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ORIGINAL RESEARCH

Systematic nutrition management for locally advanced nasopharyngeal carcinoma patients undergoing radiotherapy

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Objective: To evaluate the impact of systematic nutrition management (SNM) on nutritional status, treatment-related toxicity, quality of life (QoL), response rates, and survival in patients with locally advanced nasopharyngeal carcinoma (LA-NPC) treated by radiotherapy (RT).

Methods: In this retrospective study, 56 patients with LA-NPC were selected as nutrition management group (NG) for SNM during RT till 1 month later. Another 56 patients with LA-NPC receiving RT without SNM as control group (CG) were identified from the hospital database and matched pairs with NG patients according to age, gender, stage, and body mass index (BMI) prior to RT.

Results: At 1 month after RT, the percentage of malnourished patients with BMI <18.5 kg/m^2 was statistically significant reduced in NG as compared to the CG group (35.7% vs 58.9%, P=0.014). Nutritional indexes of body weight, hemoglobin, prealbumin, and lymphocyte in the NG were statistically significant higher than those in the CG group (P<0.05). NG patients had statistically significant less grade 3–4 oral mucositis during RT compared with the CG group (32.1% vs 51.8%, P=0.035). Furthermore, at 1 month after RT, an improved QoL was observed in NG patients with respect to physical, role and social functions, symptom scales of fatigue and pain, and the global health status as compared to the CG group (P< 0.05). With a median follow-up of 24.8 months, there were no statistical differences between NG and CG (P>0.05) for the 2-year progression-free survival and overall survival (84.2% versus 79.5% and 94.7% versus 92.3%, respectively.).

Conclusion: SNM for LA-NPC patients treated by RT resulted in better nutritional status, reduced treatment-related toxicity and improved QoL.

Keywords: nasopharyngeal carcinoma, radiotherapy, nutrition management, clinical outcome

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most prevalent malignancies in the Southeast Asia populations, and most patients are diagnosed with locally advanced disease (LA-NPC).[1] With intensity-modulated radiotherapy (IMRT) and systemic treatment, disease control and survival of LA-NPC patients have been substantially improved.[2–4] Nevertheless, nutritional problems such as weight loss and reduced protein-calorie intake remain quite common during RT, which have been found to be associated with lower survival rate and worse quality of life (QoL).[5–9] Systematic nutritional monitoring and intervention for patients with head and neck cancer could improve treatment outcomes.[10–12] So far, however, there is little research focusing on

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nutrition management for LA-NPC patients, which differ greatly from non-NPC head and neck cancer patients in terms of epidemiology, etiology, pathology, clinical presentation, treatment method, and response to treatment.

In this matched-pair retrospective study, LA-NPC patients who received definitive IMRT with or without SNM were analyzed. The aim of this work was to evaluate the impact of SNM on nutritional status, treatment-related toxicity, QoL, response rates, and survival in LA-NPC patients treated by RT.

Methods

Patient selection

Inclusion criteria were as follows: 1) newly diagnosed NPC with histological confirmation; 2) clinically staged $T_{3–4}N_{0–3}M_0$ or $T_{1–4}N_{1–3}M_0$; 3) Eastern Cooperative Oncology Group performance status 2 or lower; 4) no severe cardiopulmonary diseases; 5) treated by IMRT, and SNM was given in NG during RT till 1 month after treatment.

Between April 2014 and August 2017, 56 eligible patients with LA-NPC were selected as nutrition management group (NG) who treated at Affiliated Hospital of Jiangnan University and met the inclusion criteria; another 56 patients with LA-NPC receiving RT without SNM as control group (CG) were identified from the hospital database and matched pairs with NG according to age, gender, stage, and body mass index (BMI) prior to RT. Patients' characteristics at baseline in both groups are detailed in Table 1. All patients were staged according to 2010 Union for International Cancer Control staging system. This study was conducted in accordance with the principles of the Declaration of Helsinki, and it was approved by the Institutional Ethics Committee of Affiliated Hospital of Jiangnan University. All patients with LA-NPC in the NG obtained written informed consent prior to RT and SNM. For those matched-pair patients with LA-NPC, an exemption of written informed consent for inclusion was granted by the Institutional Ethics Committee, since the retrospective data are already there and clinical follow-up should be always needed for all treated patients anyway. Non-parametric tests were used to ensure that there was no statistically significant difference in the concerned factors between the matched pairs.

Treatment modality

IMRT was administered to all patients. The doses of RT were consistent with the recommendations of the National Comprehensive Cancer Network guidelines, with a total dose of 66–76 Gy to the primary tumor and involved cervical lymph nodes in 30–35 daily fractions. Dose constraints to organs at risk were in agreement with the Radiation Therapy Oncology Group (RTOG) 0225 protocol.

All enrolled patients received two cycles of neoadjuvant chemotherapy with the doublet regimen of docetaxel (75 mg/m^2 on day 1) plus nedaplatin (80 mg/m^2 on day 2). Concurrent systemic regimens during the course of IMRT are detailed in Table 1. Most patients (76.8%) received concurrent chemotherapy (CCT) with the doublet regimen of docetaxel (75 mg/m^2 on day 1) plus nedaplatin (80 mg/m^2 on day 2).

Nimotuzumab (200 mg, weekly) was administered in 17 patients (8 in NG and 9 in CG), and the other 9 patients (5 in NG and 4 in CG) received IMRT alone without any systemic therapy.

Nutrition management

NG patients received systematic nutrition management (SNM). Briefly, nutritional assessment was performed weekly from the beginning of RT till 1 month after RT by a registered dietician using Patient-Generated Subjective Global Assessment (PG-SGA), which has been accepted by the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association as the standard for nutritional assessment for cancer patients. They were scored and classified in three degrees: normal-nutrition (0–3 scores, PG-SGA A), moderate malnutrition (4–8 scores, PG-SGA B), and severe malnutrition (≥9 scores, PG-SGA C). Individualized nutritional interventions were administrated according to the total PG-SGA score of each patient. Patients with PG-SGA A were provided with nutritional counseling by a personalized dietary prescription. In addition to nutritional counseling, the malnourished (PG-SGA B or C) patients received oral supplements (Nutrison, Nutricia Ltd, Milupa GmbH) consisting of an energy-dense, high-protein, ready-to-use formula (4.62 kcal/g; 16% proteins, 36% lipids, 48% carbohydrates). The daily energy requirements were estimated by Harris-Benedict equation with a correcting factor of 1.5, and the total daily protein requirements were calculated at 1.5 g/kg of body weight. If patients were unable to maintain an adequate oral intake (less than 50% of the estimated requirements for two consecutive weeks), enteral nutrition by a nasogastric tube was administrated.

Table 1 Baseline characteristics of patients

Characteristics	NG	CG	*P*-value
	n (%)	n (%)	
Age, years			0.693
<54	35 (62.5)	37 (66.1)	
≥54	21 (37.5)	19 (33.9)	
Gender			0.809
Male	45 (80.4)	46 (82.1)	
Female	11 (19.6)	10 (17.9)	
Clinical T category			0.978
T1	5 (8.9)	5 (8.9)	
T2	9 (16.1)	8 (14.3)	
T3	24 (42.9)	26 (46.4)	
T4	18 (32.1)	17 (30.4)	
Clinical N category			0.893
N0	4 (7.1)	4 (7.1)	
N1	17 (30.4)	18 (32.1)	
N2	26 (46.4)	25 (44.6)	
N3	9 (16.1)	9 (16.1)	
Clinical stage			1.000
II	7 (12.5)	7 (12.5)	
III	30 (53.6)	30 (53.6)	
IVa	10 (17.9)	10 (17.9)	
IVb	9 (16.1)	9 (16.1)	
Concurrent systemic therapy			0.919
Concurrent chemotherapy	43 (76.8)	43 (76.8)	
Nimotuzumab	8 (14.3)	9 (16.1)	
None	5 (8.9)	4 (7.1)	

Abbreviations: NG, nutrition management group; CG, control group; T, tumor; N, lymph node.

Patients in CG received general nutrition counseling and a booklet with nutrition advice for radiation-induced toxicity. Referral to Nutrition Department for nutritional intervention usually occurred when symptoms or weight loss were manifest but patients with less severe side effects generally did not receive a specialized evaluation.

Patient evaluation and follow-up

Response rates were evaluated by the Response Evaluation Criteria in Solid Tumors at 3 months after RT. All patients were followed-up at intervals of 3 months after RT for 3 years, biannually for the next 2 years and annually thereafter.

Treatment-related toxicity during RT was assessed and recorded weekly by the radiotherapists using the Acute and Late Radiation Morbidity Scoring Criteria of RTOG. Radiation treatment breaks were defined as the interruption time of radiation >7 days.

Nutritional indexes, including body weight, BMI, hemoglobin, albumin, prealbumin, and lymphocyte were retrospectively collected. Changes of these indexes between pre-RT and 1 month after RT were analyzed. Patients with BMI <18.5 kg/m^2 were defined as malnutrition.

Patients' QoL was assessed with the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire core 30 (EORTC QLQ-C30) by the dietician before RT and 1 month after RT. In the EORTC QLQ-C30, there were five functional scales, three symptom scales, six single items, and a global health status scale. Higher scores indicated better QoL on global health status and functional scales and worse QoL on symptom scales and single items. Changes of these scales or items between pre-RT and 1 month after RT were analyzed.

Statistical analysis

The data were entered into an Excel spreadsheet and analyzed using the STAT software, version 12.0. The chi-squared test was used to analyze the enumeration data. Differences in continuous variables between groups were assessed using the Student *t*-test. Progression-free survival (PFS) was defined as the time between pathological diagnosis and the first occurrence of locoregional or distant recurrence or the last follow-up date. Overall survival (OS) was measured from the time of pathological diagnosis to the date of death or the last follow-up date. The estimated PFS and OS were calculated by the Kaplan–Meier method. The PFS or OS was compared between the two groups with log-rank test. A two-tailed $P<0.05$ was accepted as statistically significant.

Results

Response rates and survival

Objective response rate was 100% in both groups at 3 months after RT, with complete response and partial response rates of 82.1% vs 80.4% ($P>0.05$) and 17.9% vs 19.6% ($P>0.05$) in NG and CG.

At a median follow-up of 24.8 months [range, 8.7–54.2 months], a total of 19 patients failed with distant metastasis: 9 in NG and 10 in CG, and 11 of them (5 in NG and 6 in CG) died of disease progression. Another patient in the CG developed locoregional failure. The 2-year OS of NG and CG patients was 94.7% (95% confidence interval [CI]: 82.2–99.3%) and 92.3% (95% CI: 79.1–98.3%), respectively ($P>0.05$, Figure 1). The 2-year PFS of NG and CG

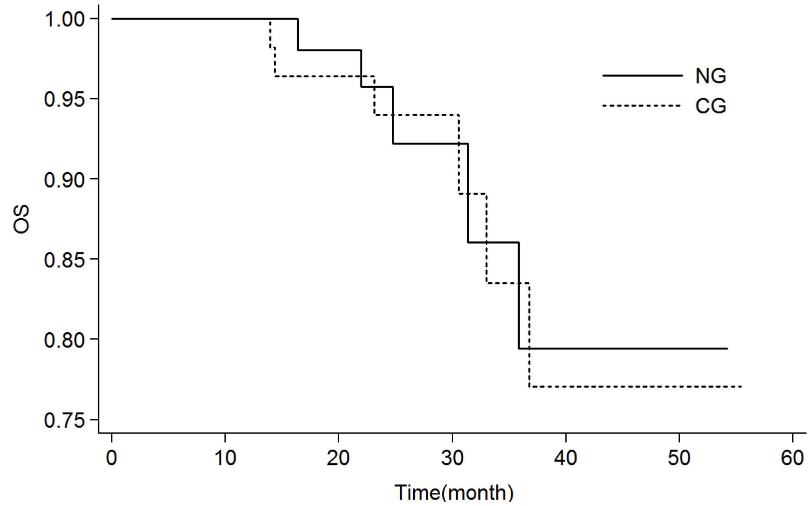

Figure 1 Kaplan–Meier survival curves of OS for NG and CG patients.
Abbreviations: OS, overall survival; NG, nutrition management group; CG, control group.

patients was 84.2% (95% CI: 68.7–93.9%) and 79.5% (95% CI: 63.5–90.7%), respectively ($P>0.05$, Figure 2).

Nutritional status

There were no statistical differences between NG and CG patients ($P>0.05$) for nutritional status prior to induction chemotherapy. Table 2 illustrates the changes of nutritional status between pre-RT and 1 month after RT in the two groups. The results showed that NG and CG patients had comparable nutritional status before RT in terms of body weight, BMI, levels of hemoglobin, albumin, prealbumin, and lymphocyte. At 1 month after RT, however, patients' nutritional status has deteriorated dramatically in both groups for almost all of the indexes, except levels of albumin, where there is a trend of deterioration ($P>0.05$). The results also indicated that the nutritional indexes of body weight, levels of hemoglobin, prealbumin, and lymphocyte in NG were statistically significant higher than those in CG at 1 month after RT ($P<0.05$). In addition, 35.7% of NG patients and 58.9% of CG patients experienced malnutrition (BMI<18.5 kg/m^2) at 1 month after RT, and the difference was statistically significant ($P=0.014$). Nasogastric tubes were administrated in four NG patients and three CG patients, respectively.

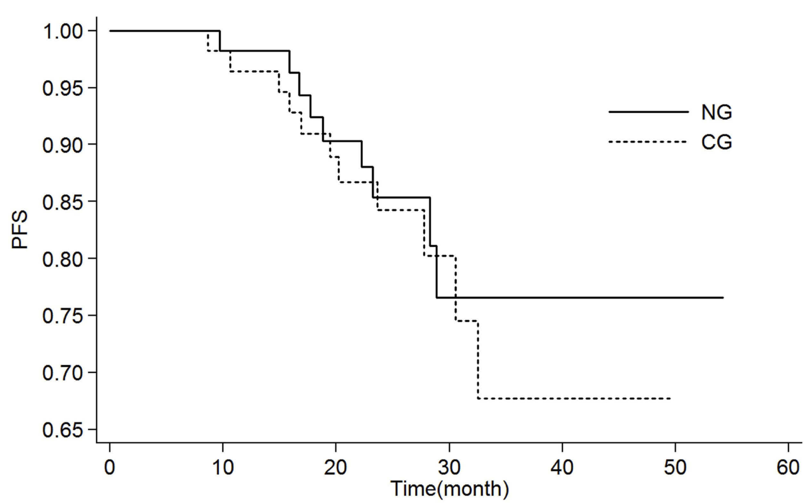

Figure 2 Kaplan–Meier survival curves of PFS for NG and CG patients.
Abbreviations: PFS, progression-free survival; NG, nutrition management group; CG, control group.

Table 2 Changes of nutritional status between pre-RT and 1 month after RT in both groups

Indexes	NG	CG
Weight (kg)[a]		
Pre-RT	69.2±8.3	68.9±7.5
1 month after RT	64.8±9.5*	60.2±6.1*△
BMI<18.5 kg/m^2, n (%)		
Pre-RT	7 (12.5)	8 (14.3)
1 month after RT	20 (35.7)*	33 (58.9)*△
Hb (g/L)[a]		
Pre-RT	138.5±20.6	139.7±16.5
1 month after RT	128.6±18.1*	120.4±15.7*△
ALB (g/L)[a]		
Pre-RT	42.7±5.8	42.3±8.4
1 month after RT	41.3±5.2	40.1±7.7
PA (mg/L)[a]		
Pre-RT	280.9±25.8	278.7±31.2
1 month after RT	258.2±27.2*	246.7±28.6*△
LC (×10^9/L)[a]		
Pre-RT	1.8±0.5	1.9±0.2
1 month after RT	0.9±0.3*	0.7±0.2*△

Notes: [a]Data expressed as mean ± standard deviation (SD). *P< 0.05, vs pre-RT at indicated groups; △P < 0.05, vs NG at 1 month after the end of RT.
Abbreviations: RT, radiotherapy; NG, nutrition management group; CG, control group; BMI, body mass index; Hb, hemoglobin; ALB, albumin; PA, prealbumin; LC, Lymphocyte.

Treatment-related toxicity

Table 3 shows the comparison of treatment-related toxicity during RT in both groups. The results demonstrated that NG patients had statistically significant less grade 3–4 oral mucositis during RT as compared to the CG (32.1% vs 51.8%, P=0.035). Instead, no statistically significant differences were found between the two groups in the percentage of patients who suffered from grade 3–4 neutropenia, thrombocytopenia, anemia or radiodermatitis, as well as radiation treatment breaks for more than 7 days due to toxicity (P>0.05).

Table 3 Treatment-related toxicities during radiotherapy in two groups

Parameters	Number of patients (%)		P-value
	NG	CG	
Grade 3–4 acute toxicities			
Neutropenia	6 (10.7)	10 (17.9)	0.280
Thrombocytopenia	0 (0)	0 (0)	–
Anemia	0 (0)	1 (1.8)	–
Oral mucositis	18 (32.1)	29 (51.8)	0.035
Radiodermatitis	2 (3.6)	3 (5.4)	0.647
Radiation treatment breaks	3 (5.4)	7 (12.5)	0.185

Abbreviations: NG, nutrition management group; CG, control group.

Quality of life

As detailed in Table 4, QoL of patients has worsened significantly in both groups for most of the scales or items between measurements before RT and 1 month after completion of RT, except the emotional function, the symptom scales of nausea and vomiting, and the single item of diarrhea (P>0.05).

It is noteworthy, however, that NG patients showed statistically significant improvements in physical, role and social functions comparing with the CG at 1 month after RT (P<0.05). Statistically significant improvements conferred by nutrition management were also observed for symptoms dimension of fatigue, pain, and the global health status. Instead, no statistically significant difference was found between the two groups in terms of financial conditions.

Discussion

Malnutrition is a frequent comorbidity in cancer patients and the incidence ranges from 39% to 71%.[13–15] In patients with LA-NPC who received RT, malnutrition is further worsened by radiation-induced oral mucositis. Even worse, although a significant survival benefit has been achieved, the addition of concurrent chemotherapy results in increased acute toxicity and a higher incidence of malnutrition as compared to RT alone, which in turn compromise treatment tolerance and efficacy.[16–18] Consequently, as an important aspect for the management of LA-NPC patients, appropriate nutritional support is imperative. In the present study, the effect of SNM on clinical outcomes of LA-NPC patients who received definitive IMRT was retrospectively evaluated.

Our study showed that the implementation of SNM was able to effectively mitigate treatment-related reductions of body weight, hemoglobin, prealbumin, and lymphocyte, which have been widely used to serve as nutrition indicators.[19] The percentage of malnourished patients with BMI <18.5 kg/m^2 at 1 month after RT was significantly reduced in the NG as compared to the CG (P=0.014). In fact, similar results of nutritional status improvements were also observed by cervical esophagostomy or prophylactic placement of percutaneous endoscopic gastrostomy tubes.[19,20] Most recently, a randomized Phase II trial of nutritional counseling with or without oral nutritional supplements (ONS) for head and

Table 4 Changes of QoL between pre-RT and 1 month after RT in both groups

Scales or items	Score, mean±SD			
	Pre-RT		1 month after RT	
	NG	CG	NG	CG
Functional scales				
Physical function	92.7±15.3	95.3±10.5	68.3±15.2*$^{\Delta}$	50.1±10.2*
Role function	95.2±22.7	94.5±15.8	56.5±8.6*$^{\Delta}$	25.1±9.1*
Emotional function	76.3±10.6	78.7±18.6	85.6±12.4*	82.1±15.3
Congnitive function	85.4±21.5	83.6±9.3	75.2±15.1*	70.2±15.7*
Social function	70.2±10.1	73.2±17.7	51.6±8.3*$^{\Delta}$	45.8±10.0*
Symptom scales				
Fatigue	17.3±5.3	19.0±5.1	80.1±8.7*$^{\Delta}$	94.5±7.9*
Nausea and vomiting	10.6±2.7	9.8±2.8	11.3±3.5	10.5±3.3
Pain	17.5±4.6	15.8±4.5	70.7±15.6*$^{\Delta}$	80.8±10.5*
Single items				
Dyspnea	5.6±1.0	5.9±1.4	14.9±4.7*	16.3±3.4*
Sleep disturbance	10.8±2.1	11.6±3.9	15.7±3.3*	17.3±5.4*
Appetite loss	21.8±5.8	20.7±3.6	46.7±10.9*	50.6±10.5*
Constipation	8.6±1.4	7.4±2.3	27.2±5.2*	25.5±7.3*
Diarrhea	4.2±0.9	3.7±1.0	3.8±1.1	4.0±1.3
Financial difficulties	16.1±4.5	15.5±4.2	27.3±4.5*	25.5±5.7*
Global health status	72.0±20.5	70.7±18.2	41.8±10.2*$^{\Delta}$	25.6±5.7*

Notes: *P<0.05, vs pre-RT at indicated groups; $^{\Delta}P$<0.05, vs CG at 1 month after the end of RT.
Abbreviations: QoL, quality of life; RT, radiotherapy; SD, standard deviation; NG, nutrition management group; CG, control group.

neck cancer patients undergoing RT conducted by Cereda et al, demonstrated that the additional provision of ONS from the beginning of RT and continuing for up to 3 months after the end of RT resulted in better weight maintenance, increased protein-calorie intake and improved anti-cancer treatment tolerance.[21] These results strongly suggested that intensive nutrition support was crucial for nutritional status maintenance in cancer patients.

Interestingly, our study also showed that the implementation of SNM was associated with reduced treatment-related side effects and improved QoL. As with other studies of RT for LA-NPC, oral mucositis was the most common acute toxicity. In our cohort, comparing with CG, the incorporation of SNM in NG significantly reduced the percentage of patients who suffered from grade 3–4 mucositis (51.8% vs 32.1%, P=0.035). We also noted that, at 1 month after RT, patients' QoL has worsened in both groups for most of the scales or items. However, an improved QoL was observed in NG patients with respect to physical, role and social functions, symptom scales of fatigue and pain, and the global health status as compared to the CG (P<0.05). We attribute this to the nutritional status improvement of NG patients. Likewise, treatment toxicity and QoL improvements conferred by nutritional intervention have also been found in head and neck cancer patients.[22,23]

It is noteworthy that, although survival benefit of nutritional intervention for cancer patients has been reported in several series,[10,24–26] in our study, however, at a median follow-up of 24.8 months, there was no significant difference between the two groups in terms of OS and disease-free survival. These results should be regarded as preliminary because of the relatively short follow-up and small sample size, as well as the selection bias in patient population. Further prospective studies are needed to determine the survival benefit of SNM.

The study here dose has some limitations. The main limitation aroused from the retrospective data which obtained through the past records. Another drawback was the potential bias introduced by patient selection. Further, the nutritional status and patients' QoL were not assessed for a longer period more than 1 month post-RT, so the effects of nutritional support on long-term QoL improvement could not be analyzed in the present study. Additionally, some of the patients had financial difficulties to afford the costs of the nutritional interventions, so other cheaper and easier ways should be explored.

Conclusion

SNM for LA-NPC patients treated by RT resulted in better nutritional status, reduced treatment-related toxicity and improved QoL. Since the limitations of this retrospective study, the results should be interpreted cautiously and further clinical trials are needed to confirm these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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