 (Mean ± SD)/(*M*, *IQR*)	T_3 (Mean ± SD)/(*M*, *IQR*)	Wald χ^2	*P* value
Functional scales					
Physical function	96.00 ± 6.19[b,c]	89.25 ± 11.55[a,c]	86.12 ± 11.56[a,b]	73.108	< 0.001**
Role function	94.51 ± 13.21[b,c]	90.59 ± 16.56[a,c]	83.73 ± 19.24[a,b]	26.641	< 0.001**
Emotional function	86.86 ± 19.56[c]	86.47 ± 16.72[c]	81.76 ± 16.54[a,b]	7.861	0.020*
Cognitive function	88.62 ± 16.83	88.24 ± 14.37	87.06 ± 15.08	1.632	0.442
Social function	80.59 ± 27.20	78.82 ± 28.45	76.67 ± 26.75	3.562	0.168
Symptom subscales/items					
Fatigue	0.00, 22.22[b,c]	33.33, 22.22[a,c]	33.33, 11.11[a,b]	145.327	< 0.001**
Nausea/vomiting	0.00, 16.67[c]	16.67, 33.33[a]	16.67, 33.33[a]	29.134	< 0.001**
Pain	0.00, 0.00[c]	33.33, 33.33[a,c]	50.00, 16.67[a,b]	511.949	< 0.001**
Dyspnea	0.00, 0.00	0.00, 0.00	0.00, 33.33	2.494	0.287
Insomnia	0.00, 0.00[b,c]	0.00, 33.33[a,c]	33.33, 33.33[a,b]	45.934	< 0.001**
Appetite loss	0.00, 33.33[b,c]	33.33, 16.67[a,c]	33.33, 16.67[a,b]	116.650	< 0.001**
Constipation	0.00, 0.00[c]	0.00, 33.33[a]	0.00, 33.33[a]	28.187	< 0.001**
Diarrhea	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.351	0.839
Financial difficulties	33.33, 66.67	33.33, 66.67	33.33, 66.67	1.226	0.542
GHS	77.84 ± 15.62[b,c]	65.20 ± 16.38[a,c]	58.92 ± 14.65[a,b]	91.410	< 0.001**

T_1, baseline; T_2, the midpoint of RT; T_3, the completion of RT.
*$P < 0.05$, **$P < 0.001$.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; GHS, global health status.
[a] Compare with 'T_1' time point, $P < 0.05$.
[b] Compare with 'T_2' time point, $P < 0.05$.
[c] Compare with 'T_3' time point, $P < 0.05$.

associated with role function (Wald $\chi^2 = 4.105$, $P = 0.043$). (3) Nutritional status: Patients with a high nutritional risk (NRS 2002 score ≥ 3) were more susceptible to worse physical function (Wald $\chi^2 = 5.880$, $P = 0.015$) and constipation outcome (Wald $\chi^2 = 5.895$, $P = 0.015$). Furthermore, the PG-SGA outcome suggested that poorer nutritional status was related to a worse physical function (Wald $\chi^2 = 13.311$, $P = 0.004$), role function (Wald $\chi^2 = 8.559$, $P = 0.036$), GHS (Wald $\chi^2 = 18.878$, $P < 0.001$), fatigue ($\chi^2 = 16.482$, $P = 0.001$), nausea/vomiting ($\chi^2 = 18.478$, $P < 0.001$), insomnia ($\chi^2 = 13.356$, $P = 0.004$), and appetite loss ($\chi^2 = 49.266$, $P < 0.001$). (4) RIOM: The RIOM severity was related to the deterioration of pain (Wald $\chi^2 = 13.697$, $P < 0.001$) and insomnia (Wald $\chi^2 = 4.761$, $P = 0.029$). In addition, tumor stage, BMI, smoking status, alcohol consumption, diabetes history, and some hematological indexes (prealbumin, hemoglobin, and WBC) showed no association with QoL.

Discussion

In this longitudinal study, we included 98 NPC patients who received RT, of which 85 patients completed full follow-up. This study documented a significant deterioration of QoL, nutritional status, RIOM, and hematological indexes. The most prominent declines were observed in the physical function and role function domains of the functional subscales. Additionally, significant deteriorations were noted in the symptom subscales, specifically in the areas of pain, appetite loss, and fatigue. Furthermore, the GHS also showed a substantial decline during the course of RT. The analysis revealed that female gender, older age, lower educational level, cisplatin-based chemotherapy, lower KPS score, more severe RIOM, worse nutritional status, and lower lymphocyte counts were associated with poorer QoL outcomes.

Research has stressed the importance of maintaining QoL during cancer treatment.[24] Patients with NPC undergoing RT tend to experience a range of adverse reactions that impact QoL substantially.[25] In this study, patients' physical function and role function declined the most of all functional subscales. This finding contrasts with previous studies on patients with NPC, where social function and role function were found to be most affected by RT.[14] It is worth noting that the discrepancy in findings could potentially be attributed to the older age of patients in our study, as older individuals tend to have poorer physical function.[27,26] Notably, the average age of patients in our study was higher than that in previous studies (49.41 ± 12.33 vs 44.3 ± 9.8), which may explain the differences in the specific functional domains most affected by RT. In addition, we found that patients' social function received the lowest score among all functional subscales, highlighting the degree of impact that cancer can have on social interaction, which was consistent with previous studies.[28] Unfortunately, we failed to detect the significant variation in social function during RT. The data of this study were collected during the COVID-19 pandemic, and only the patients who were hospitalized throughout the whole course were included. Under the epidemic control policy, patients could only commute between the RT treatment room and the inpatient ward until all RT sessions were completed. It restricted family life and social activities, and it also resulted in a relatively isolated environment, leading to a lack of social engagement and limited opportunities for interpersonal relationships.

In addition, the decline in symptoms is noteworthy. The symptoms of pain, fatigue, and appetite loss were most significantly aggravated during RT, which confirmed relevant studies.[28] Previous studies had shown that the pain experienced by patients with NPC receiving RT was mainly caused by RIOM.[29] It was also confirmed in the face-to-face oral assessment for patients in this study that pain caused by RIOM greatly affected patients' eating and sleeping. Chen et al[30] reported increased levels of fatigue across all dimensions in patients with NPC undergoing CCRT, as measured by the Multiple Dimensional Inventory-20 Questionnaire. Additionally, our observations showed that almost all patients experienced taste abnormalities, hyposalivation, and xerostomia, which may be the primary reasons for appetite loss in patients with NPC undergoing RT.

This study revealed significant disparities in the QoL based on gender, age, and education level. We found that female patients had worse physical function and emotional function, as well as more severe constipation symptoms. A study examining the QoL of 5,339 cancer survivors found that female patients reported worse physical functioning compared to male patients, which might be primarily related to biological differences.[31] McCrea et al[32] evaluated the gender difference related to constipation in 519 patients and found that women were more likely to have constipation than men, and constipation symptoms lasted longer, which may be due to the influence of women's physiological structure and hormone levels. In addition, a Spanish study found that women reported more emotional symptoms than men among patients with cancer.[33] This disparity could be associated with women's susceptibility to changes in body image caused by RT and its negative impact on their daily lives.

Table 4
Univariable modeling of EORTC QLQ-C30, analyzed by GEE ($n = 85$) (Wald χ^2, P).

Item	Values	Physical function	Role function	Emotional function	GHS	Fatigue	Nausea/ vomiting	Pain	Insomnia	Appetite loss	Constipation
Time point	T_1=1 T_2=2 T_3=3	73.108, <0.001	26.641, <0.001	7.861, 0.020	91.410, <0.001	145.327, <0.001	29.134, <0.001	511.949, <0.001	45.934, <0.001	116.650, <0.001	27.187, <0.001
Gender	Male=1 Female=2	5.525, 0.019	0.002, 0.962	13.428, <0.001	2.605, 0.106	7.463, 0.006	7.326, 0.007	4.018, 0.045	2.739, 0.098	0.209, 0.648	5.039, 0.025
Age	<60=1 ≥60=2	9.174, 0.002	9.081, 0.003	0.769, 0.381	2.335, 0.127	2.682, 0.101	0.003, 0.954	1.960, 0.162	0.785, 0.376	4.287, 0.038	2.936, 0.087
Education level	Less than compulsory education=1 Senior high school, vocational school, or junior college=2 Bachelor or above=3	0.502, 0.778	1.850, 0.397	7.335,0.026	8.006, 0.018	2.231, 0.328	0.317, 0.853	3.306,0.191	0.441, 0.802	3.382, 0.184	4.205, 0.122
Chemotherapy regimen	RT=1 CCRT (cisplatin)=2 CCRT (nedaplatin)=3	2,157, 0.340	1.725, 0.422	0.979, 0.613	4.741, 0.093	7.237, 0.027	5.634, 0.060	1.214, 0.545	3.192, 0.203	0.353, 0.838	1.534, 0.464
Tumor stage	Stage I or Stage II=1 Stage III=2 Stage IV=3	0.701, 0.704	3.062, 0.216	0.751, 0.687	0.638, 0.727	0.353, 0.838	0.006, 0.997	0.211, 0.900	1.522, 0.467	1.764, 0.414	1.322, 0.516
Smoking status	Non-smoker=0 Ever/current=1	0.115,0.735	0.328, 0.567	1.923, 0.165	1.451, 0.228	0.021, 0.886	0.947, 0.330	0.444, 0.505	0.556, 0.456	0.293, 0.589	0.002, 0.966
Alcohol consumption	Non-drinker=0 Ever/current=1	1.060, 0.303	0.233, 0.629	0.300, 0.584	1.141, 0.285	6.524, 0.011	7.275, 0.007	0.057, 0.811	4.068, 0.044	2.415, 0.120	0.627, 0.429
Diabetes history	No=0 Yes=1	0.331, 0.565	1.289, 0.256	0.036, 0.850	0.609, 0.435	1.078, 0.299	2.754, 0.097	0.011, 0.916	0.004, 0.948	0.243, 0.622	0.003, 0.958
KPS score		15.612, <0.001	9.059, 0.003	1.379, 0.240	1.318, 0.251	4.537, 0.033	0.936, 0.333	0.982, 0.322	0.009, 0.923	0.079, 0.778	0.639, 0.424
BMI, kg/m^2	<24=1 ≥24=2	7.280, 0.007	3.293, 0.070	0.002, 0.961	3.007, 0.083	7.413, 0.006	1.684, 0.194	13.839, <0.001	0.035, 0.853	3.381, 0.066	0.288, 0.592
NRS 2002	<3=1 ≥3=2	47.063, <0.001	27.263, <0.001	1.474, 0.225	47.031, <0.001	55.091, <0.001	19.898, <0.001	66.006, <0.001	12.428, <0.001	29.299, <0.001	16.859, <0.001
PG-SGA	≤1=1 2~3=2 4~8=3 ≥9=4	101.126, <0.001	35.632, <0.001	10.703, 0.013	110.832, <0.001	153.164, <0.001	92.245, <0.001	351.458, <0.001	67.514, <0.001	258.448, <0.001	35.289, <0.001
RIOM		51.617, <0.001	15.826, <0.001	7.620, 0.006	87.563, <0.001	79.931, <0.001	23.292, <0.001	351.039, <0.001	34.070, <0.001	57.542, <0.001	34.576, <0.001
Prealbumin, g/L		12.561, <0.001	13.903, <0.001	0.149, 0.700	11.653, 0.001	14.433, <0.001	1.231, 0.267	25.623, <0.001	0.043, 0,837	0.772, 0.380	3.267, 0.071
Hemoglobin, g/L		28.006, <0.001	8.234, 0.004	3.270, 0.071	5.811, 0.016	18.288, <0.001	2.124, 0.145	13.070, <0.001	0.079, 0.779	2.428, 0.119	3.039, 0.081
WBC count, ×10^9/L		0.288, 0.592	1.048, 0.306	3.075, 0.080	1.215, 0.270	3.722, 0.054	0.730, 0.393	9.633, 0.002	8.200, 0.004	2.030, 0.154	1.707, 0.191
Lymphocyte count, ×10^9/L		24.917, <0.001	23.853, <0.001	0.690, 0.406	39.387, <0.001	45,106, <0.001	9.386, 0.002	106.849, <0.001	32.002, <0.001	31.975, <0.001	15.719, <0.001

Color, $P < 0.1$.
T_1, baseline; T_2, the midpoint of RT; T_3, the completion of RT.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GEE, generalized estimating equation; GHS, global health status; RT, radiation therapy; CCRT, concurrent chemoradiotherapy; KPS, Karnofsky performance status; BMI, body mass index; NRS 2002, the Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; RIOM, radiation-induced oral mucositis; WBC, white blood cell.

QoL also varied by age group. This study found that patients under 60 years old were more likely to show poor role function during RT, which was consistent with a previous study.[34] The reason may be attributed to the increased burden of family and social responsibilities experienced by younger patients. These individuals may face a significant reduction in their role function due to physical decline and work interruptions caused by the side effects endured over the course of 6–7 weeks of RT. A study of 1796 patients with bladder cancer showed that long-term overall QoL deteriorated with age.[35] Nevertheless, while age and gender cannot be changed, it is crucial to develop coping strategies to mitigate the impact of cancer and symptoms on QoL.[36]

Patients with less education had a worse emotional function and GHS. Education is related to overall health, including physical health and mental health.[37] Wang et al[38] investigated the psychological status of 232 patients with NPC during RT and found that patients with lower education level had higher levels of anxiety and depression. Yu et al[39] investigated emotional disorders of 190 patients with NPC and found that the lower the educational level of patients, the more serious the emotional disorders. Education level is closely related to the ability to cope with stressful events and affects the emotional regulation ability of patients with cancer. It has been observed that patients with higher levels of education tend to exhibit a wider range of regulatory styles and possess enhanced self-regulation abilities, particularly in the realm of emotion. In addition, educational level was related to the GHS of patients. Previous studies of patients with NPC confirmed the positive correlation between education level and GHS.[41,40] Patients with higher educational levels often demonstrate higher health literacy, greater income, and improved access to more healthcare resources and financial support. These factors collectively contribute to a more favorable health outcome.[42,43,44] Therefore, it is suggested that clinical practitioners should pay attention to patients with low education level and provide more tailored support where necessary.

Additionally, patients who received cisplatin for chemotherapy had poorer GHS during RT than those who received RT alone. A meta-analysis showed that the addition of CCRT to IMRT increased the severity of acute toxic reactions for patients with NPC.[45] Moreover, compared with RT alone, patients with NPC receiving CCRT had a higher incidence of severe late toxic reactions.[47,46] Compared with patients receiving RT alone, patients receiving CCRT experience a higher rate and more severe toxic effects. These adverse effects directly impact the patients' GHS. It emphasizes that healthcare professionals should closely monitor the side effects of patients who take cisplatin for CCRT.

Table 5
Multivariable modeling of EORTC QLQ-C30, analyzed by GEE ($n = 85$) (Wald χ^2, P).

Item	Values	Physical function	Role function	Emotional function	GHS	Fatigue	Nausea/ vomiting	Pain	Insomnia	Appetite loss	Constipation
Time point	T_1=1 T_2=2 T_3=3	0.239, 0.888	12.155, 0.002	9.646, 0.008	5.116, 0.077	2.594, 0.273	0.241, 0.886	34.704, <0.001	15.858, <0.001	5.164, 0.076	0.887, 0.642
Sex	Male=1 Female=2	4.462, 0.035	-	11.394, 0.001	-	1.859, 0.173	1.980, 0.159	1.888, 0.169	0.625, 0.429	-	7.748, 0.005
Age	<60=1 ≥60=2	3.752, 0.053	5.477, 0.019	-	-	-	-	-	-	2.957, 0.086	3.198, 0.074
Education level	Less than compulsory education=1 Senior high school, vocational school, or junior college=2 Bachelor or above=3	-	-	11.515, 0.003	7.400, 0.025	-	-	-	-	-	-
Chemotherapy regimen	RT=1 CCRT (cisplatin)=2 CCRT (nedaplatin)=3	-	-	-	6.356, 0.042	5.425, 0.066	4.305, 0.116	-	-	-	-
Alcohol consumption	Non-drinker=0 Ever/current=1	-	-	-	-	2.668, 0.102	3.819, 0.051	-	2.419, 0.120	-	-
Diabetes history	No=0 Yes=1	-	-	-	-	-	2.955, 0.086	-	-	-	-
KPS Score		6.950, 0.008	2.556, 0.110	-	-	2.705, 0.100	-	-	-	-	-
BMI, kg/m^2	<24=1 ≥24=2	0.711, 0.399	0.072, 0.789	-	1.509, 0.219	0.726, 0.394	-	1.171, 0.279	-	0.004, 0.952	-
NRS 2002	<3=1 ≥3=2	5.88, 0.015	3.124, 0.077	-	0.204, 0.652	1.114, 0.291	2.211, 0.137	0.061, 0.804	0.069, 0.792	0.401, 0.527	5.895, 0.015
PG-SGA	≤1=1 2~3=2 4~8=3 ≥9=4	13.311, 0.004	8.559, 0.036	3.501, 0.321	18.878, <0.001	16.482, 0.001	18.478, <0.001	3.837, 0.280	13.356, 0.004	49.266, <0.001	3.902, 0.272
RIOM		3.096, 0.078	0.416, 0.519	2.570, 0.109	2.893, 0.089	2.504, 0.114	0.022, 0.882	13.737, <0.001	4.761, 0.029	0.001, 0.970	3.441, 0.064
Prealbumin, g/L		0.010, 0.919	3.594, 0.058		0.392, 0.531	1.740, 0.187	-	0.969, 0.325	-	-	0.075, 0.784
Hemoglobin, g/L		0.159, 0.690	0.002, 0.962	0.006, 0.936	0.004, 0.950	2.616, 0.106	-	2.297, 0.130	-	-	0.521, 0.470
WBC count, ×10^9/L		-	-	0.689, 0.407	-	0.565, 0.452	-	0.179, 0.672	0.563, 0.453	-	-
Lymphocyte count, ×10^9/L		1.795, 0.180	4.105, 0.043	-	0.031, 0.859	3.526, 0.060	0.311, 0.577	0.166, 0.684	2.581, 0.108	0.646, 0.422	<0.001, 0.996

Color, $P < 0.05$.
T_1, baseline; T_2, the midpoint of RT; T_3, the completion of RT.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GEE, generalized estimating equation; GHS, global health status; RT, radiation therapy; CCRT, concurrent chemoradiotherapy; KPS, Karnofsky performance status; BMI, body mass index; NRS 2002, the Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; RIOM, radiation-induced oral mucositis; WBC, white blood cell.

Patients with a lower KPS score at baseline had a greater decline in physical function during RT. KPS is a method to assess patients' functional status.[48] It is an observer- and clinically oriented measurement method and is generally used as an admission criterion for oncology-related trials.[49] It is widely used to assess the physical functional status of patients with cancer.[51,50] A cohort study comparing toxic effects and oncology outcomes in patients with NPC found that KPS scores were correlated with overall survival, progression-free survival, and toxic effects.[52] Another study found a higher prevalence of cancer cachexia in patients with lower KPS scores.[53] KPS score can reflect the physical function of patients with NPC and has an important role in prognosis. Assessing the KPS score upon admission is essential to evaluate patients' functional capacity. For patients with low KPS scores, it is crucial to provide prospective individualized nutrition and toxicity management. By tailoring interventions to address the specific needs of these patients, their overall treatment outcomes and QoL can be improved.

The results have shown that more severe RIOM was associated with more serious pain and insomnia. These correlations may be attributed to more severe mucosal damage that resulting in a more intense pain sensation. Other similar studies have also reported that RIOM was the major cause of pain in patients with head and neck cancer.[54] A study for patients with NPC by McDowell et al[55] demonstrated that RIOM significantly reduced the QoL and lasted for a long period. We surveyed patients and found that pain was the most important factor of sleep disturbance. It suggests the importance of prevention and management of RIOM to maintain patients' QoL over the course of RT.

The reduction in QoL was associated with deteriorating nutritional status. The nutritional guidelines for patients with cancer emphasized the important role of nutritional status in QoL and stated that weight loss may increase the risk of radiation-related toxicity, impair physical function, and shorten survival.[56] In this study, patients with nutritional risk (NRS 2002 $\geq$ 3) were more likely to have constipation and poorer physical function. A study of 101 consecutive hospitalized patients found that the incidence of constipation was higher in patients with nutritional risk than in patients without it (52% vs. 34%).[57] Results of a systematic review showed that nutritional risk was associated with lower functional status in hospitalized patients with cancer.[58] There are several reasons that can explain these observations. First, patients with symptoms such as hypoptyalism, xerostomia, pain, and dysphagia may experience changes in their dietary habits. They tend to consume a higher proportion of liquid intake while reducing their fiber intake, which can lead to the exacerbation of constipation. Second, due to these symptoms, patients eat less food, resulting in nutritional deficiencies, which in turn lead to decreased physical function.

Furthermore, malnourished patients have a poorer QoL than well-nourished patients. In this study, the PG-SGA score was significantly associated with physical function, role function, GHS, fatigue, nausea/

vomiting, insomnia, and appetite loss, which is similar to previous findings.[59] Vergara et al[60] evaluated the nutritional status and QoL of 97 patients with cancer and found that compared with malnourished patients, well-nourished patients had better GHS, physical function, role function, emotional function, and cognitive function, along with less fatigue, nausea/vomiting, pain, insomnia, and appetite loss. A cross-sectional study involving 265 patients with cancer found a negative correlation between the degree of malnutrition and functional status.[61] The symptoms section of the PG-SGA included early satiety, nausea/vomiting, and decreased appetite. In a cross-sectional study by Barajas et al[62] involving patients with cancer, a significant association was observed between role function and decreased appetite and early satiety, which was confirmed by this study. In addition, Tański et al[63] found that malnutrition was an important independent determinant of QoL, and it adversely affected patients' daily and cognitive functions. A study that investigated the nutritional status and QoL of 312 patients with cancer found that early nutritional monitoring could prevent malnutrition and improve QoL.[64] It is suggested that nutrition monitoring could be carried out for patients with NPC during the early stages of RT as a means of improving patient outcomes.

Furthermore, the results showed that patients with a lower lymphocyte count had worse role function; however, the evidence to support this association did not reach statistical significance. Moreover, the levels of other hematological indexes examined did not demonstrate a significant influence on QoL. It is possible that hematological indexes of patients with NPC cannot directly influence QoL over RT, and future studies may consider the regulating effect of hematological indexes on QoL outcomes.

Limitations

This study has several limitations that should be acknowledged. First, the study samples were collected exclusively at a single research center, which may limit the generalizability of the findings. Second, another important aspect to consider is the long-term effects of RT. The duration of this study may be relatively short in the context of patients with NPC, and therefore, further follow-up studies with extended periods of observation are warranted. Third, this study relied on self-reported measures of QoL, which can be prone to subjectivity. Future studies should consider incorporating objective measures, such as monitoring sleep quality, to complement self-reported data. Fourth, this study only included hospitalized patients. To obtain a more comprehensive understanding, future studies should further include patients in the outpatient department and compare whether there is a gap between the two groups. Finally, this study only examined one type of toxicity reaction (RIOM). However, it is crucial for further research to broaden its scope and include a wider range of toxicity reactions and their impact on QoL. For instance, future investigations should explore the effects of salivary gland inflammation, xerostomia, and altered smell, among other relevant reactions.

Conclusions

This study aimed to investigate the QoL outcomes of patients with NPC at three crucial stages during RT. The findings revealed a significant decline in QoL as radiation doses increased. Specifically, the functional subscales, the physical function and role function, experienced the largest decrease. In terms of symptom dimensions, patients reported higher levels of pain, appetite loss, and fatigue. Additionally, several factors were identified as closely associated with worse QoL. These included female gender, older age, lower educational level, cisplatin for chemotherapy, lower KPS score, more severe RIOM, worse nutritional status, and lower lymphocyte count. Based on these findings, healthcare professionals should prioritize patients who are at higher risk for malnutrition, address RT-related symptoms, and implement interventions to help maintain QoL throughout treatment. It is worth noting that the results emphasize the need for longer and more comprehensive multicenter studies. Such studies should include a wider range of toxicity reactions that may have an impact on QoL. By encompassing these additional factors, a more comprehensive understanding of the effects of RT on QoL can be obtained, enabling the development of more targeted and effective interventions.

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CRediT author statement

Zhang San: Conceptualization, Methodology, Software. **Priya Singh**: Data curation, Writing – Original draft preparation. **Wang Wu**: Visualization, Investigation. **Jan Jansen**: Supervision. **Ajay Kumar**: Software, Validation. **Sun Qi**: Writing – Reviewing and Editing.

Yajing Kan: Conceptualization, Investigation, Writing – Original Draft. **Shuang Yang**: Conceptualization, Resources, Writing – reviewing and editing. **Xueting Wu**: Investigation, Writing – original draft. **Siqi Wang**: Data curation, Software. **Xueyu Li**: Formal analysis, Software. **Fangyuan Zhang**: Formal analysis, Software. **Peiguo Wang**: Methodology, Project administration. **Jing Zhao**: Methodology, Supervision. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

All authors have none to declare.

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Ethics statement

The study was approved by the Tianjin Medical University Cancer Institute and Hospital (IRB No. bc2021149). All participants were provided with informed consent.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2023.100251.

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