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Randomized study of nutritional status and treatment toxicities of oral arginine, glutamine, and Omega-3 fatty acids during concurrent chemoradiotherapy for head and neck cancer patients

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ABSTRACT

Background: Patients with head and neck cancer (HNC) undergoing concurrent chemoradiotherapy (CCRT) are at high risk for dysphagia, malnutrition, and immunosuppression. Accordingly, arginine, glutamine, and Omega-3 fatty acidsare immune-enhanced nutrition can promote cellular immunity. We aimed to examine the impact of immunonutrition diet on nutritional status, in addition to CCRT toxicities, within this group of patients.

Methods: Forty patients with HNC who were treated with curative CCRT were randomized into group A (n = 20), patients who received a regular diet and dietary counseling by a protocol dietician, and group B (n = 20), patients who received a regular diet plus immune-enhanced nutrition supplements and dietary counseling by the same protocol dietician. Outcome measures were weight loss, protein and energy intake, serum pre-albumin and albumin, and toxicities of CCRT were evaluated at baseline, weekly and at the end of treatment.

Results: Both groups were well balanced at baseline. One patient from group A (1/20) withdrew consent. Seven patients from group B (7/20) withdrew from the study; 1 patient could not tolerate the side effect of chemotherapy and 6 patients could not tolerate the taste of oral immune-enhanced nutrition. A significant loss in total body weight was observed in group A patients ($p<0.001$), whereas in group B there no significant weight loss ($p=0.109$). Median percentage change from baseline of energy intake was 19.6%, and 22.9% at the end of treatment for group A and B respectively. The circulating levels of nutritional markers,

pre-albumin and albumin, decreased after CCRT in both groups. There was a significantly decreased level of albumin in group A compared to that of group B, at the end of treatment. During CCRT; 4 patients (20%) in group A and 1 patient (5%) in group B developed grade 3 mucositis, respectively. One patient (5%) in group A had grade 3 radiation dermatitis. Grade 3–4 hematologic toxicities, mainly in absolute neutrophil count (ANC), were significantly higher in group A than group B: 20% versus 0% (p=0.035). Over the 7-week period of CCRT, both the intention to treat analysis and per protocol analysis revealed similar results in scaled for all endpoints.

Conclusions: Nutritional counseling and immuno-nutrition can reduce the deterioration of nutrition status and also significantly reduced hematologic and non-hematologic toxicity of CCRT in head and neck cancer.

Keywords: immune-enhanced nutrition, concurrent chemoradiotherapy, head and neck cancer

BACKGROUND:

Concurrent chemoradiotherapy (CCRT) is one of the standard treatments for locally advanced head and neck cancer. The common toxicities of this treatment include the following: radiation induced oral mucositis, dysphagia, xerostomia, and nausea/vomiting [1-5] resulted in decreasing of oral intake of the patients. Malnutrition is frequently seen with patients suffering from head neck cancer at diagnosis, which is also aggravated by CCRT. Hematotoxicities are also a form of common toxicity in CCRT. All of these complications leads to unplanned treatment break, prolongation hospitalization, and increased overall treatment time, which has been associated with the poor treatment outcome in these patients [6-10]. A recent narrative review of nutritional interventions in head and neck cancer patients undergoing CCRT recommended to use nutritional counseling and oral nutritional supplements to increase oral intake, and to prevent treatment associated weight loss and treatment break [11]. There are some reports on immune enhanced nutrition using in preoperative or perioperative and postoperative in head and neck cancer and gastrointestinal cancer [12-18]. However, the studies in the application of immune-modulated nutrition for head and neck cancer patients who received CCRT are limited. The primary objective of this study was to measure nutritional parameters (body weight, energy intake, protein intake and nutritional markers). The secondary objective was to evaluate the acute toxicities and compliance of CCRT.

METHODS:

This non-blinded prospective, randomized study was approved by the institutional ethics committee. Patients were recruited between December 2013 and February 2015. Each patient provided written informed consent before entering in the study. The eligibility criteria were head and neck cancer patients with age more than 18 years intended for CCRT either definitive treatment or adjuvant setting, Eastern Cooperative Oncology Group (ECOG) performance status 0-1 [19]. Exclusion criteria included patients with metastatic disease, history of diabetes mellitus, renal disease, and liver disease. Forty patients were randomly assigned in a 1:1 ratio by a computer program to the control arm (group A); diet counseling

by protocol dietician only or the study arm (group B); diet counseling by protocol dietician and immunonutrition oral supplementation.

ASSESSMENT:

Baseline assessment 3-7 days prior to the study was performed for an objective measurement of malnutrition. Blood samples for complete blood cell count (CBC), albumin, and pre-albumin were obtained as a marker of nutritional status. Energy and protein intake were calculated at baseline and weekly by a protocol dietician. Body weight and side effect of CCRT were recorded weekly. Acute toxicities of CCRT were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [20] at baseline, and weekly until the end of treatment.

Nutritional counseling and immunonutrition supplements: All patients received individualized nutritional counseling by a protocol dietician on the first week of CCRT and weekly for the whole course of treatment. For group B; patients received immunonutritional supplement [Neo-Mune; Thai Otsuka Pharmaceutical Company, Bangkok, Thailand]. The nutritional formulas used in this study are shown in Table 1. The nutritional supplements were provided for the patients in the study arm by the protocol nurse with 2 glasses per day (1 glass = 250 ml: 250 kCal), 1 hour before and after radiotherapy session. Sachets of nutritional supplements were provided to the patients on the weekend and holiday.

Table 1: Nutritional Formulas

Energy (kcal/ml)	1.0
Fat (g/L)	28.5
Fat Source	
Corn oil	29%
Medium chain triglyceride (MCT)	52%
Fish oil	19%
Protein (g/L)	61.5
Protein source	
Casein	70%
Arginine	20%
Glutamine	10%

Concurrent chemoradiotherapy (CCRT): Definitive curative radiotherapy was administered to the enrolled patients with standard fractionation 2.0 Gy/fraction for conventional radiotherapy technique to a total of 70 Gy in 35 fraction; or 2.12 Gy/fraction for simultaneous integrated boost (SIB) used in nasopharyngeal cancer to a total of 69.96 Gy in 33 fraction for intensity modulated radiotherapy (IMRT). Adjuvant postoperative radiotherapy was given with standard fractionation 2.0 Gy/fraction to a total of 60-66 Gy in 30-33 fractions, either by conventional or conformal technique. Concurrent chemotherapy was weekly cisplatin 40 mg/m^2 or weekly carboplatin AUC2 (if the creatinine clearance of patient less than 50).

STATISTICAL ANALYSIS:

From the results of a pilot study, we assume that the weight loss is normally distributed with mean of 5 kg and a variance of 4 kg. This study is being conducted to examine the effect of

oral nutrition supplements on weight loss. It is hypothesized that the mean weight loss of group B (study arm) is less than the mean weight loss of group A (control arm). A minimum sample size of 40 patients (20 patients per arm) was then calculated to detect a difference in weight loss of 1.9 kg with a 5% level of significance (1-sided test) and a power of 90%.

All randomized patients are included in the final intent to treat analysis. Although randomization was the first step to balance known and unknown covariates between study arms, we compared the distribution of all baseline characteristics among arms (chi-square test for qualitative variables and Wilcoxon test for continuous variables). Median of nutritional parameters during treatment between control arm and study arm were analyzed using the Wilcoxon-Mann Whitney test. Data related to incidence, prevalence, or frequency (symptoms, cancer sites, and nutritional status categories) were expressed as number and/or percentage, with age, energy and protein intakes being expressed as the median, interquartile range (IQR). Continuous variables were analyzed using Wilcoxon-Mann Whitney test, and categorical variables were evaluated by the chi-square test.

RESULTS:

A total of 40 patients were recruited in the study, including 26 men (65%) and 14 women (35%), with a median age of 51.5 years (IQR 48.0-60.0). The patient and clinical characteristics are shown in Table 2. Most of the patients were well-balanced between two groups. Laboratory assessments (complete blood count, renal function, serum electrolytes, liver function test, and thyroid hormone) at baseline in both groups were comparable. A comparison with the control arm for the main study's end points with the intention to treat analysis was performed, although this study was completed only 32 patients. The number of patients remaining in the study decreased mainly in group B by approximately 20% over 7 weeks of treatment. One patient in group A withdrew consent, whereas 7 patients (35%) in group B withdrew from the study (due to intolerable of the taste of immune-enhanced nutrition in 6 patients, and due to the toxicity of CCRT in 1 patient). Per protocol analysis was also studied in these 32 patients. The consort diagram was shown in Figure 1.

Table 2: Baseline Characteristics of the patients

IQR	Group A	Group B	p-value
Median Age(years)(IQR)	54.0 (49.5-60.5)	49.5 (41.5-55.0)	0.064*
Sex			
Male	13 (65%)	13 (65%)	1.000†
Female	7 (35%)	7 (35%)	
Type of Cancer			
Nasopharynx	9 (45%)	8 (40%)	0.599†
Oral cavity	3 (15%)	5 (25%)	
Oropharynx	6 (30%)	4 (20%)	
Hypopharynx	2 (10%)	3 (15%)	
Stage			
III	6 (30%)	2 (10%)	0.286†
IVA	10 (50%)	13 (65%)	
IVB	4 (20%)	5 (25%)	
Karnofsky performance status score			0.490†

0 1	15 (75%) 5 (25%)	13 (65%) 7 (35%)	
Median Baseline body weight (kg)(IQR)	56.3 (50.0-59.5)	60.0 (50.3-67.0)	0.267*
Median Baseline serum pre-albumin (mg/dL)(IQR)	0.208 (0.129-0.256)	0.252 (0.137-0.273)	0.189*
Median Baseline serum albumin (mg/dL)(IQR)	4.4 (4.1-4.5)	4.4 (4.1-4.6)	0.806*

*Wilcoxon-Mann Whitney test
†Chi-square test

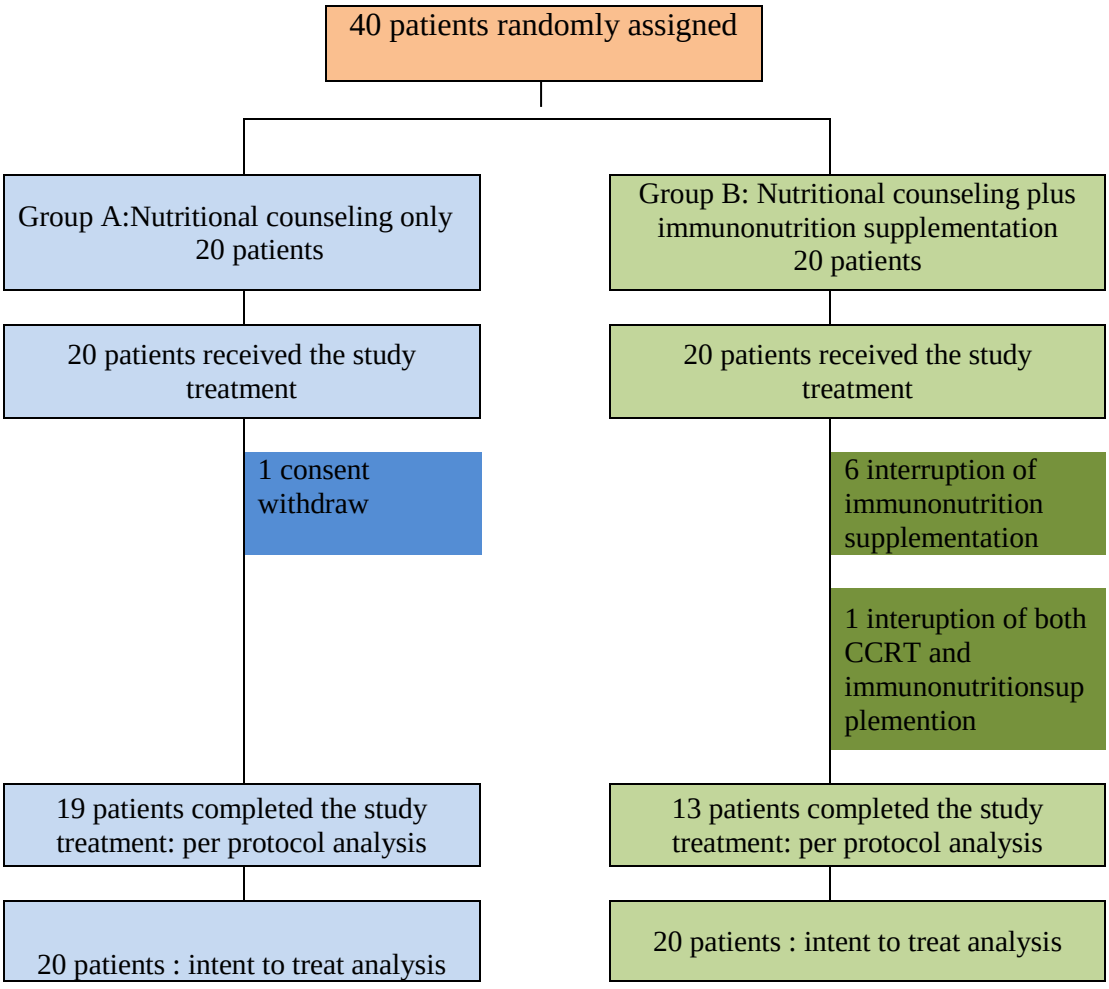

Figure 1: Consort diagram

1. Nutritional parameter:

1.1 Weight loss

The median weight changed significantly from 56.3 kg (IQR 50.0-59.5) at baseline to 47.0 kg (IQR 45.5-50.5) at the end of treatment ($p<0.001$) in group A, but did not significantly decrease from 60.0 (IQR 50.3-67.0) at baseline to 53.0 (45.0-62.0) at the end of treatment ($p=0.109$) in group B. (Table 3). In the per-protocol group changes were similar in scale.

Table 3: Median body weight

Variables	Group A (n=20)			Group B (n=20)			p-value*
	n	Median	(IQR)	n	Median	(IQR)	
Weight**							
Baseline	20	56.3	(50.0-59.5)	20	60.0	(50.3-67.0)	0.267
Week 3	20	52.5	(49.0-56.5)	15	59.1	(49.0-67.0)	0.151
End of treatment	13	47.0	(45.5-50.5)	6	53.0	(45.0-62.0)	0.251

Note.*n, Number of patients in each group; N, Total number of patients*

** Wilcoxon-Mann Whitney test for median comparison*

*** Median body weight at the end of treatment of overall ($p<0.001$) and group A ($p<0.001$) decreased from baseline but maintained in group B ($p=0.109$)*

1.2 Energy Intake

Median percentage change of energy intake decreased overtime in both groups (Figure 2). However, the median energy intake of group B was significantly higher than group A. The Figure 3 shows the median energy intake in this study. In the per-protocol group, changes were similar in scale.

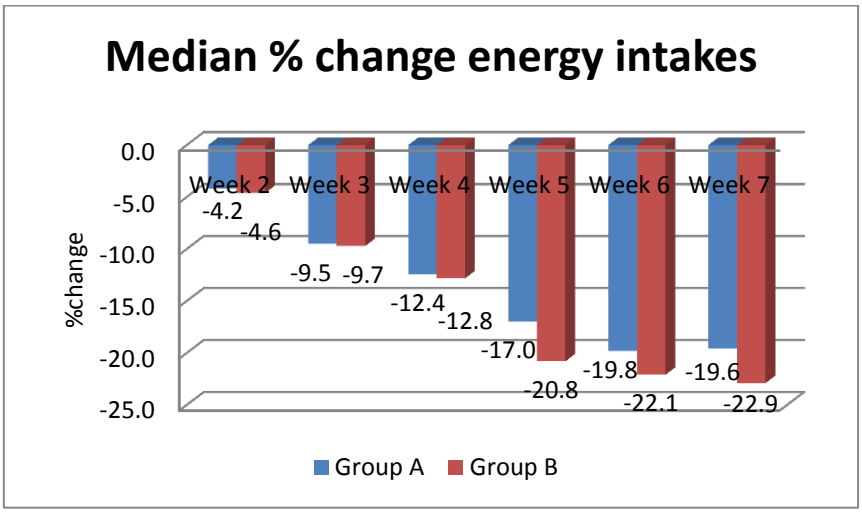

Figure 2: Median percentage change energy intake

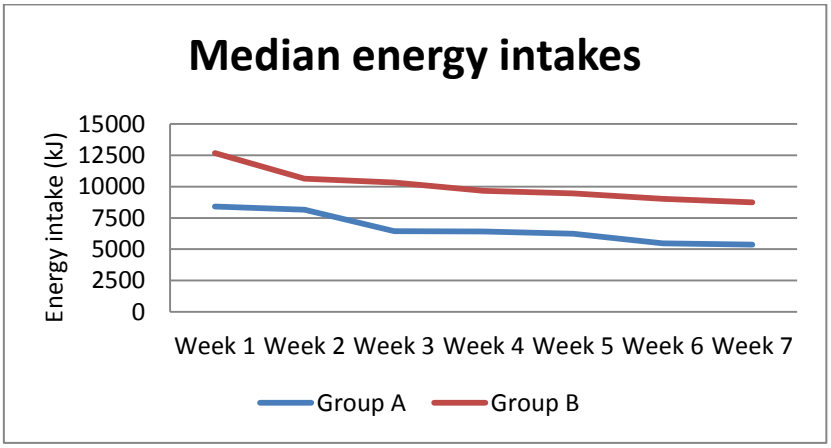

Figure 3: Median energy intakes

1.3 Protein Intake

Median percentage change of protein intake decreased over time during CCR Tin both groups of patient (Figure 4). However, patients who received immune- enhanced nutrition had increase protein intake compared to those who did not during the second week (Figure 5). In the per-protocol group, we found the statistically significant higher protein intake in group B in the 2nd, 4th, and 5th week of treatment.

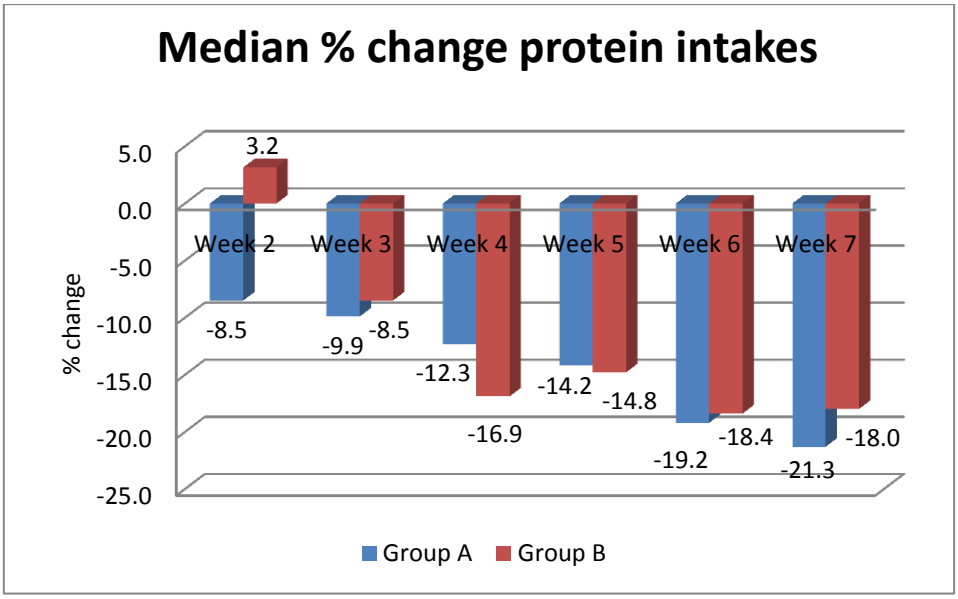

Figure 4: Median percentage change protein intakes

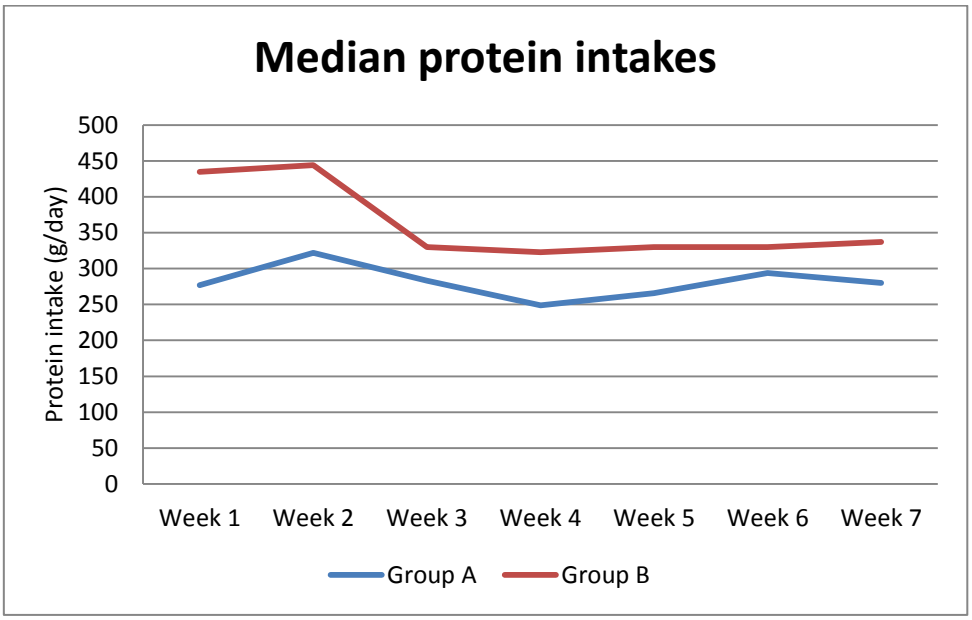

Figure 5: Median protein intakes

1.4 Nutritional markers

Both nutritional markers (albumin and pre-albumin) decreased during CCRT in both groups of patient. However, median circulating albumin at the end of treatment of group B was significantly higher than group A (p= 0.028), whereas median pre-albumin did not significantly different between the groups (p=0.272) (Table 4). We found similar results in the per-protocol group.

Table 4. Median circulating levels of nutritional markers

Variables	Baseline			p-value*	End of treatment			p-value*
	n	Median	(IQR)		n	Median	(IQR)	
Pre-albumin								
Group A	20	0.188	(0.136-0.260)	0.502	17	0.154	(0.087-0.199)	0.812
Group B	17	0.205	(0.164-0.269)		14	0.138	(0.115-0.185)	
Albumin								
Group A	20	4.4	(4.1-4.5)	0.806	19	3.9	(3.7-4.2)	0.028
Group B	20	4.4	(4.1-4.6)		14	4.3	(4.0-4.6)	

Note. *n, Number of patients in each group; N, Total number of patients*
**Wilcoxon-Mann Whitney test for median comparison*

2. Toxicities of CCRT:

For non-hematologic toxicity, radiation induced oral mucositis was the most common affliction for both groups of patients. 20% (4/20) of group A developed grade 3 mucositis, whereas only 5% (1/20) of patients did in group B. Radiation dermatitis was found to be 5% (1/20) and 0% in group A and B respectively. For hematologic toxicity, the severe grade 3-4 hematologic toxicities were also found to be significantly higher in group A than group B significantly (p=0.035). Whereas we did not find any grade 3-4 hematologic toxicities in group B patients, but we found grade 3, and 4 neutrophil count decrease in 3 patients and 1 patient from group A respectively. One patient in group A had grade 3 thrombocytopenia. These were the causes of extension of the overall treatment time (OTT) between the two groups, 55 days in group A versus 51 days in group B. However, this did not make a significant statistical difference, measured at p=0.316. These severe toxicities were also the cause of the incomplete planning of CCRT. The patients in group B had statistically significantly higher complete CCRT than patients from group A, p=0.013. We found similar results in the per-protocol group, in higher grade 3-4 hematologic toxicities in group A patients, but not statistically significant (p=0.132) as intent to treat analysis.

3. Adverse event of Immune-enhanced nutrition:

No immune-enhanced nutrition related serious adverse events occurred. The most common observed events were nausea (35%), due to the taste of the samples. Additionally, nausea was also the cause of intolerance and withdrew from the study before the last week of CCRT.

DISCUSSION:

A recent review from Bossola M [11] suggested that nutritional counseling and oral nutritional supplements should be used to increase dietary intake and to prevent treatment-associated weight loss and interruption of radiotherapy or concurrent chemoradiotherapy for head and neck cancer patients. However, all the evidence [21-28] used drew from standard enteral nutrition, rather than an immune modulating enteral nutrition formula. We are aware of only a few published randomized trials that studied immune-enhanced nutrition in CCRT for head and neck cancer [29-30].

The present study shows that, head and neck cancer patients undergoing CCRT who received nutritional counseling or had immune-enhanced nutrition supplementation both had

weight loss overtime during the treatment. A study by Arnold et al. [21] also found the same results as this present study, with that weight loss can occur in both groups (either received nutritional supplements or not) during the observation period of 6 months. Median weight loss was about 5.2% within patients from group A and 4.2% in group B. Study of Vasson MP et al. [30] had 5.6%, and 6.2% weight loss at the end of treatment in patients who received standard nutrition and immune-enhanced nutrition, respectively. The patient who received immunonutrition in our study had less percentage weight loss than the Vasson MP et al [30] study, as nearly 50% of patients in their study had esophageal cancer, whereas none of our patients did. The median energy and protein intake in both groups of patients were also decreased significantly from the first week of treatment until the end of CCRT. Our results demonstrate that adding immune-enhanced nutrition may improve energy and protein levels in certain patients.

This study demonstrated that immune-enhanced nutrition can significantly slow the deterioration of serum albumin in patients treated by CCRT. However, pre-albumin level may be more specific in detecting a malnourished state than albumin level. Our results did not demonstrate that immune-enhanced nutrition had a significant effect on pre-albumin levels.

Severe grade 3-4 hematological toxicities were strongly affected as much as 20% by CCRT especially in patients who did not receive immuno-nutrition, whereas the patients who received immuno-nutrition had none. Sunpaweravong S. et al. [31] reported 5.7% of patients receiving immuno-nutrition developed severe neutropenia, which was higher than ours. However, their study only focused on esophageal cancer patients who were treated with different chemotherapy regimens from ours by using cisplatin 75 mg/m^2/day and the field of radiotherapy for esophageal cancer is wider than head and neck cancer. Moreover, a higher proportion of group A patients compared to those of group B developed high grade oral mucositis and dermatitis during CCRT. As a result, it appears that immune-nutrition during CCRT could also have a positive effect on non-hematologic toxicities occurrence. This would be the useful benefit to decrease the numbers of patients who need the CCRT treatment break. Although it has no statistically significant difference in the median overall treatment time, the patients who received immuno-nutrition can complete their CCRT treatment in a shorter period of time. We also performed per protocol analysis and found that the baseline characteristics in both groups were almost similar in every variable, except for the statistically significant younger age in group B patients (48 VS 54 years old; p= 0.003). However, all the endpoints, including weight, energy and protein intake, nutritional marker, toxicities of CCRT, overall treatment time, and rate of incomplete planned of chemotherapy were similar in scale.

A limitation in our study is our sample size. This study is being conducted to examine the effect of oral nutrition supplements on weight loss. A minimum sample size of 40 patients (20 patients per arm) was calculated to detect a difference in weight loss of 1.9 kg with a 5% level of significance (1-sided test) and a power of 90%. However, the number of patients including in the analysis is lower than the statistical number of 30 in each group which is scientifically desirable.

CONCLUSION:

In conclusion, the present study shows that immune-enhanced nutrition combined with nutritional counseling in head and neck cancer patients undergoing CCRT is beneficial in reducing the deterioration of nutritional status and also the severity of CCRT toxicities.

List of abbreviations used: HNC: head and neck cancer**;** CCRT: concurrent chemoradiotherapy**;** ANC: absolute neutrophil count**;** ECOG: Eastern Cooperative Oncology Group**;** CBC: complete blood cell count**;** CTC AE: Common Terminology Criteria for Adverse Events**;** SIB: simultaneous integrated boost**;** IMRT: intensity modulated radiotherapy**;** AUC: area under curve**;** IQR: inter-quartile range

Competing interest: The authors declare that they have no competing interests.

Authors' Contributions: IC conceived and coordinated the study, analyzed the data, and drafted the manuscript, VP coordinated and analyzed the study, ET, SJ, PK, WO, BS participated in acquisition of data. PT performed the statistical analysis. WMS and SR helped to draft the manuscript. All authors read and approved the final manuscript.

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