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Predictors of weight loss during and after radiotherapy in patients with head and neck cancer: A longitudinal study

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ABSTRACT

Purpose: Weight loss is a multifactorial condition that commonly affects patients receiving radiotherapy for head and neck cancers. The aims of this study were to 1) describe body weight changes over time in patients receiving radiotherapy for head and neck cancers and 2) explore the influence of pretreatment weight loss, body mass index (BMI) category, symptom burden, mucositis, and nutritional support on body weight changes over time.
Methods: Using a longitudinal design, this study investigated a consecutive cohort of head and neck cancer patients who were treated with radiotherapy between January 2015 to January 2016 in a Taiwan medical center (n = 128). Data regarding symptom burden, mucositis severity, and body weight were collected before radiotherapy (T1), one month after the initial radiotherapy (T2), at the completion of radiotherapy (T3), and one month after the completion of radiotherapy (T4).
Results: On average, the participants' body weight decreased by 3.09 kg (SD = 2.79) from T1 to T2, 1.72 kg (SD = 2.06) from T2 to T3, and continued to decrease by 1.04 kg (SD = 2.87) from T3 to T4. The results of a generalized estimating equation showed that BMI category, symptom burden, mucositis, and nutritional support were directly and independently related to body weight changes over time in patients with head and neck cancers.
Conclusions: Head and neck cancer patients experience significant weight loss during and after radiotherapy. The study findings are relevant for assessing nutritional status and providing necessary support measures at critical moments for patients treated with radiotherapy.

1. Introduction

Head and neck cancer (HNC) is the seventh most common malignant tumor in the world, with more than 800,000 new diagnoses in 2018 (Bray et al., 2018). Patients with HNCs represent a group that experience substantial weight loss (WL) during and after treatment (Ottosson et al., 2013). The tumor itself may hinder the passage of the bolus, causing swallowing problems (Schindler et al., 2015). Metabolic changes can affect a patient's appetite and physical strength (Baxi et al., 2016). Acute toxicity due to tissue damage in the treated area may directly affect eating ability (Mallick et al., 2013; Peng et al., 2015). Dysphagia and odynophagia secondary to radiotherapy (RT) related mucositis or nausea, vomiting, and anorexia resulted from chemoradiotherapy (CRT) can further reduce caloric intake and compromise nutritional status in patients with HNCs (Mallick et al., 2013).

RT is the core for treatment of HNCs (Marur and Forastiers, 2016). WL is a prevalent problem among patients receiving RT for HNCs (Nourissat et al., 2012; Ottosson et al., 2013). Up to 51% of patients lose more than 5% of their body weight (BW) during a course of curative RT (Ghadjar et al., 2015). WL not only can decrease the tolerance and response to treatment, but can also increase the risk of adverse outcomes (Baxi et al., 2016). Critical WL, defined by > 5% WL during RT, has been significantly associated with worse 5-year disease-specific and overall survival rates in HNC patients (Langius et al., 2013a). Considering the widespread prevalence of WL and its negative impacts, timely identification and proper management is necessary. The discovery of risk factors for WL will be helpful for identifying at-risk persons and developing appropriate interventions.

WL in patients undergoing RT is a multifactorial process that involves various tumor-, treatment-, toxicity-, and nutrition-related factors. Most previous investigations have focused on the influences of demographics as well as tumor- and treatment-related factors on WL.

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The results of these previous investigations showed that WL was more pronounced in HNC patients with tumors located in the oropharynx (Ehrsson et al., 2012; Langius et al., 2016; Mallick et al., 2013; Ottosson et al., 2013; Silander et al., 2013) and in those receiving adjuvant concurrent CRT (Silander et al., 2013; Vangelov and Smee, 2017; Zhao et al., 2015). However, the findings regarding the influences of age, cancer stage, pretreatment WL, and the total dose of RT on WL are inconsistent. Cancer stage was negatively associated with WL in some studies (Baxi et al., 2016; Ehrsson et al., 2012; Langius et al., 2016; Nourissat et al., 2012; Zhao et al., 2015) but not in others (Ghadjar et al., 2015; Ottosson et al., 2013). The total dose of RT was found to be related to WL in the Dawson et al. (2015) and Mallick et al. (2013) studies, but no association was found in the Nourissat et al. (2012) study. Ottosson et al. (2013) examined the influences of different RT regimens on WL and found no significant difference.

Both pretreatment WL and body mass index (BMI) have also been linked to WL during RT in HNC patients. However, the findings from previous studies are inconclusive. Some patients with significant pretreatment WL were found to have a greater risk for WL (Beaver et al., 2001), some a lower risk for WL (Brown et al., 2014), and some were not found to be related to WL during RT (Langius et al., 2016). Regarding BMI, most investigators found that patients with a higher BMI prior to RT experienced greater WL during treatment (Baxi et al., 2016; Lonbro et al., 2016; Ottosson et al., 2013; Silander et al., 2013; Wallace et al., 2018; Zhao et al., 2015), and only a few others found no significant association between preradiotherapy (pre-RT) BMI and WL during treatment (Dawson et al., 2015).

A high number of HNC patients develop radiotherapy-related acute toxicities, such as dysphagia, trismus, altered taste, dry mouth, pain, nausea, and vomiting. These symptoms can affect individuals' food intake and contribute to WL (Baxi et al., 2016; Bressan et al., 2016). Furthermore, the total symptom burden is an important risk factor for WL in HNC patients. Farhangfar et al. (2014) investigated 635 HNC patients and found that the aggregate symptom index from 17 targeted symptoms was a significant predictor of WL (OR = 1.04; CI = 1.02–1.08, P < 0.001). For every 1-point increase in the total symptom index, weight loss increased by 4%. The individual symptoms significantly associated with reduced dietary intake were difficulty chewing, dry mouth, thick saliva, loss of appetite, and pain. Kubrak et al. (2013) also found that decreases in pain, difficulty swallowing, mucositis, dry mouth and appetite during radiotherapy could predict postradiotherapy WL. The impacts of symptom burden on WL in patients receiving RT for HNCs deserve further investigation.

Oral mucositis is one of the most prominent radiotherapy-related side effects and can have a severe impact on individual nutritional status (Baxi et al., 2016). Oral mucositis has been a focus of interest in HNC patients in terms of WL. Most previous studies show that the more severe the oral mucositis is, the more obvious the WL during RT will be (Cacicedo et al., 2014; Nourissat et al., 2012; Ottosson et al., 2013).

Nutritional support is an important part of cancer treatment and helps patients maintain body weight (BW). Personalized nutrition plans are usually developed for HNC patients during RT to ensure adequate caloric intake and maintain BW. For patients with severe mucositis or dysphagia, enteral feeding may be administered through a nasogastric tube or a percutaneous gastrostomy tube. However, the starting time of enteral feeding varies among patients. Some patients may have a nasogastric tube or a percutaneous gastrostomy tube placed prior to RT to prevent malnutrition. Furthermore, some patients may start enteral feeding at any time point during the course of RT in response to their nutritional status. Other patients may take in food by mouth during the entire course of RT. These differences in nutritional support may affect BW changes during RT. However, only a few studies have investigated the effects of timing and the types of nutritional support for WL in patients receiving RT for HNCs, and the results are inconsistent (Wang et al., 2014).

In short, various individual-, tumor-, treatment-, toxicity-, and nutrition-related factors contribute to WL in HNC patients during RT. Most previous studies have focused on less modifiable individual-, tumor-, and treatment-related factors as the influences of pretreatment WL, BMI category, symptom burden, mucositis, and nutritional support on WL over the course of RT are indeterminate in patients with HNCs. Additionally, in most of these studies, BW was measured both before and after the course of RT, and information regarding how BW changed over time was lacking (Dawson et al., 2015; Ghadjar et al., 2015; Langius et al., 2016; Nourissat et al., 2012; Platek et al., 2013). This information is essential for nutritional assessment and providing necessary support measures at critical moments. Hence, this study aimed to prospectively investigate the influences of pre-RT BMI, symptom burden, mucositis, and nutritional support on weight change over time in patients receiving RT for HNCs.

2. Methods

2.1. Study design

The study was based on a longitudinal descriptive design. The purposes of this study were to 1) describe BW changes over time in patients receiving RT for HNCs and 2) explore the influence of pretreatment WL, BMI category, symptom burden, mucositis, and nutritional support on weight changes over time after controlling for demographic and clinical variables. Ethics approval for this study was obtained from the Taipei Veteran Hospital Institutional Review Board (IRB No. 2014-10-008CC).

2.2. Participant recruitment

This study investigated a consecutive cohort of HNC patients who were treated with RT between January 2015 to January 2016 from otolaryngology wards in a medical center in Taiwan (n = 128). Volunteers who met the following eligibility criteria were recruited: (1) diagnosed with HNCs, (2) scheduled for the first RT, (3) 20 years of age or older (the age of majority in Taiwan), and (4) able to read or communicate verbally. Potential participants were excluded if they (1) had other cancers in addition to HNCs, (2) had distant metastasis, or (3) were cognitively impaired. The sample size was estimated using G*power software (version 3.1) (Faul et al., 2007) with four repeated measures, a within-factor design, a significance level of 0.05, a moderate effect size (f = 0.15), correlations of 0.5, and a power of 80%. A sample size of 87 was required for analyzing BW changes over time. The final population was composed of 101 patients. All participants received written and verbal information about the study and gave written consent.

2.3. Data collection and instruments

Each participant was asked to complete a self-report demographic questionnaire. Data regarding disease variables, including the tumor site, cancer stage, cancer treatments, RT type and dose, WL three months prior to RT, timing of the start of enteral feeding, and comorbid conditions were collected from the patients' charts. According to the timing of the start of enteral tube feeding, patients were categorized into three nutritional support groups: prophylactic tube feeding, reactive tube feeding, and oral intake groups. Patients who had a percutaneous endoscopic gastrostomy (PEG) tube inserted for feeding prior to the beginning of RT were categorized as the prophylactic tube feeding group. Those who had a PEG tube or nasogastric tube inserted for feeding at any time point during the course of RT were categorized as the reactive tube feeding group. Those who ate and drank by mouth during the entire course of RT were categorized as the oral intake group. The Charlson comorbidity index (CCI) (Charlson et al., 1987) was used to represent the participants' comorbidity severity. Data on 22 potential comorbid conditions were collected. A score of 1, 2, 3, or 6

was allocated to each condition according to its associated mortality risk. The total score of all the conditions represents the CCI, which predicts one-year mortality (Hall et al., 2004).

Data regarding symptom burden, mucositis severity, and BW were collected from each participant immediately before the first RT (T1), one month after the start of RT (T2), at the completion of RT (about 6–7 weeks) (T3), and one month after the completion of RT (T4). BW and mucositis severity were measured by a research nurse.

The National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Head and Neck Cancer Symptom Index-22 (NFHNSI-22) (Pearman et al., 2013) was used to measure symptom burden. The NFHNSI-22 is a brief symptom index to assess HCN-related symptoms with a 7-day recall period. These 22 symptoms are categorized as disease-related physical symptoms (11), disease-related emotional symptoms (1), treatment-related side effect (7), and related to general function and well-being (3). The scale was modified from the Functional Assessment of Cancer Therapy-Head and Neck to reflect symptom and side effect concerns of HCN patients and oncologists. Items are scored on a 0–4 response scale, with answers ranging from "Not at all" to "Very much so". Items are reverse scored when appropriate to provide a scale in which higher scores represent lower symptom burden. All items are summed to create a single index score with a range from 0 to 88. The scale has shown an acceptable level of reliability and validity in a study involving HNC populations (Pearman et al., 2013). In the current study, Cronbach's alpha was .86, indicating good internal consistency.

The WHO oral mucositis scale (WHO, 1979) was used to measure mucositis severity with a possible grade of 0 to IV, according to its anatomical, symptomatic, and functional components. The inter-observer reliability was 0.98 in a previous study of oral cancer patients (Chen et al., 2015). In the current study, four research nurses were trained to measure mucositis severity in a standardized fashion, with an inter-observer reliability of 0.97.

A digital electronic body-weight scale (Omron, model HBF-371) was used to measure each participant's BW in kilograms. The scale was calibrated by the Office of Metrology, Taipei City Government prior to the study. The weight was measured with the patient's gown on but without shoes, wallets, or other heavy accessories. Categories of BMI $< 20\,kg/m^2$, $20–25\,kg/m^2$, and $> 25\,kg/m^2$ were used for people younger than 70, and categories of BMI $< 22\,kg/m^2$, $22–27\,kg/m^2$, and $> 27\,kg/m^2$ were used for people 70 or older as the cutoff points for underweight, normal weight, and overweight, respectively (Vallén et al., 2011).

2.4. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were used to describe the study variables. One-way analysis of variance (ANOVA) was used to determine whether there were significant differences in BW changes among different nutritional support groups. Generalized estimating equations (GEEs) were used to analyze 1) the patients' BW changes over time and 2) the potential influence of the study variables on BW changes over time.

3. Results

3.1. Demographic and clinical variables as well as pretreatment WL, BMI category, and nutritional support

A total of 128 potentially eligible HNC patients were approached; two patients refused to participate, and 22 patients did not meet the eligibility criteria. A total of 104 participants enrolled in the study, but three of them were lost to follow up. Data from the 101 participants who completed the study were included in the analysis. Their average age was 54.3 years (range, 28–86 years). The majority of them were male (86.1%), married (79.2%), and with a stage IV cancer (66.3%). Most participants were treated with intensity modulation radiation therapy (IMRT) (88.1%). The average RT fraction dose was 205.1 cGy (range, 200–220 cGy) with an average total dose of 6725.8 cGy (range, 6000–7095 cGy). Most participants (71.3%) had no or less than 5% pretreatment WL. The average BMI at baseline was 25.0 (SD = 4.1) and only few participants (9.9%) were underweight. During RT, 60, 23, and 18 participants had oral intake, reactive tube feeding, and prophylactic tube feeding, respectively (Table 1).

Table 1
Demographics, clinical variables, pre-treatment weight loss, BMI category, and nutritional support (N = 101).

Variables		Frequency	Percentage
Gender	Male	87	86.1
	Female	14	13.9
Marital status	Married	80	79.2
	Devoiced or widowed	13	12.9
	Single	8	7.9
Education level	Elementary or below	18	17.8
	Middle school	30	29.7
	High school	28	27.7
	College or above	25	24.8
Tumor site	Nasopharynx	28	27.7
	Hypopharynx	14	13.9
	Oral cavity	37	36.6
	Oropharynx	22	21.8
Cancer stage	I or II	11	10.9
	III	23	22.8
	IV	67	66.3
Cancer therapy	RT	7	6.9
	CCRT	47	46.5
	CCRT after Surgery	47	46.5
Type of radiation	IMRT	89	88.1
	Tomography	12	11.9
Pre-treatment weight loss	none	27	26.7
	≦5%	45	44.6
	5–10%	11	10.9
	> 10%	18	17.8
BMI category	Normal weight	48	47.5
	Underweight	10	9.9
	Overweight	43	42.6
Nutritional support	Oral intake	60	59.4
	Prophylactic tube feeding	18	17.8
	Reactive tube feeding	23	22.8

Variables	Mean	*SD*	Range
Age	54.3	10.8	28–86
RT fraction dose	205.1	6.2	200–220
RT total dose	6725.8	344.6	6000–7095
CCI	3.5	1.2	2–7

SD, standardized deviation, CCI, Charlson comorbidity index; BMI, body mass index; BW, body weight; CCRT, Concurrent Chemo radiotherapy; RT, radiation therapy; IMRT, intensity modulation radiation therapy.

3.2. Symptom burden and grades of mucositis measured at different time points

The mean symptom index was 69.35 (SD = 12.5), 46.79 (SD = 12.73), 41.10 (SD = 13.51), and 58.91 (SD = 15.11) measured at T1, T2, T3, and T4, respectively. The majority of participants' mucositis severity was grade 0 (90.1%) at T1, grades II (32.7%) to III (31.7%) at T2, grade III (49.5%) at T3, and grades 0 (38.6%) to I (28.7%) at T4 (Table 2). These results suggest that the participants' symptom burden and mucositis severity gradually increased from T1 to T3 and then decreased from T3 to T4.

3.3. Body weight changes over time

The participants' average BW was 69.36 kg (SD = 13.23), 66.27

Table 2
Body weight, symptom burden, and grades of mucositis and measured at different time points (N = 101).

Variables	Time	Mean	*SD*	Range
Body weight (kg)	T1	69.36	13.23	42.9–115.6
	T2	66.27	12.04	41.2–106.6
	T3	64.54	11.85	37.2–107.2
	T4	63.41	10.71	39.4–95.4
Symptom burden	T1	69.35	12.50	38–88
	T2	46.79	12.73	10–78
	T3	41.10	13.51	11–80
	T4	58.91	15.11	25–87

	Time	Grade	Frequency	Percentage
Mucositis	T1	0	91	90.1
		I	8	7.9
		II	2	2.0
		III	0	0
		IV	0	0
	T2	0	3	3.0
		I	23	22.8
		II	33	32.7
		III	32	31.7
		IV	10	9.9
	T3	0	0	0
		I	4	4.0
		II	28	27.7
		III	50	49.5
		IV	19	18.8
	T4	0	39	38.6
		I	29	28.7
		II	23	22.8
		III	9	8.9
		IV	1	1.0

SD, standardized deviation, T1, at the beginning of RT; T2, one month after RT started; T3, the completion of RT; T4, one month after RT completed.

Table 3
Parameters of the generalized linear model for body weight change over time (N = 101).

Variables	B	SE	95% CI		Wald X^2	p
			lower	upper		
Intercept	69.36	1.31	66.80	71.93	2802.57	< .001***
T4	−5.96	.51	−6.96	−4.95	134.08	< .001***
T3	−4.82	.38	−5.56	−4.08	163.66	< .001***
T2	−3.09	.28	−3.63	−2.55	125.69	< .001***
T1	Reference					

Using generalized estimation equations for repeated measurements and an AR (1) correlation structure.
*P < 0.05; **P < 0.01; ***P < 0.001.

(SD = 12.04), 64.54 (SD = 11.85), and 63.41 (SD = 10.71) measured at T1, T2, T3, and T4, respectively (Table 2). On average, the participants achieved 6.7% (SD = 5.0%) WL during RT. Among the 101 participants, 38 (37.6%) had less than 5% WL, 37 (36.6%) achieved 5%–10% WL, and 26 (25.7%) showed WL greater than 10%. The participants' BWs continued to decrease after the completion of RT. From T3 to T4, the participants' BWs decreased by 1.03 (SD = 2.86) kg, on average, with a range of −11.8 kg to 6.5 kg. The GEE results showed a statistically significant effect of time (p < 0.001), indicating significant changes in BW over time (Table 3). For the parameter estimates, the patients' BWs decreased by 3.09 kg (p < 0.001) at T2, 4.82 kg (p < 0.001) at T3, and 5.96 kg (p < 0.001) at T4 from the baseline BWs (Table 3). During the course of RT (from T1 to T3), the participants' mean BWs decreased by 4.82 (SD = 3.81) kg, with a range of −16.4 kg to 3.3 kg (Table 2).

Table 4
Parameters of the generalized linear model for exploring the potential influences of the study variables on body weight change over time (N = 101).

Variables	B	SE	95% CI		Wald X^2	p
			Lower	Upper		
(Intercept)	−56.26	27.34	−109.85	−2.67	4.23	.040*
Time (ref:T1)						
T4	-.94	.71	−2.33	.45	1.75	.185
T3	.31	.81	−1.27	1.89	.15	.701
T2	.10	.62	−1.12	1.32	.03	.870
Tumor site (ref: Nasopharynx)						
Oropharynx	−1.29	1.95	−5.11	2.54	.43	.510
Oral cavity	−3.30	2.20	−7.60	1.01	2.25	.113
Hypopharynx	−2.87	1.89	−6.57	.82	2.32	.128
Fraction dose	-.05	.11	-.27	.17	.22	.639
Height	78.90	10.76	57.80	99.99	53.72	< .001***
Pre-Treatment weight loss (ref: None)						
> 10%	.27	1.62	−2.90	3.44	.03	.866
> 5–10%	-.86	1.77	−4.32	2.61	.23	.628
≦5%	.87	1.61	−2.28	4.02	.29	.588
BMI category (ref: Normal weight)						
Overweight	14.97	1.44	12.14	17.79	107.82	< .001***
Underweight	−10.88	1.50	−13.81	−7.94	52.80	< .001***
Interaction						
T4 * Overweight	−3.09	.90	−4.85	−1.33	11.84	.001**
T4 * Underweight	1.79	1.01	-.19	3.78	3.14	.076
T3 * Overweight	−1.50	071	−2.89	-.10	4.41	.036*
T3 * Underweight	.44	.93	−1.38	2.26	.23	.635
T2 * Overweight	−1.24	.53	−2.28	.21	5.56	.018*
T2 * Underweight	.47	.74	-.98	1.91	.40	.525
Symptom burden	.05	.01	.03	.07	19.25	< .001***
Mucositis (ref: Grade 0)						
Grade 4	−1.20	.67	−2.50	.11	3.24	.072
Grade 3	−1.19	.57	−2.30	-.08	4.37	.037*
Grade 2	-.59	.41	−1.40	.22	2.04	.153
Grade 1	-.58	.37	−1.31	.15	2.41	.121
Nutritional support (ref: Prophylactic tube feeding)						
Reactive tube feeding	−3.28	1.89	−7.00	.43	3.00	.083
Oral intake	−1.99	1.78	−5.48	1.50	1.25	.263
Interaction						
T4 * Reactive tube feeding	−3.98	1.21	−3.45	−1.62	10.88	.001**
T4 * Oral intake	−3.51	.87	−5.21	−1.82	16.43	< .001***
T3 * Reactive tube feeding	−2.86	.99	−4.80	-.93	8.42	.004**
T3 * Oral intake	−2.57	.86	−4.26	-.88	8.90	.003**
T2 * Reactive tube feeding	−1.53	.78	−3.05	-.00	3.86	.049*
T2 * Oral intake	-.80	.72	−2.21	.62	1.22	.270

Using generalized estimation equations for repeated measurements and an AR (1) correlation structure.
Ref, reference group, *P < 0.05; **P < 0.01; ***P < 0.001.

3.4. Influence of the study variables on body weight changes over time

GEEs were used to analyze the univariate influence of demographic variables (age, gender, education, marital status) and clinical variables (tumor site, cancer stage, cancer therapy, radiation type, RT fraction dose, RT total dose, CCI) on BW changes over time. The results show that tumor site and RT fraction dose were significant influencing factors of BW changes. Both variables were then entered as covariates in the final GEE analysis for the influences of pretreatment WL, BMI category, symptom burden, mucositis, and nutritional support on BW changes over time.

The GEE results showed significant main effects of symptom burden,

mucositis, BMI category, as well as interaction effects of BMI category by time and nutritional support type by time on BW after controlling for tumor site, RT fraction dose, height, and pretreatment WL (Table 4). Patients with higher symptom burden had lower BWs. For every 1-point decrease in the NFHNSI-22 score, BW decreased by 0.05 kg ($p < 0.001$). Patients with grade III mucositis had 1.19 kg more WL ($p = 0.037$) than patients without mucositis had. Compared to patient with normal weight, the overweight group had 3.09 kg ($p = 0.001$), 1.50 kg ($p = 0.036$), and 1.24 kg ($p = 0.018$) extra weight loss from T1 to T4, T1 to T3, and T1 to T2, respectively, in addition to the difference of 14.97 ($p < 0.001$) already recorded. The difference in BW between the underweight group and patients with normal weight was significant across all time points ($B = -10.88$, $p < 0.001$). However, the interaction terms involving time and BMI category (T2*Underweight, T3*Underweight, and T4*Underweight) were not significant. These findings suggest no extra weight loss affect the underweight patients during each point in time, in addition to the difference of 10.88 already recorded.

In terms of the parameter estimates of nutritional support by time interaction, WL in the reactive tube feeding group was 3.98 kg ($p = 0.001$), 2.86 kg ($p = 0.004$), and 1.53 kg ($p = 0.049$) more than that in the prophylactic tube feeding group from T1 to T4, T1 to T3, and T1 to T2, respectively. WL in the oral intake group was 3.51 kg ($p < 0.001$) and 2.57 kg ($p = 0.003$) more than that in the prophylactic tube feeding group from T1 to T4 and T1 to T3, respectively. From T1 to T2, WL in the oral intake group was not significantly different from that in the prophylactic tube feeding group (Table 4).

4. Discussion

The results of the study supported that HNC patients are at increased risk for WL while receiving RT. Similar to what was reported in previous studies (Cacicedo et al., 2014; Dawson et al., 2015; Langius et al., 2013b), we found that, on average, HNC patients lose 5.43 (SD = 3.63) kg during RT, which is approximately 6.7% (SD = 5.0%) of their pre-RT BW. This WL was higher than that of other cancer patients. In a prospective study, Cacicedo et al. (2014) found a mean weight loss of 0.64 (SD = 2.39) kg during RT in patients with cancers other than head and neck ($n = 24$) compared to ($p = 0.028$) a mean weight loss of 3.25 (SD = 5.30) kg in head and neck cancer patients ($n = 50$). In our study, 25.7% of HNC patients had greater than 10% WL at the completion of RT compared to only 15% of HNC patients in the Dawson et al. (2015) study. This finding may be attributable to the fact that only 17.8% of patients in our study but 62.5% of patients in the Dawson et al. (2015) study received prophylactic percutaneous gastrostomy feeding. At one month after the completion of RT, participants' BWs continued to decrease by 1.03 (SD = 2.86) kg, which was approximately 7.96% (SD = 6.25%) of their pre-RT BW. Ottosson et al. (2013) reported that WL in patients with HNCs continued up to 5 months after RT. Therefore, future studies may want to extend the follow-up time to better explore WL and its risk factors in patients receiving RT for HNCs.

The results of GEE analysis showed significant main effects of symptom burden, mucositis, and BMI category, and interaction effects of BMI category by time and nutritional support type by time on BW. These findings suggest that symptom burden, mucositis, BMI category, and nutritional support type are important factors that influence WL during RT. We found that patients with higher symptom burden had lower BWs and patients with grade III mucositis had more WL than patients without mucositis. These results support findings in previous studies (Farhangfar et al., 2014; Ottosson et al., 2013) where HNC patients with more severe disease-related symptoms or treatment side effects, especially mucositis, experienced greater WL during RT. Therefore, patients undergoing RT for HNC should be assessed regularly and should be appropriately managed for disease-related symptoms and acute treatment side effects, especially mucositis.

As for the BMI category, similar to what was reported in previous studies (Baxi et al., 2016; Lonbro et al., 2016; Ottosson et al., 2014), we found overweight HNC patients experienced greater WL than normal weight patients did. Compared to patients with normal weight, the overweight group showed 3.09 kg more WL during the course of RT. Although no extra weight loss affects the underweight patients during each point in time as indicated by the insignificant interaction terms of time and BMI category, the difference between the underweight and normal weight group was significant across all time points. This observation has clinical relevance because the underweight are at a higher risk of weight loss, and they may benefit more from the advantages of prophylactic tube feeding.

We found that the prophylactic tube feeding group had the least WL among the three nutritional support groups. The advantage of prophylactic tube feeding is an important result. Although statistically significant, the average differences (in kilograms), in comparison with oral intake, was 2.57 in T3, and 3.51 in T4. These numbers may be too small to justify recommending the prophylactic PEC tube feeding, taking into consideration its higher cost and impact on the quality of life. However, each kilogram lost has a higher proportional for underweight patients, and the prescription of a prophylactic tube feeding may be advantageous. Results of previous studies (Lonbro et al., 2016; Ottosson et al., 2013; Vangelov and Smee, 2017; McClelland III, Andrews, Chaudhry, Teckie and Goenka, 2018) also support prophylactic PEG tube feeding for preventing WL in patients receiving RT for HNCs. However, most of these studies are observational. Additionally, PEG has been associated with prolonged tube dependence and a higher incidence of esophageal strictures (Langmore et al., 2012) and PEG may not be an ideal prophylaxis for all patients. Therefore, randomized clinical trials with rigorous designs are called for to better define the roles of prophylactic PEG tube feeding in the maintenance of BW during RT in HNC patients.

Similar to what was reported by Langius et al. (2016), we found no significant influence of pretreatment WL on WL during RT. However, significant pretreatment WL has also been associated with a relatively higher risk (Beaver et al., 2001) or relatively lower risk (Brown et al., 2014) of WL during RT in previous studies. These inconsistent results indicate the complexity and variability of WL during RT.

This study had several limitations. First, the participants were recruited from outpatient RT clinics and inpatient oral surgery or otolaryngology wards of a medical center and thus may vary from those seen in other clinical settings. Thus, the study results may not be generalizable outside this sample population. Second, most study participants were treated with IMRT; therefore, the study results may not be generalizable to patients treated with other types of radiation. Third, we followed participants up to one-month post RT and found that they were still losing weight. A longer duration of follow-up is needed to examine the post RT impacts on BW. Finally, the influences of WL on patients' treatment outcomes were not examined. Future studies with a longitudinal design and clinical outcome measures could further expand our knowledge in this area.

5. Conclusion

HNC patients experience significant WL during and after RT. BMI category, symptom burden, mucositis, and nutritional support were directly and independently related to BW changes over time in our sample of HNC patients. WL was more pronounced in those who were overweight, had greater symptom burden, and had grade III mucositis. Interestingly, we found that a higher level of body WL in patients with oral intake or enteral tube feeding after starting RT than that in patients who had enteral tube feeding throughout the course of RT. This finding suggests that prophylactic enteral tube feeding may provide better nutritional support than reactive tube feeding or oral intake in this group of patients. However, randomized controlled trials are required to better define the role of prophylactic enteral tube feeding in the prevention of body WL during RT in HNC patients. Although further

research is needed, this study provides a promising first step in exploring the potential beneficial effect of prophylactic enteral tube feeding on maintaining BW.

6. Clinical implications

WL during RT affects the treatment efficacy and survival of HNC patients. The results of the study supported that HNC patients are at a great risk for body WL while receiving RT. Clinicians should closely assess patients' nutritional status and provide appropriate nutritional support during RT to avoid WL. Special attention should be paid to those who have greater symptom burden and severe mucositis. Furthermore, overweight patients can also experience substantial WL during RT, and their needs for nutritional support should not be overlooked. Additionally, the effects of prophylactic enteral tube feeding on maintaining BW during RT should be further explored.

IRB approval

The study was approved by the Taipei Veteran Hospital Institutional Review Board (IRB No. 2014-10-008CC).

Conflicts of interest

None declared.

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