Impact of weight loss on treatment interruption and unplanned hospital admission in head and neck cancer patients undergoing curative (chemo)-radiotherapy in Hong Kong

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Abstract

Purpose:

Malnutrition is of high prevalence in head and neck cancer (HNC) patients with weight loss being one of the major nutrition indicators. The objective of this study is to investigate the impact of weight loss on treatment interruptions and unplanned hospital admissions in HNC patients undergoing radiotherapy with or without chemotherapy.

Methods:

In this retrospective cohort study, consecutive HNC patients who started (chemo)radiotherapy between January 2011 and December 2019 were included. Body weight was measured before, during and after RT treatment. Factors associated with ≥ 10% weight loss and treatment interruption and unplanned admissions were analyzed using multivariate logistic regression.

Results:

A total of 1086 subjects with 747(68.8%) nasopharyngeal carcinoma (NPC) and 339(31.2%) non-NPC patients were included. Prevalence of radiotherapy (RT) delay, chemotherapy as planned and cisplatin dose < 200mg/m^2 in patients with ≥ 10% vs < 10% weight loss were 6.2% vs 7.0%(p = 0.668), 29.2% vs 31.7%(p = 0.555), 23.8 vs 17.8%(p = 0.127) in NPC patients, and 42.2% vs 50.5%(p = 0.300), 25.6% vs 32.1%(p = 0.464) and 100.0% vs 81.4%(p = 0.245) in non-NPC patients. Prevalence of unplanned admissions in patients with ≥ 10% vs < 10% weight loss was 51.9% vs 25.3% (p < 0.001) in NPC patients and 68.9% vs 27.0% (p < 0.001) in non-NPC patients.

Conclusion:

In our study, ≥ 10% weight loss was found to be associated with a higher rate of unplanned admissions, but not with RT delay or chemotherapy interruption.

Introduction

HNC is the sixth most common cancer worldwide, with 93,193 new cases and 418,982 deaths in 2020 [1]. The age-standardized incidence and mortality for HNC were 13.7% and 4.0%, respectively [2]. HNC treatment include single modality of surgery or RT alone with disease eradication and organ preservation approach and for locally advanced disease, multimodality treatment with a combination of surgery, radiotherapy with or without chemotherapy [3–5]. Due to the anatomic location of HNC and the aggressiveness of intensive treatment, majority of HNC patients would encounter considerable treatment related toxicities. Symptoms of loss of appetite, chewing and swallowing difficulty, xerostomia, taste alteration and oral pain are highly prevalent in HNC patients [6–7]. Patients frequently experience difficulties in eating and drinking leading to inadequate fluid and nutrition intake and consequently resulting in malnutrition and weight loss. To assess a patient's nutrition status, weight loss is considered as one of the major nutrition indicators [8]. Weight loss > 5% has been defined

as critical weight loss and was found to be a major prognostic factor for inferior treatment outcomes and poor survival in HNC patients [9–15]. Studies showed that the prevalence of > 5% weight loss ranges from 14–32% before and 32–54% after HNC treatment [15–18]. Prevalence of severe weight loss ranges from 12–44% in HNC patients [19–21]. Critical weight loss was also found to be associated with adverse outcomes including increased treatment toxicities and decreased treatment response [22–23], increased enteral feeding dependence [24], unplanned hospital admissions [25] and worse survival outcomes [26].

Studies demonstrated that treatment interruptions detrimentally impact treatment outcomes including increased loco-region failure, increased relapse rate and poor survival [16, 27–29]. Meng et al. showed weight loss was correlated with RT delay and chemotherapy intolerance in locally advanced NPC patients [30]. Cisplatin is used as the standard chemotherapy regimen [31–33] and is characterized by its highly nauseating and vomiting inducing nature [34]. A high dose cisplatin regimen for HNC treatment is often poorly tolerated and patients frequently experience profound side effects requiring dose reduction, treatment delay, or even termination of treatment [35]. However, studies showed that patients receiving a cumulated cisplatin dose of $\geq 200 mg/m^2$ had better survival [35–37]. The high occurrence of treatment intolerance in patients on cisplatin regimen often leads to incomplete treatment resulting into impaired survival [37]. Therefore, the use of cisplatin regimen is likely a risk factor for weight loss in HNC.

In cancer care, unplanned hospital admissions during and after treatment is common particularly in HNC patients [38]. Unplanned hospital admissions impose a heavy economic burden to the health care system and negatively impacts patients' quality of life. The impact of nutrition support on reducing unplanned hospital admission in HNC patient was reported in several studies [39–42]. High weight loss during radiotherapy was associated with increased hospital admission [13]. Therefore, knowledge of the prevalence of weight loss and its association with treatment interruption and unplanned hospital admissions was sought to be evaluated for HNC patients undergoing (chemo)radiotherapy. This knowledge is mandated for developing strategies to improve the treatment outcomes of HNC patients.

Materials And Methods

Study subject

This retrospective cohort study included consecutive newly diagnosed adult HNC patients who were started on curative-intent radiotherapy with or without chemotherapy during the period of 1 January 2011 to 31 December 2019. These HNC patients were referred to dietitian for nutrition support under the blanket referral policy in our center. Patients with metastatic disease, double primary, cancer recurrence or progressive disease, unknown primary, cancer of the ear, thyroid cancer, lymphoma, patients who did not complete the planned treatment and patients who died during treatment were excluded. This study was approved by the New Territories West Cluster Hospital Cluster Research Ethics Committee / Institutional Review Board of Hospital Authority in Hong Kong. Individual informed consent was waived due to the retrospective nature of this study.

Data Collection

Data was collected retrospectively. Demographic data included age, gender, social history, smoking and drinking habits were collected from dietetic records. Clinical characteristics and treatment outcomes including diagnosis, staging, treatment modality, chemotherapy and radiotherapy regimen and hospital admissions were collected from electronic medical records. Nutrition data including body weight, height, number of dietitian outpatient consultations and feeding tube placement were obtained from dietetic and oncology records.

Outcome Variables

The primary outcomes were weight loss < 10% and ≥ 10% at the end of RT treatment, RT delay for more than 2 days of the prescribed schedule, chemotherapy dose given as planned with > 90% prescribed dose received, cumulated cisplatin dose < 200mg/m^2 and ≥ 200mg/m^2, and unplanned hospital admissions from the beginning of concomitant chemoRT or RT until 1 month after the end of RT.
Body weight(BW) in kilograms(kg) and height in meters(m) were routinely measured and recorded in our oncology and dietetic clinics before, during and after treatment. Pre-treatment percentage weight loss was calculated as unintentional weight loss from 6–12 months before treatment to the time patient starts treatment. Past BW was obtained from documentations in medical records or as reported by patient. Weight loss was defined and calculated as the difference between the weight before treatment deducted by the weight at the end of treatment. The calculation is given as following:

- Pre-treatment percentage weight loss = [(BW at the beginning of treatment -BW 6–12 months ago)÷BW 6–12 months ago x 100]
- Percentage weight loss at the end of RT treatment = [(BW at the end of RT treatment – BW at the beginning of treatment)÷BW at the beginning of treatment x 100]

Weight loss ≥ 10% was chosen as the cut off of high weight loss according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 [43]. Body mass index(BMI) was calculated as [BW(kg) ÷ height(m) ÷ height(m)]. Pre-treatment BMI cut-off was categorized as underweight with BMI < 18.5kg/m^2, normal weight with BMI 18.5–24.9 kg/m^2 and obese with BMI ≥ 25 kg/m^2 [44]. Mean imputation method was used for missing BW data in order to provide a consistent data. The time point for body weight data was pre-treatment, weekly during RT and at the end of RT treatment. Body weight and BMI were recorded to the nearest 0.1kg/m^2.

Treatment Interruption: Rt Delay

Patients were treated with radical RT using Volumetric Modulated Arc Therapy (VMAT) with or without chemotherapy. The total dose ranged from 50 to 74Gy and consisted of 5–6 fractions per week of 2-2.5Gy per fraction administered to the primary tumor and if needed, to neck nodes either bilaterally or unilaterally. RT treatment duration was the time from the first day to the last day of RT. RT delay was defined as delay for more than 2 days of the originally planned treatment time according to the guideline from the Royal College of Radiologists [45].

Treatment Interruption: Chemotherapy Given As Planned And Cumulated Cisplatin Dose

There were five chemotherapy regimens used in our HNC patients who required concomitant chemoRT, including three-weekly cisplatin 100mg/m^2, weekly cisplatin 40mg/m^2, three-weekly carboplatin AUC, weekly carboplatin AUC, and Cetuximab. Chemotherapy given as planned was defined as cumulated chemotherapy dosage delivered more than 90% of the originally prescribed dosage and cumulated cisplatin dose ≥ 200mg/m^2.

Unplanned Hospital Admissions

Unplanned hospital admissions were defined as any unplanned hospital admission requiring in-patient care for more than 24 hours, from the beginning of concomitant chemoRT until 1 month after the end of RT treatment. Reasons for admission were categorized as nutrition-related and non-nutrition-related. Nutrition-related admissions included rehydration, poor oral intake, dysphagia, insertion of feeding tube, feeding tube-related causes and management of eating or nutrition related symptoms.

Statistical Methodology

Categorical variables were compared using the Chi square test. Univariate logistic regression was done to test the association between each independent variable and the adverse outcomes including treatment interruption and unplanned hospital admissions. Independent variables included RT delay, chemotherapy as planned and unplanned hospital admissions. Variables with a significant association shown in univariate analysis were entered into multivariate analysis logistic regression. The statistical significance level was considered at p-value < 0.05. Statistical Package for the Social Sciences (SPSS) software version 27 was used for the statistical analysis.

Results

Patients' characteristics

A total of 1086 patients were included with 747(68.8%) NPC and 339(31.2%) non-NPC patients. Demographics and characteristics of patients are shown in Table 1. Locally advanced stage III and IV diseases comprised of 67.3% of the cohort. The mean age of NPC and non-NPC patients was 54.2 and 61.9 years ($p < 0.001$). There were significantly more young patients < 45 years in NPC than non-NPC group (20.6% vs 6.8%, $p < 0.001$). More NPC than non-NPC patients received combined modality of chemoRT (69.6% and 36.9%, $p < 0.001$), with RT dose ≥ 65Gy (98.3% and 65.8%, $p < 0.001$), and received cisplatin regimen (63.7% and 30.4%, $p < 0.001$). Given significant differences in the characteristics of NPC and non-NPC patients, subgroup analysis was conducted.

Table 1
Demographic and patient characteristics of HNC patients undergoing RT with or without chemotherapy from 2011 to 2019 in Tune Mun hospital

	Total		NPC		Non NPC		
	N	%	N	%	N	%	p-value
N	1086	100.0%	747	68.8%	339	31.2%	
Age (mean, SD)	56.6	12.1	54.2	11.9	61.9	10.8	0.000
Age (N, %)							
<45 years	177	16.3%	154	20.6%	23	6.8%	0.000
45–64 years	644	59.3%	464	62.1%	180	53.1%	
65–74 years	194	17.9%	94	12.6%	100	29.5%	
≥75 years	71	6.5%	35	4.7%	36	10.6%	
Smoking							
Smoker or ex-smoker	532	50.2%	323	44.6%	204	60.9%	0.000
Non Smoker	527	49.8%	401	55.4%	131	39.1%	
Alcohol drinking							
Drinker or ex drinker	643	61.1%	235	32.7%	174	52.1%	0.000
Non Drinker	409	38.9%	483	67.3%	160	47.9%	
Lives with							
Live with family	958	88.6%	672	91.4%	286	86.9%	0.024
Live alone	106	9.8%	63	8.6%	43	13.1%	
Tumor site							
NPC	747	68.8%	747	100.0%			
Oropharynx	64	5.9%			64	18.9%	
Hypopharynx	31	2.9%			31	9.1%	
Larynx	99	9.1%			99	29.2%	
Oral Cavity	90	8.3%			90	26.5%	
Sinus	9	0.8%			9	2.7%	
Salivary Gland	37	3.4%			37	10.9%	
Nasal Cavity	9	0.8%			9	2.7%	
Stage of disease							
Stage I-II	346	32.7%	247	33.1%	99	31.7%	0.673

	Total		NPC		Non NPC		
Stage III-IV	713	67.3%	500	66.9%	213	68.3%	
T Classification							
T1-2	526	49.9%	373	49.9%	153	49.7%	0.093
T3-4	529	50.1%	374	50.1%	155	50.3%	
N classification							
N0	281	26.7%	127	17.0%	154	50.2%	0.000
N+	773	73.3%	620	83.0%	153	49.8%	
Treatment modality							
RT alone	441	40.6%	227	30.4%	214	63.1%	0.000
ChemoRT	645	59.4%	520	69.6%	125	36.9%	
RT dose							
<65Gy	129	11.9%	13	1.7%	116	34.2%	0.000
≥65Gy	957	88.1%	734	98.3%	223	65.8%	
Induction chemotherapy							
No	861	79.3%	541	72.4%	320	94.4%	0.000
Yes	225	20.7%	206	27.6%	19	5.6%	
Chemotherapy regimen							
No Cisplatin	66	10.2%	44	8.5%	22	17.6%	0.002
Cisplatin	579	89.8%	476	91.5%	103	82.4%	
Pretreatment BMI (Mean, SD)	23.9	4.0	24.2	4.0	23.3	4.1	0.003
Pretreatment BMI							
<18.5kg/m^2	67	6.2%	33	4.4%	34	10.0%	0.001
18.5–24.9 kg/m^2	628	57.9%	431	57.8%	197	58.1%	
≥25 kg/m^2	390	35.9%	282	37.8%	108	31.9%	

Weight Loss And Treatment Interruptions

In NPC group, prevalence of RT delay, chemotherapy as planned and cisplatin dose < 200mg/m^2 in patients with ≥ 10% vs < 10% weight loss were 6.2% vs 7.0% ($p < 0.668$), 29.2% vs 31.7% ($p < 0.555$), 23.8 vs 17.8% ($p < 0.127$) respectively. In non-NPC group, prevalence of RT delay, chemotherapy as planned, cisplatin dose < 200mg/m^2 in

patients with ≥ 10% vs < 10% weight loss were 42.2% vs 50.5% (p < 0.300), 25.6% vs 32.1% (p < 0.464) and 100.0% vs 81.4% (p < 0.245), respectively (Fig. 1, Appendix 1).

Weight Loss And Unplanned Admissions

Prevalence of unplanned admissions in patients with ≥ 10% vs < 10% weight loss was 51.9% vs 25.3% (p < 0.001) in NPC patients and 68.9% vs 27.0% (p < 0.001) in non-NPC patients, respectively (Fig. 1, Appendix 1). In both NPC and non-NPC groups, unplanned admission was significantly higher in patients with ≥ 10% weight loss. A univariate analysis was conducted to assess association of weight loss and unplanned admission.

In NPC group, a significantly higher rate of unplanned admissions was observed in patients with stage III-IV disease, with induction chemotherapy given, on cisplatin regimen, with chemotherapy not given as planned, with cisplatin dose < 200mg/m^2, with feeding tube placement and weight loss 5–10% at week 2. In non-NPC group, a significantly higher prevalence of unplanned admissions in patients with stage III-IV, with chemotherapy added, with chemotherapy not given as planned, with tube feeding, with dietitian consultation ≥ 2 and with no surgery (Table 2).

These statistically significant factors in univariate analysis were entered into a multivariate analysis (Table 3). In NPC patients, multivariate logistic regression analysis showed that factors significantly associated with unplanned admissions were stage III-IV disease (OR 1.73, 95% CI 1.0–3.0, p = 0.049), chemotherapy as planned (OR 0.61, 95% CI 0.39–0.97, p = 0.036), feeding tube placement (OR 30.35, 95% CI 7.15-128.72, p < 0.001), and ≥ 10% weight loss at the end of RT (OR 1.9, 95% CI 1.24–2.89, p = 0.003). In non-NPC patients, multivariate logistic regression analysis showed that factors significantly associated with unplanned admissions were treatment modality of chemoRT (OR 6.34, 95%CI 3.04–13.22, p = 0.001), chemotherapy as planned (OR 0.34, 95% CI 0.13–0.89, p = 0.034), feeding tube placement (OR 11.42, 95% CI 5.21–25.01, p = 0.001) and weight loss > 5% at week 2 (OR 2.67, 95% CI 1.09–6.55, p = 0.032). In both NPC and non-NPC, feeding tube placement was the strongest independent predictor of unplanned hospital admissions.

Table 2. Univariate analysis of weight loss and unplanned admissions (variables with p<0.05)

	No admission		Admitted		
	N	%	N	%	p-value
Stage of disease					
Stage I-II	200	40.5%	47	18.6%	0.000
Stage III-IV	294	59.5%	206	81.4%	
Treatment Modality					
RT alone	197	39.9%	30	6.1%	0.000
ChemoRT	297	60.1%	223	45.1%	
Induction Chemotherapy					
No	376	76.1%	165	33.4%	0.002
Yes	118	23.9%	88	17.8%	
Cisplatin regimen					
No Cisplatin	232	47.0%	39	7.9%	0.000
Cisplatin	262	53.0%	214	43.3%	
Chemotherapy as planned					
Not as planned	190	64.0%	171	76.7%	0.000
As planned	107	36.0%	52	23.3%	
Cumulated cisplatin dose					
<200mg/m2	39	11.8%	49	25.7%	0.012
≥200mg/m2	206	84.1%	142	74.3%	
Feeding					
Oral	490	99.2%	197	77.9%	0.000
Tube Feeding	4	0.8%	56	22.1%	
Weight loss at week 2					
<5%	458	93.9%	211	85.8%	0.001
5-10%	29	5.9%	33	13.4%	
≥10%	1	0.2%	2	0.8%	
Weight loss at week 7					
<10%	373	76.1%	126	50.0%	0.000
≥10%	117	23.8%	126	50.0%	

b. Non NPC

	No admission		Admitted		
	N	%	N	%	p-value
Stage of disease					
Stage I-II	83	39.7%	16	15.5%	0.000
Stage III-IV	126	60.3%	87	84.5%	
Treatment Modality					
RT alone	177	77.3%	37	33.6%	0.000
ChemoRT	52	22.7%	73	66.4%	
Chemotherapy regimen					
3 wkly cisplatin	33	63.5%	52	71.2%	0.022
wkly cisplatin	11	21.2%	7	9.6%	
3 wkly carboplatin	2	3.8%	0	0.0%	
wkly carboplatin	2	3.8%	0	0.0%	
Cetuxumab	4	7.7%	14	19.2%	
Chemotherapy as planned					
Not as planned	29	55.8%	58	79.5%	0.005
As planned	23	44.2%	15	20.5%	
Feeding					
Oral	215	93.9%	51	46.4%	0.000
Tube Feeding	14	6.1%	59	53.6%	
Total no. of Dietitian outpatient contact					
≤1	17	7.4%	17	15.5%	0.021
≥2	212	92.6%	93	84.5%	
Weight loss at week 2					
<5%	220	97.8%	96	88.1%	0.000
5-10%	5	2.2%	13	11.9%	
≥10%		0.0%		0.0%	
Weight loss at week 7					
<10%	211	93.8%	78	71.6%	0.000
≥10%	14	6.2%	31	28.4%	

Nutrition Support Program					
Pre	18	8.7%	25	24.8%	0.000
Post	190	91.3%	76	75.2%	
Surgery					
No Surgery	104	45.4%	63	57.3%	0.041
Surgery	125	54.6%	47	42.7%	

Table 3. Multivariate logistic regression analysis of weight loss and unplanned admissions

1. NPC

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.	
							Lower	Upper
Stage III-IV	0.55	0.28	3.88	1	0.049	1.73	1.00	3.00
Chemotherapy as planned	-0.49	0.23	4.42	1	0.036	0.61	0.39	0.97
Tube feeding	3.41	0.74	21.43	1	0.000	30.35	7.15	128.72
≥10% weight loss at week 7	0.64	0.22	8.78	1	0.003	1.90	1.24	2.89
Constant	-1.05	0.28	13.78	1	0.000	0.35		

2. Non NPC

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.	
							Lower	Upper
ChemoRT	1.85	0.38	24.26	1	0.000	6.34	3.04	13.22
Chemotherapy as planned	-1.08	0.50	4.79	1	0.029	0.34	0.13	0.89
Tube feeding	2.44	0.40	37.06	1	0.000	11.42	5.21	25.01
>5% weight loss at week 2	0.98	0.46	4.61	1	0.032	2.67	1.09	6.55
Constant	-2.32	0.28	67.13	1	0.000	0.10		

Prevalence Of Weight Loss And Predictive Factors

A total of 288 patients (26.8%) had ≥ 10% weight loss at the end of RT. Prevalence of ≥ 10% weight loss increased from 2.8% before treatment to 32.7% after treatment in NPC and from 6.2% pre-treatment to 13.5% after treatment in non-NPC (Table 4). In NPC group, patients with ≥ 10% weight loss, when compared with < 10% weight loss, had a significantly higher proportion of men (80.2% vs 71.3%, p = 0.009), patients at a younger age

< 45 years old (26.3% vs 17.8%, p = 0.018), patients who lived alone (12.0% vs 7.0%, p = 0.023), patients with stage III-IV disease (75.7% vs 62.5%, p < 0.000), with N+ (95.8% vs 88.4%, p < 0.001), with chemoRT (87.2% vs 60.7%, p < 0.001) and cisplatin regimen (43.1% vs 20.5%, p = 0.004). In non-NPC, patients with ≥ 10% weight loss contained a significantly higher proportion of men (88.9% vs 73.4%, p < 0.024), patients at an age of ≥ 75 years (2.2% vs 11.8%, p < 0.018), with stage III-IV disease (86.4% vs 65.2% p < 0.005), N+ (83.7% vs 43.6%, p < 0.000), chemoRT (86.7% vs 29.1%, p < 0.001), RT > 65Gy (97.8%, vs 61.6% p < 0.000), and patients with no surgery (80.0% vs 45.0%, p < 0.001) .

In NPC patients, multivariate logistic regression analysis yielded factors that significantly associated with ≥ 10% weight loss at the end of RT were age, living alone, use of cisplatin regimen, tube feeding, unplanned admissions, pre-treatment BMI and with > 5% weight loss at week 2 (Table 5). In non-NPC patients, multivariate logistic regression analysis demonstrated that factors significantly associated with ≥ 10% weight loss were RT dose ≥ 65 Gy, chemoRT, unplanned admissions and weight loss > 5% at week 2. In both NPC and non-NPC patients, weight loss > 5% in week 2 of treatment was the strongest predictor of ≥ 10% weight loss at the end of treatment (OR 10.8, 95% CI 5.05–23.1 in NPC and OR 9.7, 95% CI 2.5–38.3 in non-NPC).

Table 4. Prevalence and characteristics of patient with weight loss

	NPC					Non NPC				
	<10%		≥10%			<10%		≥10%		
	N	%	N	%	p-value	N	%	N	%	p-value
N	499	67.3%	243	32.7%		289	86.5%	45	13.5%	
% Weight loss at week 7 (mean, SD)	-5.4	3.1	-13.1	2.8	0.000	-3.0	3.9	-12.9	2.4	0.000
Gender										
Male	356	71.3%	195	80.2%	0.009	212	73.4%	40	88.9%	0.024
Female	143	28.7%	48	19.8%		77	26.6%	5	11.1%	
Age										
<45 years	89	17.8%	64	26.3%	0.018	22	7.6%	1	2.2%	0.018
45-64 years	313	62.7%	147	60.5%		144	49.8%	33	73.3%	
65-74 years	69	13.8%	25	10.3%		89	30.8%	10	22.2%	
≥75 years	28	5.6%	7	2.9%		34	11.8%	1	2.2%	
Smoking										
Smoker	205	42.4%	115	48.7%	0.111	172	59.9%	27	62.8%	0.721
Non-smoker	278	57.6%	121	51.3%		115	40.1%	16	37.2%	
Alcohol drinking										
Drinker	147	30.7%	86	36.8%	0.105	144	50.2%	26	61.9%	0.155
Non- or ex-drinker	332	69.3%	148	63.2%		143	49.8%	16	38.1%	
Live with										
Family	454	93.0%	213	88.0%	0.023	243	87.1%	41	91.1%	0.447
Alone	34	7.0%	29	12.0%		36	12.9%	4	8.9%	
Stage of disease										
Stage I-II	187	37.5%	59	24.3%	0.000	92	34.8%	6	13.6%	0.005
Stage III-IV	312	62.5%	184	75.7%		172	65.2%	38	86.4%	
T classification										
T 1-2	264	52.9%	108	44.4%	0.031	131	50.4%	21	48.8%	0.851

T 3-4	235	47.1%	135	55.6%		129	49.6%	22	51.2%	
N classification										
N0	106	21.2%	20	8.2%	0.000	146	56.4%	7	16.3%	0.000
N+	393	78.8%	223	91.8%		113	43.6%	36	83.7%	
Treatment modality										
RT alone	196	39.3%	31	12.8%	0.000	205	70.9%	6	13.3%	0.000
ChemoRT	303	60.7%	212	87.2%		84	29.1%	39	86.7%	
Induction Chemotherapy										
No	188	62.0%	132	62.3%	0.960	75	89.3%	30	76.9%	0.071
Yes	115	38.0%	80	37.7%		9	10.7%	9	23.1%	
Chemotherapy regimen										
No Cisplatin	35	11.6%	9	4.2%	0.004	14	16.7%	8	20.5%	0.605
Cisplatin	268	88.4%	203	95.8%		70	83.3%	31	79.5%	
RT dose										
<65Gy	10	2.0%	3	1.2%	0.453	111	38.4%	1	2.2%	0.000
≥65Gy	489	98.0%	240	98.8%		178	61.6%	44	97.8%	
Surgery										
No Surgery						130	45.0%	36	80.0%	0.000
Surgery						159	55.0%	9	20.0%	
Pretreatment BMI (mean, SD)	23.6	3.8	25.3	4.2	0.000	23.2	4.1	23.9	4.0	0.328
Pretreatment BMI										
<18.5	29	5.8%	4	1.6%	0.000	31	10.7%	3	6.7%	0.633
18.5-24.9	316	63.5%	112	46.1%		169	58.5%	26	57.8%	
≥25	153	30.7%	127	52.3%		89	30.8%	16	35.6%	
Pre-treatment weight loss										
<5%	451	90.4%	214	88.1%	0.013	221	76.5%	37	82.2%	0.549
5-10%	40	8.0%	16	6.6%		51	17.6%	5	11.1%	

≥10%	8	1.6%	13	5.3%		17	5.9%	3	6.7%	
Weight loss 2 weeks										
<5%	479	97.8%	186	77.8%	0.000	278	97.2%	35	77.8%	0.000
5-10%	11	2.2%	50	20.9%		8	2.8%	10	22.2%	
≥10%	0	0.0%	3	1.3%		0	0.0%	0	0.0%	

Table 5. Multivariate logistic regression analysis of weight loss ≥10% at the end of RT

a. NPC

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.	
							Lower	Upper
Age (<45 years as Ref)			9.7	3	0.021			
Age (45-64 years)	-0.7	0.2	9.4	1	0.002	0.49	0.3	0.8
Age (65-74 years)	-0.7	0.4	4.1	1	0.042	0.49	0.2	1.0
Lives alone	0.7	0.3	4.6	1	0.032	1.97	1.1	3.7
Cisplatin regimen	1.2	0.2	24.6	1	0.000	3.37	2.1	5.5
Tube feeding	1.4	0.4	13.9	1	0.000	3.86	1.9	7.8
Unplanned admissions	0.5	0.2	5.1	1	0.024	1.60	1.1	2.4
BMI ≥25	2.1	0.7	10.8	1	0.001	8.52	2.4	30.7
Pretreatment weight loss≥10%	1.3	0.5	6.1	1	0.014	3.55	1.3	9.7
>5% weight loss at week 2	2.4	0.4	37.6	1	0.000	10.81	5.1	23.1
Constant	-3.1	0.7	20.8	1	0.000	0.05		

b. Non NPC

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.	
							Lower	Upper
RT dose ≥65 Gy	0.2	0.1	5.6	1	0.017	1.18	1.0	1.3
Chemotherapy added	1.8	0.5	11.2	1	0.001	6.24	2.1	18.3
>5% weight loss at week 2	2.3	0.7	10.5	1	0.001	9.70	2.5	38.2
Constant	-14.3	4.6	9.5	1	0.002	0.00		

Discussion

Our study aims to investigate the association of weight loss and treatment interruptions including RT delay, chemotherapy given as planned, cisplatin dose ≥ 200mg/m^2 and unplanned hospital admissions. Our study found that patients with weight loss ≥ 10% had a significantly higher rate of unplanned hospital admissions but have no significant association with treatment interruptions.

Weight Loss And Treatment Interruptions: Rt Delay

In our study, prevalence of RT delay was 20.2% (N = 219) for the whole cohort. The prevalence of RT delay ranged from 11.8–67% in previous studies [28, 46–47]. This variation among studies might be related to the different definition of RT delay and different disease entities included in various studies. In subgroup analysis, we found that NPC patients had significantly lower prevalence of RT delay than non-NPC patients (6.8% vs 49.6%, $p < 0.05$). This could likely be explained by the practice of RT schedule compensation for our NPC patients. In our center, the RT schedule and progress of HNC patients were closely monitored. However, due to historical and logistic reasons, the facility was only able to accommodate special arrangements for NPC patients to catch up on any delays. It was not until 2019 that compensatory measures could also be arranged for non-NPC HNC patients.

Our study showed no significant association between weight loss and RT delay in both NPC and non-NPC patients. Previous studies investigating the association of weight loss and RT delay yielded conflicting results. Lindberg et al reported that patients with HNC primary sites had the highest rate of RT interruptions among all cancer sites [48]. Likewise, patients with high weight loss had significantly more RT interruptions and lower RT completion rate, were observed by another research group [49]. Studies showed that weight loss with change in body contour was one of the independent predictors for re-planning [50–51]. High weight loss could lead to anatomic change and alter the external contour and position. This can potentially result in significant dosimetric changes of planning target volumes and negatively affect treatment accuracy and increase toxicities [52–54]. In subjects with obesity and sleep apnea, Wang et al showed that weight loss resulted in a significant reduction in the volume of upper airway soft tissues and tongue fat mass [55]. Wu et al reported that body contour shrinkage in patients with weight loss resulted in increased dosage to normal tissues [56]. Hou et al found that patient with BMI ≥ 25kg/m^2 and > 5% weight loss had significantly larger set-up displacement [57]. Conversely, Orell et al reported no differences in RT completion rate in patients with ≤ 10% or > 10% weight loss [25] and similarly another study reported no significant dosimetric change in organs at risk in patients with > 10% weight loss [58]. Some studies showed no correlation between set-up error and weight loss during RT [59–60].

Weight Loss And Treatment Interruptions: Chemotherapy Given As Planned

It is evidenced that addition of chemotherapy to radiotherapy improved survival [46, 61–63]. However, the addition of chemotherapy to radiotherapy frequently resulted in substantial toxicities. Kono et al reported HNC patients with concomitant chemotherapy had 5.7 times higher risk of developing severe adverse toxicity [64]. Ko et al reported 6% of HNC patients were intolerable to concomitant chemotherapy [65].

Causes of chemotherapy not given as planned were multi-factorial with weight loss as one of the widely studied factors. Our study found 30% of our HNC patients had their chemotherapy given as planned. Previous studies showed the rate of chemotherapy completion rate ranged from 38.2 to 42.7% in NPC [66–67] and 37–53% in non-NPC subjects [68–71]. Local study on NPC showed 58–62% concomitant chemotherapy completion rate [72–73]. The differences in chemotherapy completion rate between studies may possibly be due to different definition of chemotherapy compliance rate and variations in supportive care provision in different studies.

In contrast to previous studies, our result did not find a significant association of weight loss and chemotherapy given as planned. Andreyev et al reported that gastrointestinal cancer patients with weight loss experienced significantly more dose-limiting toxicities and more treatment breaks [22]. A large cross sessional study conducted in UK showed that weight loss in cancer patients was associated with systematic treatment modification and HNC is one of the cancer types with the strongest association of weight loss and treatment modification [74]. While in HNC studies, Bahl et al found that NPC patients with > 10% pre-treatment weight loss had lower rate of chemotherapy given as planned [66]. The reason for no association of weight loss and chemotherapy in our study is not known. Further research is warranted to investigate the impact of weight loss on chemotherapy compliance and the beneficial effect of nutritional intervention addressing the issue of weight loss for improving treatment outcomes.

Weight Loss And Treatment Interruptions: Cumulated Cisplatin Dose

Studies showed total dose of cisplatin patients received was an independent prognostic factor for overall survival [75–80]. Although the cut off for optimal cumulative dose of cisplatin is still debatable, ≥ 200mg/m^2 is commonly used in other studies [78–80]. Our study did not find significant association between weight loss and cumulative cisplatin dose of ≥ 200mg/m^2. Nakano et al found 46% of their HNC patients had received ≥ 200mg/m^2 with high body surface area and high BMI as predictors of tolerance of high dose cisplatin [81]. To our knowledge, no studies have been done on the impact of weight loss and cumulative cisplatin dose.

Weight Loss And Unplanned Admissions

Study showed the rate of unplanned admissions in HNC patients was 65% [82]. Among studies done on NPC patients, the incidence of unplanned admissions was between 20–36% [35, 83]. Our study found a significantly higher rate of unplanned admission in patients with ≥ 10% weight loss. These findings generally aligned with other studies. Duffy et al reported that critical weight loss of > 5% was associated with higher number of unplanned admissions in HNC patients undergoing chemoRT [13]. Capuano et al reported a significantly higher rate of unplanned admissions in HNC patients with > 20% weight loss and weight loss was positivity correlated with hospital admissions [84]. In a large cohort study on HNC surgical patients, Gourin et al found that weight loss was significantly associated with postoperative complications, morbidities and hospital length of stay [85]. In our non-NPC patients with > 5% weight loss at week 2 of RT treatment we found a significantly higher risk of unplanned admissions. We speculate that weight loss during the first few weeks of RT treatment predicts unplanned admissions, likely due to the cumulative toxicities. If patients encounter symptoms early on in their treatment journey, they would be more likely to become intolerable to the subsequent side effects and require hospitalization for side effects management.

Feeding tube placement and unplanned admissions. In the present study, the strongest factor associated with unplanned admissions was feeding tube placement. Our non-NPC patients had significantly higher rate of feeding tube placement (21.5%) than NPC (8.0%). It was likely related to the fact that many of our non-NPC patients already had their feeding tube placed after surgery or before treatment due to the early onset of eating-related symptoms prior to diagnosis. Studies on feeding tube placement and hospital admissions had mixed results. Brown et al showed a lower incidence of unplanned admissions with prophylactic feeding tube [86] and some reported no differences [87–88]. Duffy et al demonstrated a significantly higher risk of unplanned admissions with enteral feeding tube placement [13]. This variation in outcomes may be due to the timing of feeding tube placement and the availability of intensive supportive care. Nutrition status could be better preserved with prophylactic feeding tube placement but admissions for feeding tube complications were frequently observed [88]. In our center, feeding tube placements were all done in in-patient settings and majority of patients had reactive feeding tube insertions. For the majority of our HNC patients, by the time tube feeding is needed they may already have developed profound toxicities including severe weight loss requiring hospital admissions for symptoms management.

Concomitant chemoRT, cisplatin regimen and unplanned admissions. In our study, non-NPC patients with concomitant chemoRT had a significantly higher risk of unplanned admissions than patients with RT alone. Similarly, a study reported that patients with concomitant chemotherapy had 3.96 times higher risk of unplanned admissions [89]. Nugent et al reported tube feeding was required for 66–71% HNC patients on combined treatment modality required tube feeding compared to only 12% patients on single modality of RT treatment [90]. Chemotherapy was found to be a major contributing factor for more clinic visits, higher rate of RT interruption, more chemotherapy incompletion, greater need for tube feeding, and higher rates of complications and hospitalizations [69, 91]. Our results were consistent with these studies and showed concomitant chemotherapy was associated with increased rate of unplanned hospital admissions, greater weight loss and tube feeding needs. Specifically, our NPC patients with cisplatin regimen given had significantly higher risk and rate of unplanned admissions. Bright et al reported that 23% of unplanned admissions for adverse effects was found in patients received cisplatin regimen in various cancer types [92].

Prevalence of weight loss and its predictive factors.

In the present study, prevalence of $\geq$ 10% weight loss at the end of RT was 26.8%, and the prevalence was significantly higher in NPC patients (32.7%) than non-NPC patients (13.5%) ($p < 0.001$).

Pre-treatment weight loss. Greater pre-treatment weight loss in non-NPC patient can be explained partly by worse symptoms exacerbation at the time of diagnosis. Non-NPC patients more often had more eating-related symptoms included dysphagia, chewing difficulty or airway obstruction as their presenting symptoms. They commonly experience issues with eating for a period of time which already resulted in substantial pre-treatment weight loss [93–95].

Post treatment weight loss. We observed less post-treatment weight loss in our non-NPC group. This might be due to the higher rate of feeding tube placement in these patients. In our practice, feeding tube was often placed post-operatively in non-NPC patients and would be kept until the completion of adjuvant treatment. Patients with early commencement of tube feeding could had better preservation of nutrition status. In addition, more

non-NPC had single modality of RT alone and they commonly experienced less severe toxicities than those with concomitant chemoRT.

Age and weight loss. Our results showed that younger patients had significantly higher prevalence of ≥ 10% weight loss. This finding is consistent with previous studies [13, 96–101]. Some explanations include younger patients often received more aggressive treatment with substantially higher toxicities and they were more physically active with higher energy expenditures. Interestingly, Monroe et al reported that more nausea and vomiting were observed in younger patients and the reason was not known [102].

BMI and weight loss. Similar to other studies [97–98, 103–109], our results showed patients with higher BMI had significantly greater weight loss. Lønbro et al reported a 5.1 times higher risk of > 10% weight loss in HNC patients with BMI above 25 [97]. The reason for greater weight loss in patients with high BMI might partly be due to the perception of better nutrition reserve and consequently reduced supportive care and less aggressive nutrition support were provided to these patients. de Oliveira Faria et al reported that patients with obesity had been given less nutrition support when compared with normal weight patients [110]. A study demonstrated that people with obesity experienced greater satisfaction from eating than normal weight adults [111]. When patients with obesity start to experience eating-related side effects, the joy of eating diminished and they become psychologically and emotionally distressed and eventually resulted in substantial decrease in oral intake and subsequently caused significant weight loss.

Strength And Limitations

The main strength of this study is the large sample size with representative sample of both NPC and non-NPC patients. This gives more reliable results with greater statistical power and precision. To the best of our knowledge this is the first study investigating the association of weight loss on treatment outcome and hospital admissions in Asian population. This is also the first study which yielded differences in weight loss, treatment interruption and unplanned hospital admissions between NPC and non-NPC patients.

This study has some limitations. First, there are intrinsic limitations of retrospective study with potential selection bias. Second, both weight measuring methods and instruments were not standardized. This can affect measurement accuracy and affect the data's reliability and validity. Third, some important confounding factors including patient's performance status, quality of life status, comorbidity and HPV status in oropharyngeal cancer were either not available or not included. Fourth, during the selected period of nine years, many new practices and advances in treatment modalities developed. Lastly, using body weight as the sole nutrition indicator might not truly reflect patients' nutrition status and cause of weight loss is often multifactorial.

Conclusions

In our study, ≥ 10% weight loss was shown to be associated with a higher rate of unplanned hospital admissions in both NPC and non-NPC patients. High weight loss was not associated with RT delay and chemotherapy interruption in the present study. In NPC patients, factors significantly associated with unplanned admissions were stage III-IV disease, chemotherapy as planned, tube feeding placement, and ≥ 10% weight loss at the end of RT. In non-NPC patients, factors significantly associated with unplanned admissions were treatment modality of chemoRT, chemotherapy as planned, feeding tube and weight loss > 5% at week 2.

Clinical Implications: With the knowledge of the impact of weight loss on hospital admissions and the characteristics of patients with weight loss, nutrition intervention can effectively focus on helping these patients to minimize weight loss. This weight loss information helps with stratifying patients for intensive nutrition support. The findings support more targeted strategies to prevent potential unfavorable outcomes due to unplanned hospital admissions.

Declarations

AUTHOR CONTRIBUTION

CYC, TCL, PCC and KWC contributed to the study conception and design. CYC and KLW participated in data collection and writing. CYC, JJH and TCL participated in data analyses. CYC, JJH, JD and TCL participated in data interpretation. CYC, KWC, PCC, JD and TCL involved in writing, reviewing and editing. TCL and JD provided supervision. The first draft of the manuscript was written by CYC and all authors reviewed the manuscript and gave final approval to publication.

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CONFLICT OF INTEREST

The authors have no competing interests to declare that are relevant to this submitted work.

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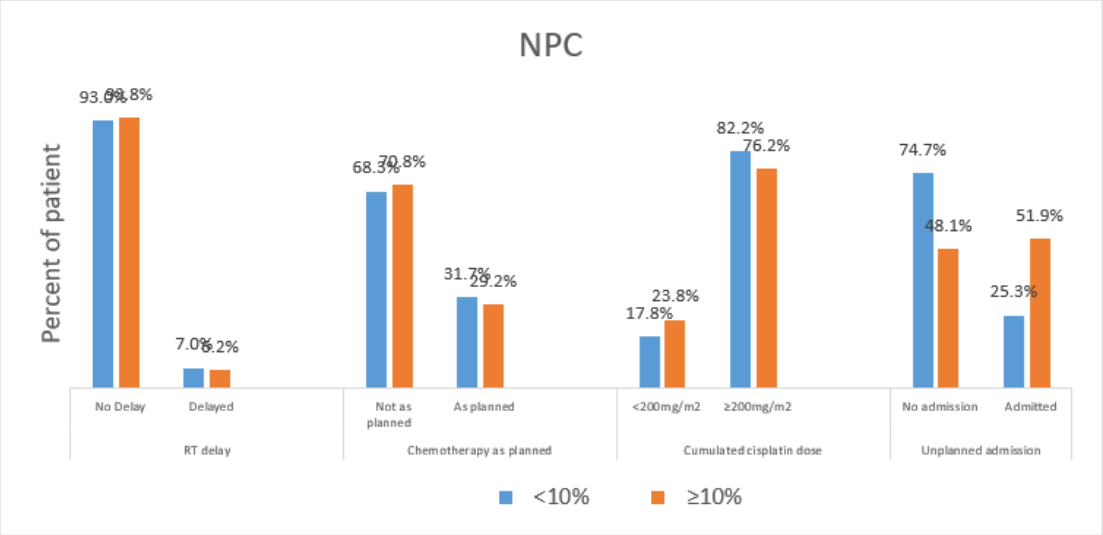
Figures



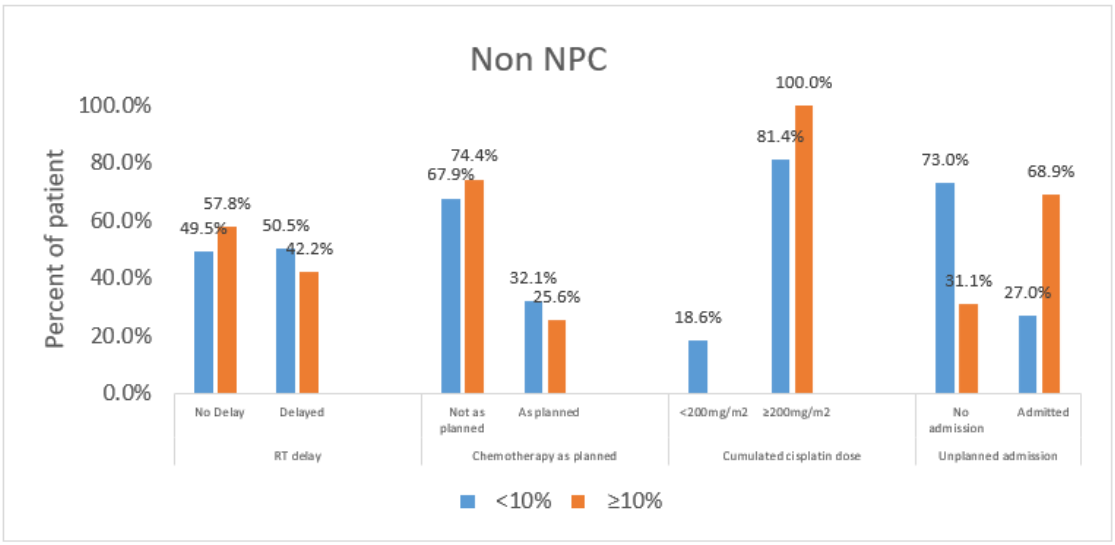


Figure 1

Prevalence of weight loss at the end of RT treatment in patient with treatment interruptions and unplanned admissions

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