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ORIGINAL ARTICLE

Individualized Whole Course Nutrition Management for Nasopharyngeal Carcinoma Patients Undergoing Radiotherapy

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SUMMARY

Background: **Radiotherapy-induced oral mucositis (RIOM) is the most common toxicity associated with radiotherapy for nasopharyngeal carcinoma (NPC). Patients with RIOM become malnourished, which can affect the delivery and dose of radiotherapy. The value of personalizing nutrition recommendations for cancer prevention and management is increasingly recognized. To investigate the effect of individualized whole course nutrition management on nutritional status and the incidence and severity of RIOM in NPCs.**
Methods: **This retrospective study included 77 patients who were provided individualized whole course nutrition management during radiotherapy (RT) and a 1-month follow-up. Seventy-one patients were included in the control group.**
Results: **During radiotherapy, severity of RIOM was significantly lower in the intervention group. There were statistically significant differences in oral mucosa recovery time and nutritional status between the two groups ($p < 0.05$).**
Conclusions: **Individualized whole course nutrition management had the potential to maintain nutritional status and decrease the adverse effects of radiotherapy in NPCs.**
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KEY WORDS

nasopharyngeal carcinoma, individualized whole course nutrition management, radiotherapy-induced oral mucositis, nutrition support, radiotherapy

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LIST OF ABBREVIATIONS

NPC - nasopharyngeal carcinoma
RIOM - radiotherapy-induced oral mucositis
BMI - body mass index
ONS - oral nutritional supplement
TEN - total enteral nutrition
PEN - partial enteral nutrition
PPN - partial parenteral nutrition
TPN - total parenteral nutrition
WBC - white blood cell count
Hb - hemoglobin
LYM - lymphocyte
ALB - albumin
PG-SGA - patient-generated subjective global assessment
RTOG - radiation therapy oncology group
IMRT - intensity modulated radiation therapy

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant cancer arising from the mucosal epithelium of the nasopharynx [1]. The world's highest incidence rates of NPC occur in China, where NPC prevention and treatment are a public health priority [2]. First-line treatment for NPC is radiotherapy, as most NPCs are radiosensitive squamous cell carcinoma. Surgical resection of NPC is challenging because of the anatomical location of the nasopharynx and its proximity to the cranial nerves and internal carotid artery [3,4].

Radiotherapy-induced oral mucositis (RIOM) is the most common toxicity associated with radiotherapy for head and neck cancer. RIOM is characterized by acute inflammation of the oral mucosa, tongue, and pharynx [4]. RIOM can become life-threatening if food and water intake are obstructed or septic complications due to loss of protective epithelial and basement membrane barriers occur. The Radiation Therapy Oncology Group classifies the anatomical, symptomatic, and functional elements of oral mucositis as Grade 0 (none), Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (life threatening) [5]. Grade 1 and 2 RIOM and grade 3 and 4 RIOM have been reported in 34.6% and 65.4% of patients with NPC, respectively [6,7].

Nutrition intervention is required from diagnosis through treatment and recovery in patients with NPC to improve patients' nutritional status, ability to tolerate treatment, and quality of life [8]. Patients with NPC are frequently malnourished at the time of diagnosis, and malnutrition can progress during treatment [9]. Adequate nutrition is critical for the management of patients with RIOM, as malnutrition can delay healing [10,11]. The use of an Oral Nutritional Supplement (ONS) or Enteral Nutritional (EN) Therapy from the beginning to the end of radiotherapy effectively alleviates the side effects of radiotherapy in patients with NPC [12]. Indicators of nutritional status, such as albumin and prealbumin, are improved and the severity of RIOM is reduced in patients with NPC provided early oral nutritional support compared to patients who received no nutritional intervention [13].

The value of personalizing nutrition recommendations for cancer prevention and management is increasingly recognized. Whole course nutrition management [14] refers to risk screening, evaluation, and the development of an appropriate nutrition intervention personalized to the patient. The present study investigated the effect of an individualized whole course nutrition management intervention on nutritional status and the incidence and severity of treatment-related adverse effects in patients with NPC treated with radiotherapy.

MATERIALS AND METHODS

Patients

Patients with NPC who received treatment at the Department of Radiotherapy, First Affiliated Hospital of our University were eligible for this retrospective study. Inclusion criteria were 1) initial diagnosis of NPC; 2) age $\geq$ 18 years; and 3) informed consent and willingness to participate in the study. Exclusion criteria were 1) history of severe cognitive impairment; 2) co-existing tumors or systemic diseases; or 3) history of severe hearing or communication impairment that impacted the patient's ability to complete the study.

The intervention group included 77 patients recruited between January, 2019, and December, 2019. The control group was historical data collected from 71 patients recruited between January, 2018, and December, 2018. This study was approved by the hospital ethics committee (No. 2020-031).

Treatment

Patients were treated with intensity modulation radiation therapy (IMRT) at a total dose of 68 - 72 Gy delivered over 31 - 33 fractions, daily, 5 times each week, for a total 6 - 7 weeks, with concomitant paclitaxel 135 mg/m^2 and cisplatin 75 mg/m^2 (or nidaplatin 80 mg/m^2).

Nutrition management

All patients were educated by nurses on proper oral care. Patients with grade 1 RIOM were instructed to use a super soft toothbrush soaked in warm water for 30 minutes before use, a fluoride toothpaste without granules, and a neutral mouthwash such as saline. Patients with grade 2 - 3 RIOM experiencing pain that did not improve with medication or bleeding for more than 2 minutes were instructed not to use a toothbrush but to rely on oral irrigation. Patients with grade 4 RIOM were instructed not to use a toothbrush or dental floss but to use oral irrigation 4 times a day and systemic painkillers.

Control group

Patients in the control group received routine nutrition management [15]. When RIOM caused eating difficulties, nutritional support was provided according to a 5-step program [16]: food and drink and nutrition education, nutrition education, and oral nutrition support (ONS), total enteral nutrition (TEN), partial enteral nutrition (PEN), partial parenteral nutrition (PPN), and total parenteral nutrition (TPN). Patients moved sequentially through the steps progressing to the next step when 60% of their target energy requirements were not met for 3 ~ 5 days. During radiotherapy, nurses monitored the patients' nutrient and fluid intake daily, and after radiotherapy nurses conducted a weekly follow-up by telephone for one month.

Intervention group

Patients in the intervention group received individualized whole course nutrition management. A nutrition management team, including the patients' clinician, a dietitian, a specialist nurse, and a pharmacist, was established, and a nutrition diary was initiated. When the patient was diagnosed with NPC, the nurse completed a nutrition assessment by recording demographic and clinical data and the results of a nutritional risk screening, physical examination, and routine blood test to ascertain the nutritional status of the patient. Patients were educated about diet, including how to make good food choices and keeping a dietary food log, and patients were provided some recipes as examples. Total calorie intake was calculated based on the patients' ideal body weight as *25 kcal/kg/d. In addition to a normal diet, patients were provided an oral nutrition supplement[1] (ONS[1]). Total calorie intake from the ONS[1] was calculated as the patient's ideal body weight (women: height - 105 cm, men: height - 100 cm) * 10 kcal/kg, (Figure 1). Within 48 hours of beginning radiotherapy, the nutrition management team conducted another nutrition assessment. During radiotherapy, diet was assessed daily, and a nutrition assessment, blood test and evaluation of oral mucositis were conducted weekly. Patients with RIOM grade 0 received a normal diet + ONS[1]; patients with RIOM grade I received a soft diet + ONS[1]; patients with RIOM grade II - III received a semi-fluid or liquid diet + ONS[1]. Patients who did not reach their calorie target (ideal body weight *25kcal/kg/d + ONS[1] calories) received additional ONS[2], according to how far they fell below their target (target total calories - total calories provided by the diet - total calories provided by the ONS[1]). Patients who did not reach their calorie target after increasing the ONS[2] received an individualized parenteral nutrition (PN) program developed by their nutrition management team. Patients with RIOM grade IV used a percutaneous endoscopic gastrostomy (PEG) tube and added parenteral nutrition, if necessary (Figure 1).

Patient evaluation and follow-up

Patients diagnosed with NPC underwent a nutrition assessment. Demographic and clinical data were recorded and the results of a nutritional risk screening, physical examination, and routine blood test were used to ascertain the nutritional status of the patient. Based on the results of the evaluation, the dietitian and patient worked together to develop a nutrition support plan. During radiotherapy, nurses monitored each patient's daily nutrient and fluid intake, and every week they recorded each patient's weight, results of a blood test, and nutrition score.

Measures

Demographics

At baseline, patients' demographic and clinical characteristics, including age, sex, educational level and stage of disease, were recorded. At various timepoints, including before radiotherapy, mid treatment, at the end of radiotherapy and one month after radiotherapy, patients' body mass index (BMI), white blood cell count (WBC), and hemoglobin (Hb), lymphocyte (LYM), albumin (ALB) and prealbumin levels were recorded.

***Patient-generated subjective global assessment (PG-SGA)* [17]**

Mid treatment, at the end of radiotherapy and one month after radiotherapy, the PG-SGA was used to evaluate patients' nutritional status. The PG-SGA is recommended by the American Dietetic Association and the China Anticancer Association for evaluating the nutritional status of patients with cancer. The PG-SGA includes a patient history (weight history, food intake, symptoms and activities and function) and information derived from the patient's physician (diagnosis, age, metabolic stress, and physical exam). The PG-SGA generates a numerical score and a category score. Patients scoring 0 to 1 (corresponding to Category A) are considered well-nourished without the need for a nutrition intervention. Patients scoring 2 to 8 points (corresponding to Category B) have suspected or moderate malnutrition and require nutrition education by a dietitian or collaboratively by a dietitian, physician, and nurse. Patients scoring 9 points or more (corresponding to Category C) have severe malnutrition, requiring improved symptom management and/or nutrient intervention options.

***Radiation Therapy Oncology Group* [18]**

Before radiotherapy, mid treatment, at the end of radiotherapy, and one month after radiotherapy, RTOG criteria were applied to assess the grade of RIOM. RTOG criteria for toxicity grading of oral mucositis include: grade 0, no change over baseline; grade 1, infection/ may experience mild pain not requiring analgesic; grade 2, patchy mucositis may have a serosanginuous discharge; may experience pain requiring analgesics; grade III, confluent fibrinous mucositis/may include severe pain requiring narcotics; grade IV, ulceration, hemorrhage or necrosis.

Table1. Baseline characteristics.

Characteristics	Control	Intervention	p
Age (year)	52.89 ± 12.37	52.19 ± 13.79	0.723
Gender			
Male	56	61	0.559
Female	15	16	
Educational level			
Illiterate	15	17	0.635
Primary school	21	19	
High school	24	20	
College	17	21	
Stage of disease			
I	0	3	0.372
II	4	4	
III	41	46	
IV	26	24	
BMI (kg/m^2)			
< 18.5	2	0	0.243
18.8 ~ 23.9	34	43	
≥ 24	35	34	
PG-SGA			
≤ 1	11	14	0.415
2 - 8	60	63	
≥ 9	0	0	
WBC ($10^9/L$)	6.21 ± 1.58	6.09 ± 1.72	0.494
Hb (g/L)	140.82 ± 12.12	137.29 ± 12.78	0.087
LYM ($10^9/L$)	1.44 ± 0.60	1.42 ± 0.55	0.599
ALB (g/L)	45.71 ± 2.52	45.79 ± 3.24	0.175
PAB (mg/L)	267.80 ± 45.44	265.25 ± 50.24	0.419

BMI, body mass index; PG-SGA, patient-generated subjective global assessment; WBC, white blood cell count; Hb, hemoglobin; LYM, lymphocyte; ALB, albumin; PAB, prealbumin.

Table 2. Incidence of RIOM (n, %).

Group	n	RIOM grade according to RTOG criteria																			
		Before radiotherapy					Medium radiotherapy					At the end of radiotherapy					1 month after radiotherapy				
		0	I	II	III	IV	0	I	II	III	IV	0	I	II	III	IV	0	I	II	III	IV
Control	71	69	2	0	0	0	1	35	33	2	0	0	4	53	14	0	41	24	6	0	0
Intervention	77	74	3	0	0	0	14	32	28	3	0	0	18	48	11	0	61	11	5	0	0
X^2		0.132					11.787					9.289					8.613				
p		0.717					0.008					0.010					0.013				

Data are mean ± SD.

Table 3. Time to recover from RIOM.

Group	n	Time (days)
Control	**71**	**30.48 ± 8.49**
Intervention	**77**	**24.09 ± 11.22**
t		**3.879**
p		**< 0.0001**

Data are mean ± SD.

Table 4. Time for patients to reach normal diet by mouth.

Group	n	Time (days)
Control	**71**	**49.89 ± 13.71**
Intervention	**77**	**35.16 ± 12.41**
t		**6.860**
p		**< 0.0001**

Other measures

The time from the end of radiotherapy to complete recovery of the oral mucosa and to return to a normal diet by mouth were also recorded.

Statistical Analysis

Statistical analyses were conducted using SPSS 20. Normality and variance homogeneity of the data were tested. Normally distributed data are expressed as mean ± standard deviation and were compared with the two-sample *t*-test. The incidence and degree of RIOM are expressed as percentages and were compared using the chi-squared test. $p < 0.05$ was considered statistically significant.

RESULTS

This study included 77 patients aged 52.19 ± 13.79 years (range, 18 - 80 years) in the intervention group and 71 patients aged 52.89 ± 12.37 years (range, 23 - 76 years) in the control group. Patients' demographic and clinical characteristics are shown in Table 1.

Comparison of nutritional status

Patient BMI at baseline was not significantly different between the intervention group and the control group. At the end of radiotherapy, BMI was significantly higher in patients in the intervention group compared to the control group ($p < 0.05$). One month after the end of radiotherapy, patient BMI was not significantly different between the intervention group and the control group (Figure 2).

On the PG-SGA, across both groups, more patients were considered Category C mid treatment and at the end of radiotherapy, compared to one month after the end of radiotherapy. Mid treatment, 47% of patients in the intervention group were considered severely malnourished compared to 23% in the control group. At the end of radiotherapy, significantly fewer patients in the intervention group (48%) were considered severely malnourished compared to the control group (65%) ($p < 0.05$). One month after the end of radiotherapy, 7% of patients in the intervention group were considered severely malnourished compared to 1% in the control group ($p > 0.05$) (Figure 3).

RTOG Severity and recovery

All patients in the intervention and control groups received radiotherapy. Mid treatment, the number of patients with grade 0 oral mucositis was significantly higher in the intervention group (18.2%, n = 14/77) compared to the control group (1.4%, n = 1/71) ($p < 0.05$). At the end of radiotherapy, most patients in the intervention and control groups had grade II oral mucositis (intervention group: 62.4%, n = 48/77; control group: 74.6%, n = 53/71), but the number of patients with grade I oral mucositis was significantly higher in the intervention group (23.4%, n = 18/77) compared to the control group (5.6%, n = 4/71) ($p < 0.05$). One month after the end of radiotherapy, across both groups, fewer patients had oral mucositis compared to during radiotherapy. The number of patients with grade 0 oral mucositis (intervention group: 79.2%, n = 61/77; control group: 57.7%, n = 41/71) was significantly higher and the number of patients with grade 1 oral mucositis

Table 5. Blood indices.

Group	n	Mid treatment					End of radiotherapy					One month after radiotherapy				
		WBC (10^9/L)	Hb (g/L)	LYM (10^9/L)	ALB (g/L)	Pre-albumin (mg/L)	WBC (10^9/L)	Hb (g/L)	LYM (10^9/L)	ALB (g/L)	Pre-albumin (mg/L)	WBC (10^9/L)	Hb (g/L)	LYM (10^9/L)	ALB (g/L)	Pre-albumin (mg/L)
Control	71	5.32 ± 1.68	126.49 ± 12.28	0.62 ± 0.48	42.35 ± 3.47	233.10 ± 54.27	4.58 ± 1.68	123.15 ± 14.18	0.40 ± 0.27	37.48 ± 3.66	214.66 ± 55.46	3.87 ± 1.46	120.99 ± 13.63	0.57 ± 0.31	42.05 ± 3.50	243.74 ± 63.90
Inter-vention	77	4.77 ± 1.64	122.05 ± 13.63	1.11 ± 0.51	42.89 ± 3.56	252.83 ± 47.02	4.38 ± 1.71	116.69 ± 15.15	0.73 ± 0.40	39.80 ± 4.36	239.01 ± 52.98	3.91 ± 1.37	116.92 ± 15.61	0.70 ± 0.35	42.42 ± 3.16	253.93 ± 45.85
t		2.007	2.076	-6.009	-0.925	-2.369	0.700	2.675	-5.763	-3.504	-2.729	-0.189	1.681	-2.329	-0.673	-1.121
p		0.047	0.040	0.000	0.356	0.019	0.485	0.008	0.000	0.001	0.007	0.850	0.095	0.021	0.502	0.270

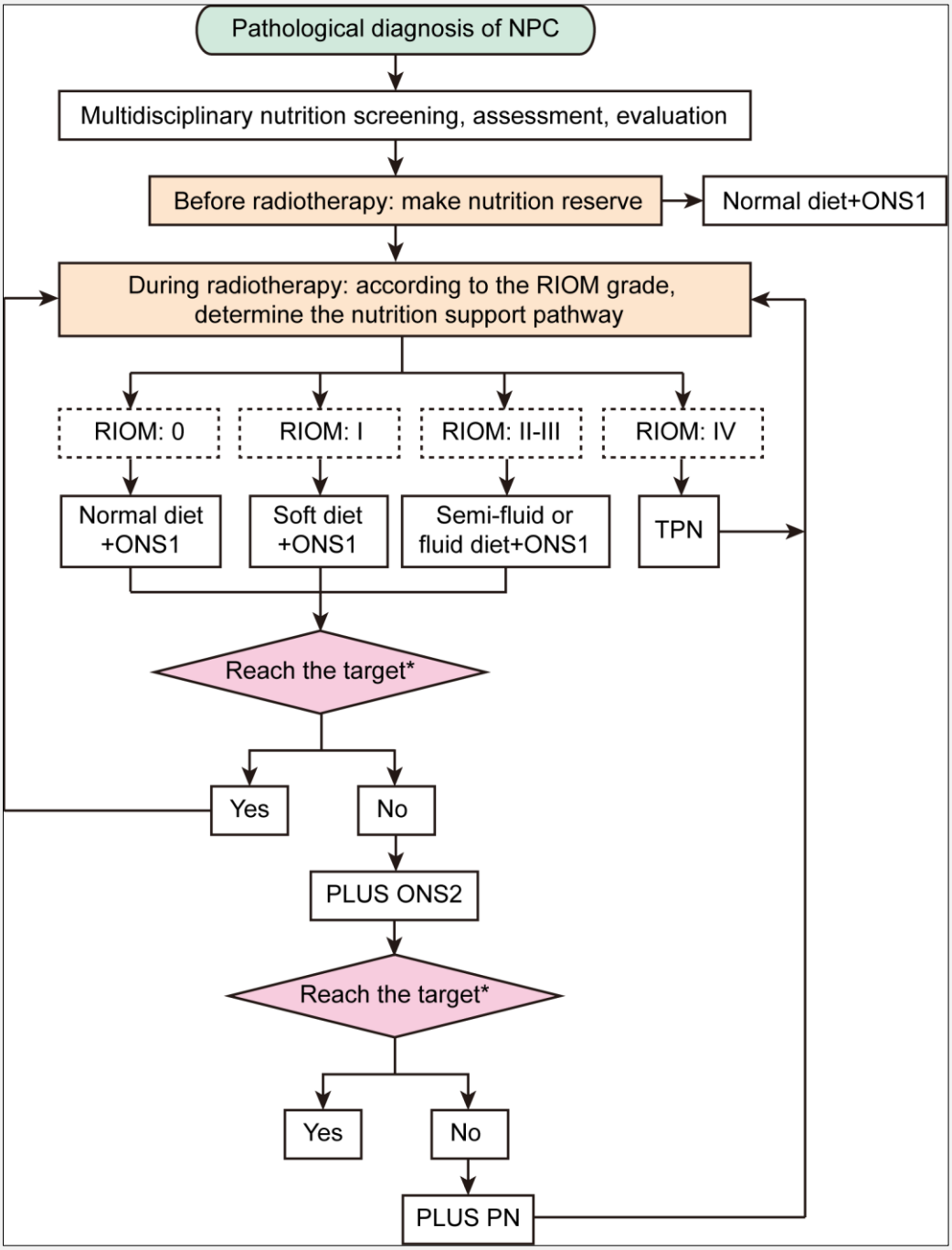

Figure 1. Flow chart showing individualized whole course nutrition management for patients with NPC undergoing radiotherapy and chemotherapy.

Note: ONS: oral nutrition supplement, RIOM: radiotherapy induced oral mucositis, PN: parenteral nutrition, TPN: total parenteral nutrition, ONS[1] calorie formula: standard weight (women: height - 105 cm, men: height - 100 cm) * 10 kcal/kg, ONS[2] calorie formula: total calorie target - total dietary calories - ONS[1] calories, target total calorie formula: standard weight * 25 kcal/kg + ONS[1] calories.

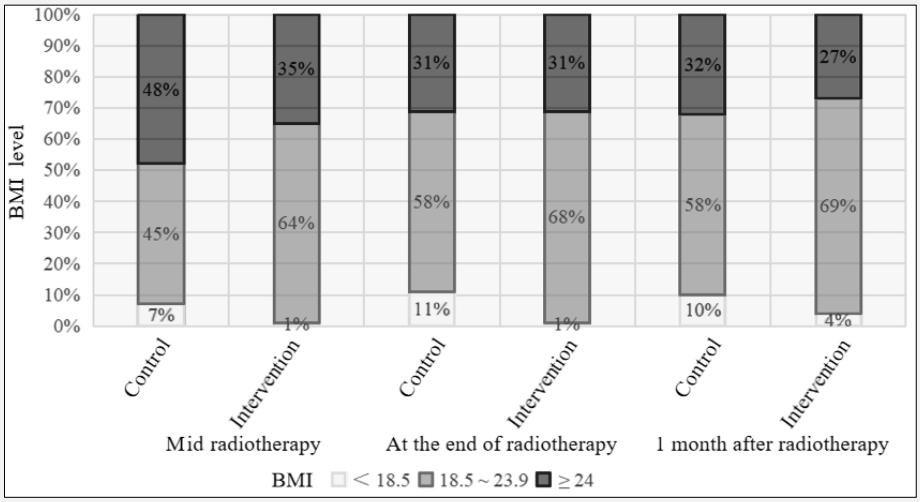

Figure 2. Patient BMI at baseline, the end of radiotherapy, and one month after the end of radiotherapy.

Note: BMI: body mass index.

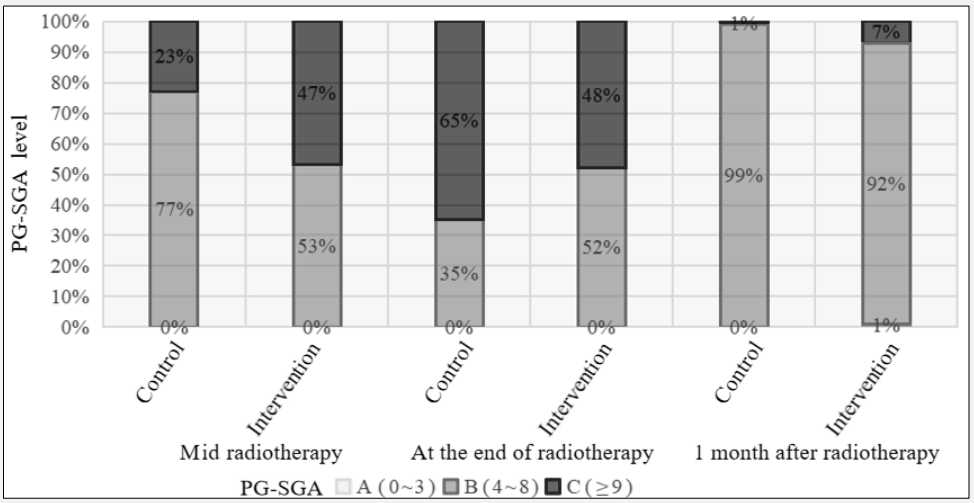

Figure 3. PG-SGA at baseline, the end of radiotherapy, and one month after the end of radiotherapy.

Note: PG-SGA: patient-generated subjective global assessment.

was significantly lower (intervention group: 14.3%, n = 11/77; control group: 33.8%, n = 24/71) in the intervention group compared to the control group ($p < 0.05$) (Table 2).

The time from the end of radiotherapy to complete recovery of the oral mucosa was significantly shorter for patients in the intervention group (24.09 ± 11.22 days) compared to the control group (30.48 ± 8.49 days) ($p <$

0.0001) (Table 3). The time from the end of radiotherapy to returning to a normal diet by mouth was significantly shorter for patients in the intervention group (35.16 ± 12.41 days) compared to the control group (49.89 ± 13.71 days) ($p < 0.0001$) (Table 4).

Comparison of blood indices

Blood indices at baseline were not significantly different between patients in the intervention group and the control group. Mid treatment, WBC ($p = 0.047$) and Hb ($p = 0.040$) were significantly lower and LYM ($p < 0.0001$) and prealbumin ($p = 0.019$) were significantly higher in the intervention group compared to the control group; there was no significant difference in ALB. At the end of radiotherapy, Hb ($p = 0.008$) was significantly lower and LYM ($p < 0.0001$), ALB ($p = 0.001$), and prealbumin ($p = 0.007$) were significantly higher in the intervention group compared to the control group; there was no significant difference in WBC. One month after radiotherapy, LYM ($p < 0.021$) was significantly higher in the intervention group compared to the control group; there were no significant differences in WBC, Hb, ALB, or prealbumin (Table 5).

DISCUSSION

This study investigated the effect of an individualized whole course nutrition management intervention on nutritional status and the incidence and severity of RIOM in patients with NPC treated with IMRT and chemotherapy. Findings showed that overall nutritional status in all patients deteriorated significantly during radiotherapy. However, significantly fewer patients in the intervention group were considered severely malnourished at the end of radiotherapy, and more patients who received the individualized whole course nutrition management intervention had a BMI > 18.5 kg/m^2 during and at the end of radiotherapy compared to patients receiving routine care. The incidence and severity of RIOM was significantly reduced in patients receiving the individualized whole course nutrition management intervention compared to patients in the control group. The time from the end of radiotherapy to complete recovery of the oral mucosa and to return to a normal diet by mouth was significantly shorter for patients in the intervention group compared to the control group.

Patients with malignant tumors may experience disease-related malnutrition before treatment. Patient's nutritional status may deteriorate further during radiation and chemotherapy, and malnutrition can adversely affect patient recovery. Radiotherapy is the primary treatment for NPC. Given that NPC are located in close proximity to vital structures such as the mouth, the throat, and the major salivary glands, side effects of radiotherapy include dry mouth and oral mucositis, which can lead to loss of appetite and malnutrition. The nutritional status of patients with NPC is also affected by therapeutic regimens that include chemotherapy, which can cause nausea and vomiting. Concomitantly, malnutrition increases the incidence and severity of toxic reactions during radiotherapy and chemotherapy [19]. Advanced radiotherapy techniques such as IMRT have reduced long-term treatment-related toxicity to normal tissues in patients with head and neck cancer, but the nutritional status of patients has not substantially improved [20]. Evidence suggests that 35% of patients with NPC have a > 5% weight loss before treatment [8, 21,22], and 46% of patients lose weight during radiotherapy.

Malnutrition in patients with cancer causes weight loss, depletes visceral and body protein, reduces immune competence and increases infections, causes psychosocial stress, lowers quality of life, and increases the risk of mortality. Eating ability after treatment is especially impaired in patients with head and neck cancer as the tumor and therapy can have a negative effect on the upper digestive tract. International guidelines recommend nutritional counseling and oral nutritional supplements as nutrition interventions for patients with head and neck cancer [21,23]. Data from the present study imply that an individualized whole course nutrition management intervention may alleviate then burden of malnutrition in patients with NPC.

Malnutrition in patients with cancer is associated with treatment toxicity. Consistent with our findings, previous studies show acute radiation toxicity was aggravated in patients with poor nutritional status receiving radiotherapy to treat head and neck tumors [24], while patients with NPC or head and neck cancer provided specifically designed nutrition support programs had decreased severity of radiation dermatitis and oral mucositis [14] or reduced toxic reactions and improved radiotherapy tolerance [25], respectively, compared to patients provided routine care.

This study investigated the levels of lymphocytes, hemoglobin, serum albumin, and prealbumin as objective indicators of nutritional status in patients with NPC undergoing IMRT and chemotherapy. These indicators have been associated with treatment responsiveness, treatment tolerance, and prognosis in patients with cancer [26-28]. In all patients, WBC and LYM decreased during radiotherapy. Mid treatment, WBC was significantly lower and LYM was significantly higher in the intervention group compared to the control group. At the end of radiotherapy and one month after radiotherapy, LYM was significantly higher in the intervention group compared to the control group. Lymphocytes can effectively reflect the immune status of patients during therapy as they are the main participants in the adaptive immune response and play an important role in the clearance of immune and residual tumor cells [29]. Previous reports showed that the neutrophil-lymphocyte ratio decreased during focal radiotherapy and concomitant temozolomide treatment in patients with histologically confirmed glioblastoma [30], and lymphocyte levels were an independent risk factor for survival and prognosis in patients with esophageal cancer [31]. Our find-

ings suggest that individualized whole course nutrition management can improve immune function in patients with NPC undergoing radiotherapy and chemotherapy. Radiotherapy and chemotherapy can lead to anemia and hypoxia, which can reduce the sensitivity of tumors to these agents as oxygen is essential for their cytotoxic activities [32]. In the present study, mid treatment and at the end of radiotherapy, Hb, which is a sensitive indicator of anemia, was significantly lower in the intervention group compared to the control group.

Serum albumin and prealbumin are important indices of nutritional status and important prognostic indicators in several diseases [33,34]. Serum prealbumin may be a more sensitive indicator of nutritional status than serum albumin in patients with head and neck cancer undergoing radiotherapy [35], likely due to the shorter half-life of prealbumin. In the present study, in all patients, ALB and prealbumin levels fluctuated during radiotherapy. Mid treatment, prealbumin was significantly higher in the intervention group compared to the control group, and there was no significant difference in ALB. At the end of radiotherapy, ALB and prealbumin were significantly higher in the intervention group compared to the control group. This may reflect the efficacy of individualized whole course nutrition management for maintaining nutritional status in patients with NPC undergoing radiotherapy and chemotherapy.

CONCLUSION

Data from the present study suggest that individualized whole course nutrition management has the potential to maintain nutritional status and decrease the adverse effects of radiotherapy in patients with NPC. As this study was associated with several limitations, including the small sample size, short follow-up time, and the use of a historical control, robust randomized controlled trials are required to further evaluate the effect of individualized whole course nutrition management on the outcomes of patients with NPC.

Availability of Data and Materials:
The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Patient Consent for Publication:
All data published here are under the consent for publiccation.

Authors' Contributions:
Juan Ji, Hui Zhu, Ke-yan Qian, Ju-ying Zhou designed/ performed most of the investigation, data analysis and wrote the manuscript; Xiao-ting Xu and Yi-qun Yang designed most of the investigation; Mu-xing Zhang provided nutrition assistance; Lin Chen provided medication assistance; Dan-dan Jiang and Zhe Xu contributed to interpretation of the data and analyses. All of the authors have read and approved the manuscript.

Ethics Approval and Consent to Participate:
This study was approved by the hospital ethics committee (No. 2020-031) and Chinese clinical trial registry (ChiCTR2000030899). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Declaration of Interest:
We declare that we have no conflict of interest.

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