Original Article

Improved nutritional support with immune-modulating formula in patients with head and neck and esophageal cancer undergoing radiochemotherapy: A retrospective clinical study

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Background and Objectives: Malnutrition is frequent in patients with head and neck (HN) and esophageal cancer, aggravated by radiochemotherapy (RCT), and increases morbidity and mortality and treatment toxicity. Recent studies suggest that the immune, nutritional, or inflammatory status can be modulated by the use of pharmaconutrients in RCT-treated patients. In this study, the effect of immunonutrition, including arginine, ω-3 fatty acid, and nucleotide enriched diet, on nutritional status in patients with HN or esophageal cancer undergoing RCT was investigated. **Methods and Study Design:** A retrospective review of 88 patients undergoing RCT was conducted. Either an immune-modulating enteral nutrition (IEN) (Impact formula) or a standard enteral nutrition (SEN) (isonitrogenous and isoenergetic formula) was administered. Anthropometric parameters, nutritional risk index (NRI), serum albumin, and functional capacity were recorded at the beginning and end of the RCT. **Results:** Approximately 45% of patients were moderate to severely malnourished (NRI <97.5) at the beginning of the RCT in the SEN (n=19) and IEN (n=21) groups alike. Significant improvement was observed in the NRI of malnourished patients of the IEN group (97.3±11.9 vs 98.0±12.0, p=0.021). Additionally, a significant difference in the body weight (BW) between the two groups was observed, and BW increased (65.4±14.8 kg vs 66.3±14.3 kg, p=0.03) in the IEM group but decreased (62.3±12.3 kg vs 61.7±12.0 kg, p=0.023) in the SEM group. **Conclusions:** Pharmaconutrient-enriched IEN had a more potent effect than SEN in preventing deterioration of nutritional status during RCT.

Key Words: immune-modulating enteral nutrition, standard enteral nutrition, radiochemotherapy, nutritional risk index, head and neck and esophageal cancer

INTRODUCTION

Malnutrition is present at an early stage in approximately 30%–40% of patients with head and neck (HN) cancer and 80% of patients with esophageal cancer.[1] The anatomic site of the tumor can considerably affect swallowing and chewing functions with dysphagia, odynophagia, and pain, which contribute to a decrease in protein intake.[2] In 2018, oral, oropharyngeal, and hypopharyngeal cancers together ranked as the sixth most common cancer in Taiwan and the fourth most common cancer among Taiwanese men.[3]

Currently, radiochemotherapy (RCT) appears to be the most effective approach to preserve organ functions in patients with advanced HN cancer and to treat esophageal cancer. RCT is commonly associated with significant acute and late toxicity effects due to its radiosensitization effects. These might cause severe mucositis, dysphagia, odynophagia, loss of taste sensation, xerostomia, nausea, vomiting, and loss of appetite, which can hinder oral feeding and deteriorate functional capacity, necessitating a break in radiation therapy.[4] These side effects aggravate malnutrition caused by mechanical tumor obstruction and are responsible for treatment disruptions, leading to a decrease in the locoregional control of the tumor and reduced overall survival of patients.[5]

Inadequate oral intake leads to weight loss, malnutrition, and eventually requirement for nasogastric (NG) tube feeding.[6] Enteral nutrition (EN) administered either through the NG tube or percutaneous endoscopic gastrostomy (PEG) before initiation of RCT is recommended in

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HN and esophageal cancer.[7] EN prevents or limits weight loss, treatment interruption, and length of hospitalization.[8] Recent studies have suggested that the immune, nutritional, or inflammatory status can be modulated by the use of pharmaconutrients in RCT-treated patients with cancer.[9] A formula containing amino acids, ω-3 fatty acids, ribonucleic acids, vitamins, and antioxidants appears to modulate inflammatory response.[10,11]

This study investigated the effect of immunonutrition consisting of arginine, ω-3 fatty acid, and nucleotide-enriched diet on the nutritional status in patients with HN or esophageal cancer undergoing RCT.

METHODS

Participants

This study consisted of 88 patients undergoing RCT. The enrolled patients were divided into two groups, patients who received immune-modulating enteral nutrition (IEN) (Impact formula) and who were given the standard enteral nutrition (SEN) (isonitrogenous and isoenergetic formula). From January 2015 to December 2015, adult patients (aged more 18 years) with a documented HN or esophageal cancer and in whom RCT was planned were considered as eligible. Before the trial, none of the selected patients in both groups had used tube feeding for nutritional support. During radiotherapy, details regarding admission for NG tube feeding was obtained from medical records. The study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving human patients and patient recruitment were approved by the Ethical Committee of the Medicine Faculty at Chung Shan Medical University Hospital (CSMUH No: CS19013).

Criteria for inclusion

Patients with HN and esophageal cancer who underwent RCT and received EN feeding for more than 7 days were included. The age of patients ranged from 18 to 80 years, and body mass index (BMI) ranged from 16 to 28 kg/m^2. The nutritional status was compared between the two groups. The basal characteristics of the two groups was not significantly different (Table 1).

Criteria for exclusion

Patients with major gastrointestinal diseases or signs of mechanical ileus, cancer recurrence, consumption of ω-3 (or arginine and nucleotides)-enriched food or supplements one month prior to the study, pregnancy, and <3 packs per day of the IEN formula (IMPACT) were excluded from this study. Additionally, those with other serious medical conditions that can affect the nutritional status as well as renal and liver failure were excluded from the study. Participants aged <18 years and those who received EN feeding for <7 days were also excluded.

IEN and SEN

A clinical dietitian provided medical nutrition therapy and recorded energy and dietary intake. Total energy requirement was determined with the Harris–Benedict equation.[12] EN was administered using a feeding tube. The IEN group was administered 3 packs per day of IMPACT (L-arginine, 11.4 g/d; ribonucleotides, 1.35 g/d; and ω-3 fatty acid 3 g/d), and the SEN group received an isocaloric, isonitrogenous polymeric formula. A nonprotein calorie-to-nitrogen (protein) ratio of 100–150 kcal per gram of nitrogen was maintained to ensure that amino acids were utilized as the energy source and therefore were available for tissue healing and repair. The average daily intake of energy and proteins was not significantly different between IEN and SEN in energy (1740±293 vs 1781±285 kcal/d, p=0.508) and in protein (1.23±0.36 vs 1.25±0.33 g/kg BW, p=0.764) (Table 2).

Study design

A retrospective study was conducted using existing clinical dietetic reports. Patient selection is depicted in Figure 1. Nutritional status was assessed with the validated scores of the Patient Generated Subjective Global

Table 1. Demographic data of the study participants receiving IEN or SEN at baseline (n=88)

	IEN (N=44)	SEN (N=44)	*P*
Age (y)	55.4±9.91	59.3±9.64	0.067
Male (%)	42 (95.4)	38 (86.4)	0.133
Tumor characteristics (%)			
Head & neck	38 (86.4)	39 (88.6)	0.500
Esophageal	6 (13.6)	5 (11.4)	0.500
TNM classification (%)			
II	18 (40.9)	15 (34.1)	0.330
III	15 (34.1)	19 (43.2)	0.256
IV	11 (25.0)	10 (22.7)	0.500
Comorbid condition (%)			
DM	8 (18.2)	6 (13.6)	0.386
Hypertension	10 (22.7)	6 (13.6)	0.204
Anthropometric parameters			
Weight (kg)	65.4±14.8	62.7±12.9	0.376
BMI (kg/m^2)	23.6±4.70	22.9±4.14	0.431

IEN: immune-modulating enteral nutrition; SEN: standard enteral nutrition; TNM: tumor, node, and metastasis; DM: diabetes mellitus; BMI: body mass index.
Data are presented as n or means±SDs.
*p<0.05.

Table 2. Composition of the enteral nutrition diets

Components	IEN (N=44)	SEN (N=44)	*P*
Total calories intake (kcal/d)	1740±293	1781±285	0.508
kcal/kg BW (energy)	27.7±7.02	29.5±8.01	0.252
Total protein intake (g/d)	76.7±15.0	75.3±12.4	0.623
g/kg BW (protein)	1.23±0.36	1.25±0.33	0.764
Immunonutrient			
L Arginine (g/d)	11.4	0	
Ribonucleotides (g/d)	1.35	0	
n-3 fatty acid (g/d)	3	0	
EPA (g/d)	1.8	0	
DHA (g/d)	1.2	0	

IEN: immune-modulating enteral nutrition; SEN: standard enteral nutrition; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.
Data are presented as n or means±SDs
$^{*}p<0.05$.

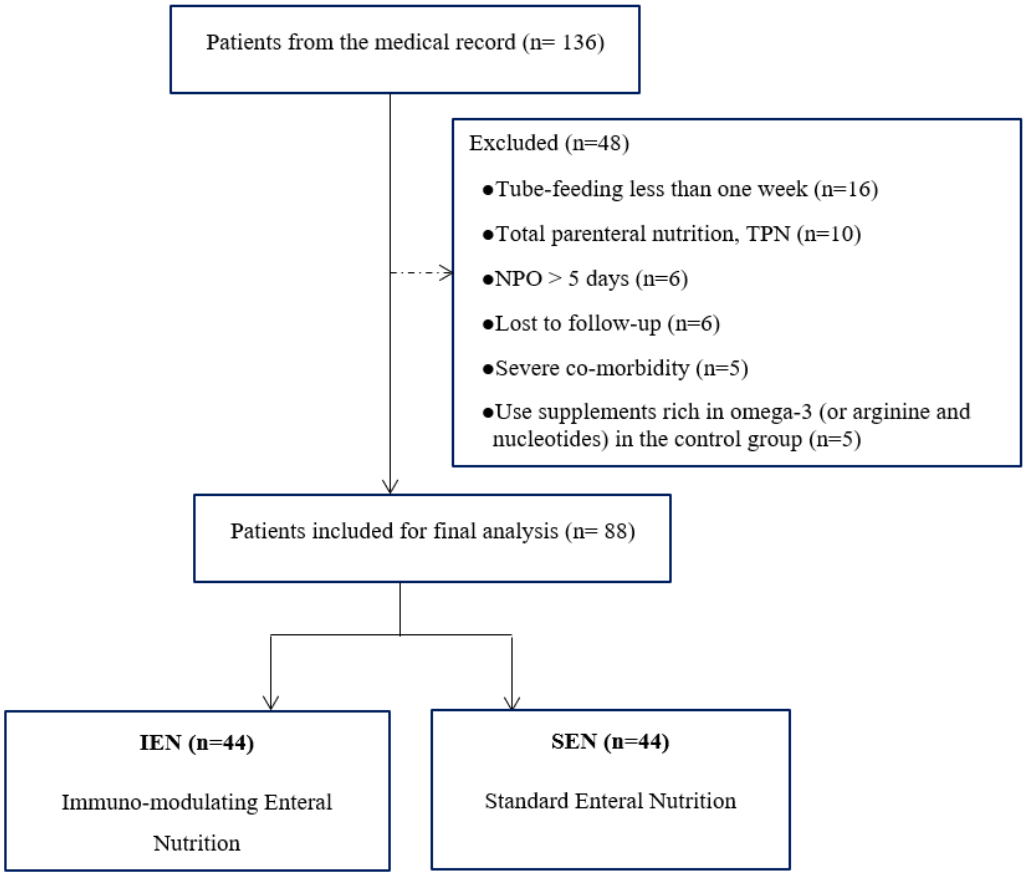

Figure 1. Flow chart of patient selection. NPO: nothing by mouth.

Assessment (PG-SGA)[13] and Nutritional Risk Index (NRI).[14] These methods were performed by dietitians subjected to inter-rater reliability on nutritional status measures. The PG-SGA is specifically designed to assess the nutritional status of patients with cancer. This tool provides a global rating of either A (well nourished), B (suspected or moderately malnourished), or C (severely malnourished). The NRI was calculated using the formula 1.519 × albuminemia (g/l) + 41.7 × [actual weight/healthy weight (kg)]. Thereafter, patients were classified as NRI, ≥97.5 well-nourished; 83.5<NRI<97.5, moderately malnourished; and NRI ≤83.5, severely malnourished.

Biochemical and parameters

Several aspects reflecting the nutritional state and organ functions of the patients with cancer were evaluated by analyzing the specific parameters. Nutritional parameters included total protein (TP), total cholesterol (TC), albumin (Alb), white blood cell count (WBC), and hemoglobin (Hb). Anthropometric parameters included BW, BMI, triceps skinfold (TSF), and midarm muscle circumference (MAMC). The NRI and PG-SGA nutritional screening tools were used to assess nutritional status of the patients.

Statistical analysis

Data are presented as the mean ± standard deviation. Continuous variables between groups were compared using the unpaired Student t-test or the paired Student t-test within groups. Chi-square analyses were performed to determine associations between categorical variables.

Distributions of patients based on the PG-SGA stage between the groups (SEN vs IEN) were compared using Fisher's exact test and McNemar's test in each group (De vs Db). Data were analyzed using SPSS statistical software (Chicago, IL, USA; version 18.5); $p<0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

Of the 136 patients, 88 were enrolled in this study; intervention was discontinued in 48 patients based on the exclusion criteria. Data of the 88 patients were collected and divided into 2 groups; patient characteristics are presented in Tables 1 and 2. Differences between the two groups based on age; gender; tumor characteristics; tumor, node, and metastasis classification; comorbidities; anthropometric parameters; TP intake (g/d); and total daily calories (kcal/d) were nonsignificant. Patients in the IEN group received a polymeric formula (Impact, Nestlé HealthCare Nutrition, Lausanne, Switzerland) enriched with arginine (11.4 g/d), eicosapentaenoic and docosahexaenoic acids (EPA+DHA, 3.4 g/d), and ribonucleotides (1.35 g/d). Patients in the SEN group received an isocaloric and isonitrogenous polymeric formula (Table 2).

Effects of IEN and SEN on nutritional status

Patient compliance with the nutritional intervention was assessed using plasma nutritional markers (Table 3). Differences between the two groups of Alb were nonsignificant but significantly decreased between day beginning (Db) and day end (De) in the SEN group (−0.20±0.55 g/dL, $p<0.05$). TP significantly increased between the Db and De in group IEN patients (0.13±0.34 g/dL, $p<0.05$) but significantly decreased between Db and De in the SEN group (−0.39±0.87 g/dL, $p<0.05$). TC significantly decreased between Db and De only in the SEN group (−0.39±0.87 g/dL, $p<0.05$). There was no difference between the mean Hb and WBC values in both the groups. NRI significantly increased between Db and De only in the IEN group (0.67±1.85, $p<0.05$).

Change in anthropometric parameters

Between Db and De, a significant increase in weight (0.97±2.7 kg, $p<0.05$), BMI (0.35±1.02 kg/m^2, $p<0.05$), TSF (0.50±1.65 mm, $p<0.05$), and MAMC (0.26±0.72 cm, $p<0.05$) was observed in IEN patients. By contrast, a significant decrease in weight (−0.90 ± 1.49 kg, $p<0.05$), BMI (−0.33±0.54 kg/m^2, $p<0.05$), and MAMC (−0.27±0.70 cm, $p<0.05$) was observed in SEN patients between Db and De. SEN patients exhibited a lower MAMC and TP after intervention than did IEN patients (MAMC: 24.4±1.96 vs 23.2±2.25, $p<0.05$; TP: 6.87±0.61 vs 6.38±0.78, $p<0.05$) (Table 3).

Repartition of patients by scored PG-SGA

Distribution of patients per stage of scored PG-SGA was modified in the SEN and IEN groups at the end of the study ($p<0.01$, De vs Db for IEN group; $p=0.009$, De vs Db for SEN group). Furthermore, the IEN group was better than the SEN group at the end of study ($p=0.048$, SEN vs IEN for De) (Table 4).

DISCUSSION

Eating difficulty is a critical problem in patients with HN as it can lead to malnutrition and to poor quality of life and treatment response.[15,16] Patients with cancer inevitably experience malnutrition due to poor gastrointestinal function. Nutritional intervention, such as tube feeding, was found to improve the overall quality of life.[17] At baseline, patients with HN squamous cell carcinoma were associated with an inflammatory status; Wang et al[18] suggested that inflammation could be a consequence of cancer. Reducing chronic inflammation is associated with better health outcomes.[19] In this study, we aimed to clarify the effectiveness of IEN in patients with HN and esophageal cancer by evaluating changes in the nutritional status when fed either SEN or IEN. Patients in both groups were administered the same number of calories and proteins, although the IEN group received a formula enriched with arginine, ω-3 fatty acids, and ribonucleotides (Table 2).

Table 3. Nutritional and anthropometric parameters

	IEN n=44		SEN n=44	
	Db	De	Db	De
NRI	97.3±11.9	98.0±12.0‡	101.1±1.49	97.5±1.48
Anthropometric parameters †				
Weight (kg)	65.4±14.8	66.3±14.3‡	62.7±12.9	61.8±12.6§
BMI (kg/m^2)	23.6±4.70	24.0±4.50‡	22.9±4.14	22.5±4.02§
TSF (mm)	14.2±5.62	14.7±5.58‡	14.1±4.52	14.0±4.96
MAMC (cm)	24.1±1.99	24.4±1.96‡	23.4±2.23	23.2±2.25‡§
Biological markers†				
Albumin (g/dL)	3.78±0.80	3.86±0.60	3.95±0.61	3.75±0.61§
Total Protein (g/dL)	6.74±0.63	6.87±0.61‡	6.77±0.66	6.38±0.78‡§
Total cholesterol (mg/dL)	177±51.0	172±46.0	179±40.0	168±40.8§
Hemoglobin (g/dL)	12.8±2.92	13.2±2.42	12.7±2.10	12.2±1.64
White blood cell count (x10^3/mm^3)	7.04±3.52	8.40±4.99	7.19±2.32	7.61±2.42

IEN: immune-modulating enteral nutrition; SEN: standard enteral nutrition; Db: day beginning; De: day end; NRI: nutritional risk index; BMI: body mass index; TSF: triceps skinfold; MAMC: mid-arm muscle circumference.
NRI ≥97.5, well-nourished; 83.5<NRI<97.5, moderately malnourished; NRI ≤83.5, severely malnourished;
†Results are expressed as the mean±SD
‡$p<0.05$; IEN vs SEN, unpaired t-test between periods;
§$p<0.05$; De vs Db, paired t-test in each group.

Table 4. Nutritional status and scored PG-SGA of patients with cancer undergoing treatment

	IEN (N=44)		SEN (N=44)	
	Db	De	Db	De
Scored PG-SGA†				
Stage A	36	39	29	32
Stage B	6	3	13	11
Stage C	2	2	2	1

PG-SGA: patient generated subjective global assessment; IEN: immuno-modulating enteral nutrition; SEN: standard enteral nutrition; Db: day beginning; De: day end; Stage A: well-nourished; Stage B: moderate or suspected malnutrition; Stage C: severe malnutrition
†Results are expressed as the number of patients. Distribution of patients per stage were compared using Fisher's Exact Test between groups (SEN vs IEN) and periods (De vs Db).
p=0.048, SEN vs IEN for De group; p<0.01, De vs Db for IEN group; p=0.009, De vs Db for SEN group.

The importance of nutritional therapy in patients with HN cancer during CCRT (concurrent chemoradiotherapy) has been reported in several studies.[8,20] In adult patients with gastrointestinal cancer, the increased mortality risk of patients with weight loss prior to chemotherapy has been attributed to decreased chemotherapy dose and increased toxicity.[21] Total energy expenditure and protein requirements of nonobese ambulatory patients using their actual BW can be estimated as follows: energy, [30–35] kcal/kg/day and protein, 1.2 g/kg/ day.[22] The Harris-Benedict equation was used to calculate energy requirements (Table 2).

According to the guidelines of the European Society for Clinical Nutrition and Metabolism, weight loss >10% in 6 months is a risk factor for postoperative complications and is a borderline value for malnutrition.[23] Clinical studies suggest that EN supplemented with different agents (ω-3 fatty acids) reduced postoperative infectious complications and length of hospital stay in different contexts such as gastrointestinal cancers,[24] HN cancers[25,26] and critically ill patients.[27] ω-3 enriched nutrition support may improve nutritional outcomes, including BW, lean body and fat mass, reduce postoperative infections, and reduce hospital stay. In our study, the IEN group had better anthropometric parameters (BW, BMI, TSF, and MAMC) (Table 3).

A meta-analysis of 11 randomized controlled trials evaluating the use of enteral nutritional support supplemented with key nutrients (L-arginine/L-glutamine) versus SEN was performed by Heys et al,[28] which showed that nutrients can stimulate a variety of host defenses, modulate tumor metabolism, increase wound healing, and reduce nitrogen loss. Some studies have suggested that nutritional indicators such as weight loss and serum albumin concentration can predict post-operative complications, particularlyinfection.[29,30] Our study indicated that supplementation with nucleotide, Arg, and ω-3 is effective in the prevention of bodyweight loss with better anthropometric parameters and biological markers (Table 3).

Malnutrition is a typical characteristic of patients with HN cancer.[31,32] Wiel et al[33] reported that nutritional status in patients with HN tumor seems to be best assessed by weight loss than by other parameters. SGA indicated a favourable nutritional status in patients with HN tumors. PG-SGA has two sections: a patient-completed section that includes data regarding weight history, symptoms, dietary intake, and activity level, and a section completed by a healthcare professionals to evaluate metabolic demand, consider disease in relation to nutritional requirements, and incorporate a physical assessment.[34] NRI uses parameters, such as the serum albumin concentration and the ratio of actual to usual BW, and was originally developed for patients with cancer.[35] Forty-four subjects in the control group had a significant decrease in overall nutritional status including BW loss. In contrast to the control group, patients in the study group maintained good nutritional status by both NRI and PG-SGA scores (Tables 3 and 4).

This study protocol expands on the current literature regarding the efficacy of immune-modulating formula as an adjuvant therapy for patients with HNC. In conclusion, nutrition support with the combination of nucleotide, Arg, and ω-3 was well tolerated and safe, and easily administered to patients undergoing CCRT. This intervention modulated the inflammatory state. However, a limitation of the current study is that it was a retrospective study with a small sample size. Larger multicenter double-blind controlled trials involving nutritional intervention in patients undergoing CCRT are required to confirm the preventative role of immunonutrition.

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AUTHOR DISCLOSURES
The authors have no conflicts of interest to declare.

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