Original Article

Pretreatment nutritional risk as a prognostic factor in head and neck cancer patients receiving radiotherapy or chemoradiotherapy

Weixin Liu MD, Li Gao MD, Xiaodong Huang MD, Jingwei Luo MD, Shiping Zhang MD, Kai Wang MD, Yuan Qu MD, Jianping Xiao MD, Guozhen Xu MD, Yexiong Li MD, Junlin Yi MD

Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background and Objectives: Head and neck cancer patients often experience nutritional deterioration, which decreases their treatment tolerance and is associated with poor outcomes. We analyzed nutritional status in head and neck cancer patients before and during treatment, and its impact on clinical outcomes. **Methods and Study Design:** Between January 2009 and April 2012, 336 head and neck cancer patients receiving radiotherapy or chemoradiotherapy were prospectively entered into the study. The Nutritional Risk Screening 2002 (NRS 2002) assessment was used to evaluate their nutritional status. **Results:** A total of 227 patients with nasopharyngeal carcinoma and 109 patients with head and neck cancers were analyzed. The proportion of patients receiving radiotherapy or chemoradiotherapy at nutritional risk was 61.3%, with 11.9% at risk before treatment and 49.4% developing risk during treatment. In multivariate analysis, nutritional risk before treatment was associated with T stage for the two groups. Risk was significantly higher in patients receiving concurrent chemoradiotherapy during treatment for nasopharygeal carcinoma patients. The prognosis of pretreatment nutritional risk patients was worse than those becoming at risk during treatment and those without nutritional risk (3-year overall survival 62.9% vs 81.7% vs 80.6%, p=0.026; 3-year disease-free survival 64.8% vs 84.5% vs 84.4%, p=0.019). **Conclusions:** The incidence of nutritional risk is high in head and neck cancer patients receiving radiotherapy or chemoradiotherapy, especially during treatment. Pretreatment nutritional risk evaluated using the NRS 2002 can predict patient prognosis.

Key Words: head and neck cancer, radiotherapy, chemoradiotherapy, nutritional risk screening 2002, prognostic value

INTRODUCTION

The deterioration or impairment of nutritional status occurs frequently in cancer patients, both before and during treatment, leading to worsening quality of life, lower treatment tolerance, a poorer response to radiotherapy or chemoradiotherapy, an increase in treatment-related toxicities and complications, prolonged hospital stay, increased medical resource consumption and even lower survival rates.[1-7] The primary site of a tumor, such as in head and neck or gastrointestinal cancers, can significantly affect swallowing and chewing functions and cause subsequent nutritional deterioration. Other factors, including pre-existing chronic disease, treatment-related toxicities and aberrant metabolisms, can also worsen nutritional status.

Nutritional screening tools are designed to detect protein and energy undernutrition and/or to predict whether undernutrition is likely to develop or worsen under the present and future conditions of the patient. There are many nutritional status screening tools adapted for different patient populations, including the Nutritional Risk Screening 2002 (NRS 2002), the Subjective Global Assessment (SGA), the scored Patient-generated Subjective Global Assessment (PG-SGA), the Malnutrition Universal Screening Tool and the Mini Nutritional Assessment (MNA).[8] The NRS 2002 was the first screening tool to detect patients who may develop nutritional deterioration and benefit clinically from nutritional support to be endorsed by the European Society for Clinical Nutrition and Metabolism (ESPEN).[9] Its predictive value has been validated by many studies since its release.[10,11] In China, the reported incidence of nutritional risk in cancer patients has ranged from 24.6% to 45.6%, with the highest rate in gastrointestinal-related cancers.[12,13] This number is 14–32% in other countries.[11,14,15] Considering the rarity of

Corresponding Author: Dr Junlin Yi, Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuannanli, Chaoyang District, Beijing, China, 100021.
Tel: +8687788504
Email: yijunlin1969@163.com
Manuscript received 26 November 2018. Initial review completed 18 December 2018. Revision accepted 04 February 2019.
doi: 10.6133/apjcn.201906_28(2).0003

nutritional risk-related studies using the NRS 2002 in head and neck cancer patients, we conducted this study to analyze the incidence rate, related factors and prognostic value of nutritional risk in head and neck cancer patients receiving radiotherapy or chemoradiotherapy.

METHODS

Patients

Between January 2009 and April 2012, 336 head and neck cancer patients treated with radiotherapy alone or combined modality therapy were prospectively enrolled. Included patients were pathologically confirmed with squamous cell carcinoma. Tumor sites included the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and cervical esophagus. Patients were divided into two groups based on tumor sites: Nasopharyngeal carcinoma and other head and neck cancers. Patient characteristics are shown in Table 1 and 2. Patients with secondary malignancies or recurrent disease were excluded. This project was approved by our institutional review board and conducted in accordance with the Declaration of Helsinki.

Diagnosis and stage

Patients received a thorough physical examination, dental care, general status evaluation, blood count, chest X-ray, head and neck computed tomography/magnetic resonance imaging, and neck and abdominal ultrasonography. A bone scan was performed for stage III/IV patients. Patients were staged according to the UICC 2010 staging system, except for non-surgical patients with cervical esophageal cancer, who were staged with UICC 2002.

Treatment

A total of 227 patients with nasopharyngeal carcinoma and 109 patients with head and neck cancers were enrolled. Of the stage I/II nasopharyngeal patients, 27 patients received radiotherapy alone and 23 patients received concurrent chemoradiotherapy (CRT) with or without targeted therapy. Of the stage III/IV patients, 148 patients were treated with concurrent chemoradiotherapy-based combined modality therapy and 13 received radiotherapy alone. Of the patients who received combined modality therapy, 21 patients had neoadjuvant chemotherapy and one patient had adjuvant chemotherapy, while 61 patients were treated with targeted therapy for clinical trials. With the exception of eight patients, the patients received intensity-modulated radiation therapy (IMRT). The median prescription dose of PGTV was 74 Gy/2.24 Gy/33 f (range 53–85 Gy) and the median doses of PTVhigh risk and PTVlow risk were 60 Gy and 51 Gy, respectively. Neoadjuvant chemotherapy consisted of a cisplatin and 5-Fu-based regimen administered every 3 weeks for one to six cycles (Median 2 cycles). For concurrent chemotherapy, 67 patients received a cisplatin regimen of 30–40 mg/m^2 weekly (Median 7 cycles) and 104 patients received cisplatin 80–100 mg/m^2 every 3 weeks (Median 3 cycles). One patient also received an adjuvant cisplatin plus 5-Fu based chemotherapy regimen for six cycles. Cetuximab, trastuzumab or lapatinib were used for targeted therapy. The eight patients who did not receive IMRT received 2D/3D conformal radiotherapy, with a median prescription dose for primary tumor of 70 Gy (range 70–74 Gy).

Table 1. Nasopharyngeal carcinoma patient characteristics and nutritional risk before and during radiotherapy

		Pretreatment		During treatment	
		NRS ≥3 (%)	*p*	NRS ≥3 (%)	*p*
Gender			0.307		0.115
M	172	14 (8.1)		96 (55.8)	
F	55	7 (12.7)		24 (43.6)	
Age			0.002		0.004
≤70	220	18 (8.2)		120 (54.5)	
>70	7	3 (42.9)		0 (0)	
Diabetes			0.667		0.423
Yes	16	1 (6.3)		10 (62.5)	
No	211	20 (9.5)		110 (52.1)	
KPS			0.002		0.191
≥80	220	18 (8.2)		118 (53.6)	
<80	7	3 (42.9)		2 (28.6)	
T stage			0.001		0.197
Tis-2	110	3 (2.7)		63 (57.3)	
T3-4	117	18 (15.4)		57 (48.7)	
N stage			0.649		0.980
N0-1	108	9 (8.3)		57 (52.8)	
N2-3	119	12 (10.1)		63 (52.9)	
Stage			0.041		0.990
I-II	51	1 (2.0)		27 (52.9)	
III-IV	176	20(11.4)		93 (52.8)	
Technology			0.170		0.515
2D+3D	34	8 (22.2)		15 (44.1)	
IMRT	302	36 (12.0)		151 (50.0)	
Treatment			0.307		0.005
CRT	172	14 (8.1)		100 (58.1)	
Non-CRT	55	7 (12.7)		20 (36.4)	

NRS: nutritional risk score; KPS: Karnofsky performance score; CRT: concurrent chemoradiotherapy.

Table 2. Head and neck cancer patient characteristics and nutritional risk before and during radiotherapy

		Pretreatment		During treatment	
		NRS ≥3 (%)	*p*	NRS ≥3 (%)	*p*
Gender			0.471		0.530
M	92	15 (16.3)		40 (51.5)	
F	17	4 (23.5)		6 (41.7)	
Age			0.619		0.319
≤70	85	14 (16.5)		38 (44.7)	
>70	24	5 (20.8)		8 (33.3)	
Diabetes			0.880		0.892
Yes	16	3 (18.8)		7 (43.8)	
No	93	16 (17.2)		39 (41.9)	
KPS			0.035		0.026
≥80	92	13 (14.1)		43 (46.7)	
<80	17	6 (35.3)		3 (17.6)	
T stage			0.013		0.696
Tis-2	45	3 (6.7)		18 (40.0)	
T3-4	64	16 (25.0)		28 (43.8)	
N stage			0.784		0.791
N0-1	49	8 (16.3)		20 (40.8)	
N2-3	60	11 (18.3)		26 (43.3)	
Stage			0.066		0.958
I-II	14	0 (0)		6 (42.9)	
III-IV	95	19 (20.0)		40 (42.1)	
Treatment			0.137		0.602
CRT	41	10 (24.4)		16 (39.0)	
Non-CRT	68	9 (13.2)		30 (44.1)	
Surgery			0.657		0.085
Yes	41	8 (19.5)		13 (31.7)	
No	68	11 (16.2)		33 (48.5)	

NRS: nutritional risk score; KPS: Karnofsky performance score; CRT: concurrent chemoradiotherapy.

Of the 109 head and neck squamous cell carcinoma patients, 42 were treated with surgery followed by post-operative radiotherapy or chemoradiotherapy according to their pathological status. The remaining head and neck patients received radical radiotherapy alone or concurrent chemoradiotherapy according to their stage and Karnofsky Performance Status (KPS). Targeted therapy was used according to the physicians' preference. Twenty-five patients received 2D/3D conformal radiotherapy and the other 79 patients received IMRT. The prescription doses were similar for the two groups. The median prescription dose of PGTVtumor bed in post-operative radiotherapy was 66 Gy/2 Gy/33 f (range 50–79 Gy) and the median doses of PTVhigh risk and PTVlow risk were 56 Gy and 51 Gy, respectively. The median prescription dose of PGTV in radical radiotherapy was 70 Gy/2.12 Gy/33f (range 51–76 Gy) and the median doses of PTVhigh risk and PTVlow risk were 60 Gy and 51 Gy, respectively. The chemotherapy and targeted therapy regimens for the head and neck carcinoma patients were similar to those of the nasopharyngeal carcinoma patients. In brief, five patients received neoadjuvant chemotherapy for one to two cycles (Median 1 cycle). For concurrent chemoradiotherapy group, 11 patients received a cisplatin regimen of 30–40 mg/m^2 weekly (Median 6 cycles) and 6 patients received cisplatin 80–100 mg/m^2 every 3 weeks (Median 2 cycles). For postoperative chemoradiotherapy group, 11 patients received a cisplatin regimen of 30 mg/m2 weekly (Median 5 cycles) and 12 patients received cisplatin 100 mg/m^2 every 3 weeks (Median 2 cycles).

Nutritional risk screening tool

Patient nutritional status and disease severity information was collected by physicians within 24 hours of admission using the NRS 2002 and was reassessed weekly during hospitalization to detect patients newly at nutritional risk. The NRS 2002 consists of three parts: a nutritional status impairment score (0–3), a severity of disease score (0–3) and a score of 1 if the patient is aged ≥70 years. According to the recommendations of the ESPEN Screening Guideline, a patient with an NRS score ≥3 is nutritionally at risk.[9]

Nutrition support

Patients were provided with nutritional consultation by a professional nutrition counsellor. However, nutritional support (enteral or parenteral nutrition) was not routinely given to patients at nutritional risk before treatment. In terms of enteral nutritional support, nine patients received prophylactic percutaneous endoscopic gastrostomy (PEG) placement and one patient received theraputic PEG. A prophylactic nasogastric (NG) tube was used in five patients and a therapeutic NG tube in three patients. Additionally, various oral nutritional supplements were provided for 107 patients, in variable quantities. Sixty-six other patients were treated with various amounts of parenteral nutrition. Due to the difficulty in evaluating the effect of nutritional support because of widespread variability in usage, we only analyzed the prognostic value of the NRS 2002 screening tool. Patient enrollment and nutrition support data are shown in Figure 1.

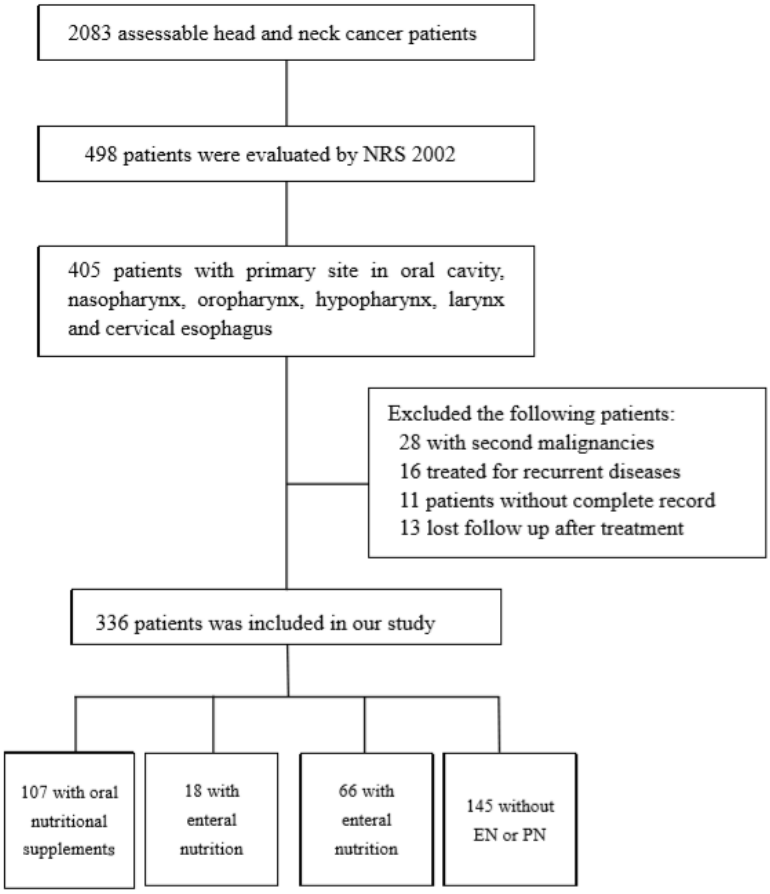

Figure 1. Patient selection flow chart and nutrition support.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS, version 19.0). Chi-square test was carried out to test for differences between groups. Factors found to have a statistically significant correlation with an NRS 2002 score of ≥3 were used as binary variables in a multivariate analysis using logistic regression. The Kaplan-Meier method was used to estimate survival results and log-rank test was used to identify the prognostic value of the NRS 2002. Results were considered significant when $p < 0.05$.

RESULTS

Incidence of nutritional risk before and during radiotherapy

The NRS 2002 was applied to all the patients. A total of 40 patients (11.9%) were identified as being at nutritional risk prior to radiotherapy. According to the parameters in the NRS 2002, nutritional risk during treatment was mainly attributable to an impaired nutritional status score. In particular, 166 patients (49.4%) lost >5% of their body weight during the 8 weeks of treatment and were classified with newly occurring nutritional risk. Of these, 125, 36 and 5 patients lost 5–10%, 10–20% and >20% of their body weight, respectively. For the 40 patients at nutritional risk before radiotherapy, 20 patients lost <5% of their base level body weight during treatment and the remaining 20 patients lost >5%; of these 20, 8 patients lost >10% body weight. We used this information to divide the patients into three groups: a pretreatment nutritionally at risk group, a group nutritionally at risk during treatment and a no nutritional risk group.

Factors related to nutritional risk

The factors associated with nutritional risk were analyzed separately for nasopharyngeal carcinoma and other head and neck patients (Table 1 and 2). For nasopharyngeal carcinoma patients, the factors revealed by univariate analysis as significantly associated with an NRS score ≥3 before treatment were age (≤70 vs > 80), KPS (≥80 vs <80), T stage (Tis–T2 vs T3–T4) and clinical stage (stage I–II vs stage III–IV). Age (≤70 vs > 80), type of treatment (CRT vs non-CRT) were significantly associated with an NRS score ≥3 during treatment (Table 1). For head and neck cancer patients, KPS (≥80 vs <80), T stage (Tis–T2 vs T3–T4) were remained as significant factors to NRS score ≥3 before radiotherapy. And only KPS (≥80 vs <80) was significant factor during treatment. Multivariate analysis gave the risk factors associated with NRS ≥3 as T stage for pretreatment patients of all patients, and treatment modality for NPC patients during treatment (Table 3).

Prognostic value of nutritional risk

With a median follow-up of 40 months (range 2–68 months), the 3-year overall survival (OS), loco-regional control (LRC), disease-free survival (DFS) and distant metastasis-free survival (DMFS) for the whole group were 79.1%, 93.2%, 82.1% and 86.4%, respectively. The 3-year OS for the pretreatment nutritionally at risk, during-treatment nutritionally at risk and the no nutritional risk groups was 62.9%, 81.7% and 80.6%, respectively

Table 3. Related nutritional risk factors before and during radiotherapy

	Variables	*p* value	OR	95% CI
Pre-RT				
NPC	T2010 (T3-4 vs Tis-2)	0.012	5.206	1.431–18.939
HNC	T2010 (T3-4 vs Tis-2)	0.028	4.678	1.179–18.554
During-RT				
NPC	Treatment (Non-CRT vs CRT)	0.032	0.479	0.3245–0.937

NPC: nasopharyngeal carcinoma; HNC: head and neck cancers; OR: odds ratio; 95% CI: 95% confidence interval.

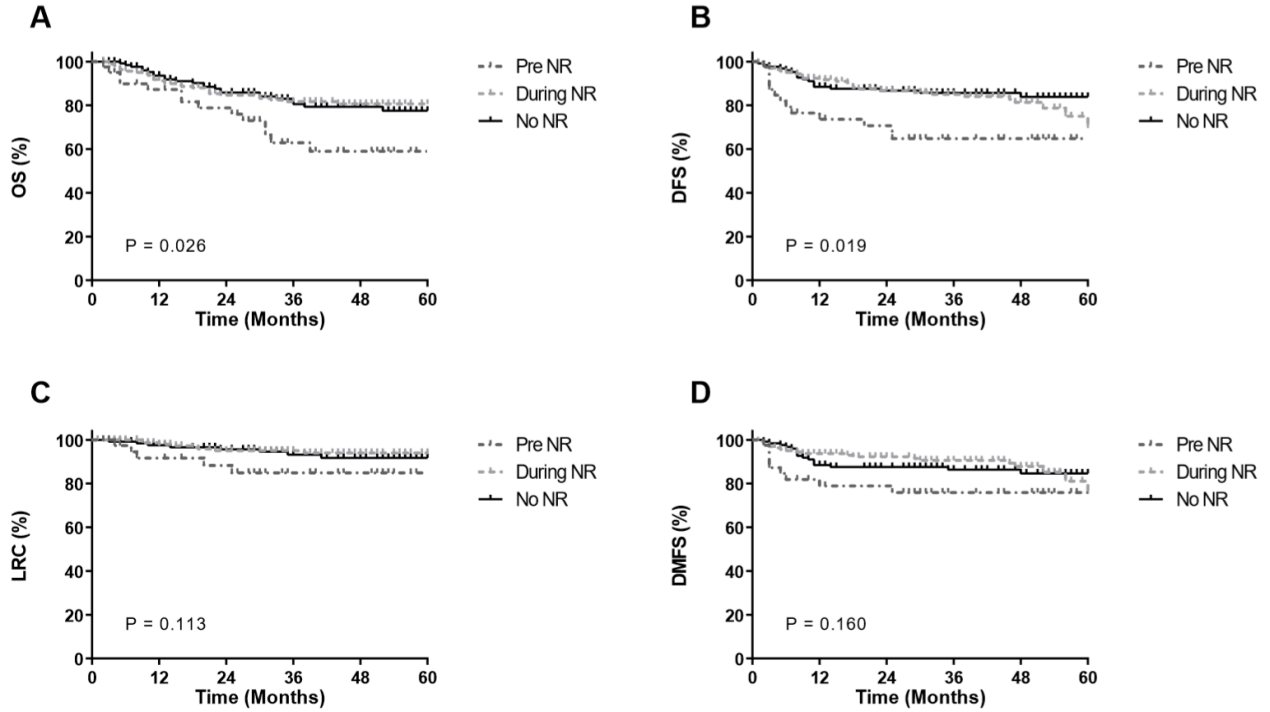

Figure 2. Survival outcomes for patients nutritionally at risk pretreatment (Pre NR), nutritionally at risk during treatment (During NR) and not at nutritional risk (No NR).

(p=0.026). The 3-year DFS for the same three groups was 64.8%, 84.5% and 84.4%, respectively (p=0.019). The 3-year LRC for the three groups was 84.9%, 95.0% and 93.2%, respectively (p=0.113), and the 3-year DMFS for the groups was 75.9%, 90.1% and 85.0%, respectively (p=0.160; Figure 2).

DISCUSSION

The NRS 2002 was first adopted for use with general hospital inpatients and has been validated by many studies since. In the largest study of its use, an international multicenter study of 5051 patients in 26 hospital departments, "at risk" patients experienced more complications, higher mortality and longer lengths of stay than those not deemed at risk and these variables were significantly related to components of the NRS 2002, even after adjusting for confounders.[11] Schiesser et al proved that the proportion of patients undergoing various elective GI operations experiencing severe post-operative complications was significantly higher in patients at nutritional risk (54% vs 15%, p<0.001).[14] Other studies have found that nutritionally at risk cancer patients had more chance of complications and anticancer treatment-related adverse events.[12,13] Proactive nutritional support, especially the provision of enteral nutrition, may minimize these risks.

In our study, nutritional risk before radiotherapy was present in 11.9% of head and neck cancer patients, and 49.4% of patients developed newly occurring nutritional risk during radiotherapy or chemoradiotherapy. The incidence rate of nutritional risk before treatment differs widely across cancer types, ranging from 14% to 45.6% in published papers.[11-15] Two studies conducted in China have shown a similar trend to that seen in our study, i.e., that the number of cancer patients at nutritional risk increases after treatment.[12,13] The main causes of this are lower food intake and acute weight loss during anticancer treatments.

T stage was found to correlate with nutritional risk before radiotherapy in our study. Tumor site and stage may directly impair the oral intake of head and neck cancer patients and a low performance status may magnify the risk of nutritional deterioration. Bozzetti et al found that primary tumor site, Eastern Cooperative Oncology Group score and presence of anorexia or fatigue were significantly associated with nutritional risk score.[15] The results of other studies have suggested that radiotherapy treatment volumes, tumor site, clinical stage and use of chemoradiotherapy are factors that can predict significant weight loss during radiotherapy.[16-19] Our study found that the factors significantly associated with nutritional risk

(mainly acute weight loss) during radiotherapy were treatment-related factor, such as concurrent chemoradiotherapy. Patients with advanced disease stage and good performance status have tended to receive more intensive treatment, such as concurrent chemoradiotherapy, which may induce more severe xerostomia, acute oral mucositis, and nausea and vomiting, reducing nutritional intake.4 Weight loss and undernutrition may then follow. The relatively low rate of nutritional risk observed in surgical patients in our study was attributed to the use of PEG or NG.

To our knowledge, this is the first study to verify the predictive value of NRS 2002 in head and neck cancer patients. Other studies have focused on investigating the relationship between different nutrition-related factors and survival in head and neck cancer. Factors previously found to negatively affect survival were severe malnutrition,[7] a pretreatment body-mass index (BMI) <25 kg/m^2,[20,21] severe pretreatment weight loss (>20%),[22] pretreatment weight loss of 10% or more of previous body weight,[23] BMI <22.8 kg/m^2 and serum albumin level <4.15 g/dL.[24] Our study also showed that lower pretreatment BMI and severe weight loss predicted shorter OS, although the various cut-off points used were derived from previous studies (data not shown).

The prognostic value of the NRS 2002 in other cancer types, especially gastrointestinal cancers, has been proven by many studies. However, no relevant studies have considered the prognostic value of the NRS 2002 in head and neck cancer patients. The NRS 2002 is a combination of several nutritional parameters and is influenced by many prognostic factors in clinical practice. Its predictive value in head and neck cancer may be as an indicator of required nutritional support and treatment adjustment.

We failed to establish a relationship between nutritional risk that occurs during treatment and survival outcomes. Patients who developed nutritional risk during radiotherapy mainly experienced acute severe weight loss resulting from the adverse effects of antitumor treatments (i.e., dysphagia, anorexia, mucositis, xerostomia and chemosensory alteration). The impact of weight loss during treatment on clinical outcomes is controversial. Two studies have not found any relationship between weight loss and patient prognosis.[20,25] However, Langius et al[26] found that patients with weight loss >5% during treatment had shorter disease specific survival, and Capuano et al.[22] reported that patients with weight loss >20% had higher rates of treatment disruption, infection, death and rehospitalization.

Shortcomings in the use of the NRS 2002 in head and neck cancer patients remain; the classification of disease severity is somewhat arbitrary and treatment- related tumor factors are not considered. These shortcomings hamper the accurate assessment of nutritional status and subsequent implementation of appropriate nutritional intervention, and may impede the adoption of effective treatments to improve survival rates.

AUTHOR DISCLOSURES

The authors declare that they have no competing interests. The study was partially supported by the National Key Projects of Research and Development of China (2016YFC0904600) and Beijing Hope Run Special Fund of Cancer Foundation of China (LC2014L12).

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