



# Matched pair analysis to evaluate weight loss during radiation therapy for head and neck cancer as a prognostic factor for survival

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**Background:** One frequent consequence of radiation therapy (RT) for head and neck cancer (HNC) is weight loss (WL). HNC patients reportedly lose about 9% of their weight during treatment, regardless of pre-treatment WL and nutritional support. We investigated whether high WL during RT has an association with overall (OS) and cancer-specific survival (CSS).

**Methods:** We retrospectively reviewed weight during RT in HNC patients treated at Roswell Park Comprehensive Cancer Center between 2003 and 2017. High WL was defined as greater than or equal to the median WL. Logistic regression analysis was performed to identify predictors for WL during RT. Multivariate Cox regression and Kaplan-Meier analyses were used to estimate survival outcomes. Propensity score matching was performed to obtain balanced matched-pairs and compare survival outcomes.

**Results:** A total of 843 patients received either definitive (71%) or post-operative (29%) RT. Median follow-up was 53.6 months [interquartile range (IQR) 35.7–88.9]. Median WL was 5.8% (IQR 0.24–10.6) from baseline weight. Patients with high WL had better OS [hazard ratio (HR) 0.75, 95% confidence interval (CI), 0.61–0.93, P=0.01] and CSS (HR 0.71, 95% CI, 0.55–0.93, P=0.01). 258 matched-pairs were analyzed. Median follow-up was 54.8 months (IQR 35.8–90.4). Median OS was 39.2 months (IQR 21.4–75.7) for high WL versus 36.7 months (IQR 14.6–61.7) for low WL cohorts (P=0.047).

**Conclusions:** Different from previous reports, this study shows that patients with less WL have worse OS. WL during RT may not be a reliable marker for worse prognosis. A better way to evaluate malnutrition in patients undergoing RT is warranted.

**Keywords:** Head and neck cancer (HNC); weight loss (WL); radiotherapy; overall survival (OS); cancer specific survival

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## Introduction

Among various cancer types, head and neck cancer (HNC) reports the second highest prevalence of malnutrition, which frequently presents as weight loss (WL) that is exacerbated by progression of disease and consequences of treatment including radiotherapy (RT) (1). HNC is also one of the most adversely affected cancers by cachexia, a paraneoplastic syndrome characterized by anorexia, sarcopenia, and systemic inflammation (1,2). Malnutrition and cachexia are associated with decreased quality of life and increased risk of morbidity and mortality (3,4). Pretreatment WL has also been shown to increase the risk of RT-induced toxicities, treatment interruptions, and mortality (5-8). Many efforts have thus been made to prevent WL during RT via diet modification and artificial support of nutrition.

Conversely, many studies have investigated the potential of calorie restriction to counter cancer growth and potentiate response to RT (9-12). Calorie restriction without causing malnutrition has shown to provide protective and therapeutic effects against cancer and other metabolic diseases by reducing adiposity and expression of pro-inflammatory and pro-angiogenic factors (13,14). HNC patients reportedly lose about 9% of their body weight during treatment, regardless of pretreatment WL and nutritional support (15). The purpose of this retrospective study was to identify factors that are associated with WL during RT and investigate the impact of WL during RT on overall survival (OS) or cancer-specific survival (CSS) of a large group of HNC patients treated at our institution. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4969>).

## Methods

### *Patient population*

A retrospective single-institution database of HNC patients treated with definitive or post-operative RT between 2003 and 2017 at Roswell Park Comprehensive Cancer Center

was used. Patients who received RT with non-curative intent were excluded. Pre-RT and post-RT weight records were retrospectively reviewed to assess the level of WL in patients from start to end of RT. Median percentage of WL was identified and patients were classified into one of two groups: low WL (if change in weight is less than the median WL) or high WL (if change in weight is greater than or equal to the median WL). Length of follow-up, for those still alive, was defined as time between date of diagnosis to last date of follow-up visit.

### *Statistical analysis*

Univariate (UVA) logistic regression and multivariate (MVA) logistic regression analyses were performed using backward selection of potential confounders to identify patient and treatment factors associated with high WL during RT. All P values were two-sided and factors with P values  $\leq 0.05$  were considered statistically significant. MVA Cox regression analysis was performed to analyze factors that are associated with survival outcomes and Kaplan-Meier analysis was used to estimate OS and CSS of unmatched and matched cohorts.

Propensity score matching in patients with low and high WL was performed and survival outcomes were compared. Baseline characteristics, including age, gender, pre-RT weight, smoking status, p16 status, tumor staging, primary tumor site, and treatments received were matched to create well-balanced matched-pairs. Matching was based on nearest neighbor matching without replacement (NNWOR) method for 1:1 ratio using a caliper width of 0.1 of the standard deviation of the logit of the propensity score (16). SAS (SAS Institute, Cary, NC) and R (version 3.6.1, R Project for Statistical Computing, Vienna, Austria) software were used for statistical analysis.

### *Ethical statement*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Roswell

Park Comprehensive Cancer Center (EDR-103707) and individual consent for this retrospective analysis was waived.

## Results

### Baseline characteristics

A total of 843 patients in the database were identified. They were 649 males (77%) and 194 females (23%) with a median age at time of diagnosis of 61 years [interquartile range (IQR) 54–69]. The baseline characteristics of these unmatched patients are summarized in *Table 1*. Median follow-up was 53.6 months (IQR 35.7–88.9). All patients received either definitive (71%) or post-operative (29%) RT, with RT start date ranging from May 2003 to August 2017. Median RT dose was 67.5 Gy (IQR 65–70) for patients with low WL and 70 Gy (IQR 70–70) for patients with high WL.

Median percentage of WL was 5.8% (IQR 0.24–10.6). There were 421 patients who had low (<5.8%) WL and 422 patients who had high (≥5.8%) WL. Patients of each gender were evenly divided between the two categories of WL (*Table 1*). Median pre-RT weight was 75.7 kg (IQR 62.3–87.2) in low WL and 83.5 kg (IQR 70.7–97.7) in high WL cohorts (*Table 1*,  $P<0.001$ ).

### Factors associated with WL

Patients with no treatment response [odds ratio (OR) 0.18; 95% confidence interval (CI), 0.05–0.67;  $P=0.03$ ] were less likely to have high (≥5.8%) WL and patients with higher hemoglobin [OR 1.81; 95% CI, 1.33–2.47;  $P<0.001$ ] were more likely to have high WL.

### Survival outcome

Multivariate analysis showed that high WL predicted better OS [hazard ratio (HR) 0.75, 95% CI, 0.61–0.93,  $P=0.01$ ] and better CSS (HR 0.71, 95% CI, 0.55–0.93,  $P=0.01$ ). The associative factors for better and worse survival outcome are summarized in *Table 2*.

Prior to matching, median OS was 35.2 months (IQR 14.4–61.1) for patients with low WL and 40.6 months (IQR 23.8–76.5) for patients with high WL ( $P<0.001$ ). OS at 5 years was 48.5% (95% CI, 43.5–54.0) and 60.6% (95% CI, 55.8–65.9) for patients with low and high WL, respectively ( $P<0.001$ ). CSS at 5 years was 57.2% (95% CI, 52.0–62.9) and 70.2% (95% CI, 65.5–75.2) for patients with low and

high WL, respectively ( $P<0.001$ ).

A total of 258 pairs were matched, with all variables well-balanced (*Table 3*). After matching, median pre-RT weight was 76.8 kg (IQR 66.7–91.2) in patients with low WL and 82.8 kg (IQR 68.5–96.8) in patients with high WL (*Table 3*,  $P=0.054$ ). Median overall follow-up was 54.8 months (IQR 35.8–90.4). Median OS was 36.7 months (IQR 14.6–61.7) and 39.2 months (IQR 21.4–75.7) for low WL and high WL cohorts, respectively ( $P=0.047$ ). OS at 5 years was 48.8% (95% CI, 42.6–55.9) for patients with low WL and 54.9% (95% CI, 48.7–61.9) for patients with high WL ( $P=0.047$ , *Figure 1*). CSS at 5 years was 58.2% (95% CI, 51.8–65.4) for patients with low WL and 64.0% (95% CI, 57.8–71.0) for patients with high WL ( $P=0.036$ , *Figure 2*).

## Discussion

WL greater than 5–10% in HNC patients is considered one of the significant parameters of malnutrition, which impedes treatment tolerance, response, and completion and thereby compromises survival (5–7). This study is the first to report that high WL (≥5.8% of pre-treatment body weight) in HNC patients receiving RT with curative intent portends better OS and CSS. As previously reported, in our expanded cohort, unexpected hospitalization, nutrition support, older age, advanced tumor stage, and current smoking status continued to be associated with worse OS and CSS (17). We controlled for these and other variables (HPV status, comorbidities, treatments received, etc.) by performing propensity score matching in patients with low and high WL and created well-balanced matched-pairs (*Table 3*). Analysis of these matched pairs (*Figures 1* and *2*) showed better 5-year OS [54.9% *vs.* 48.8%,  $P=0.047$ ] and CSS (64.0% *vs.* 58.2%,  $P=0.036$ ) in the high WL cohort. Median OS was increased to 39.2 months for patients with high WL compared to 36.7 months for patients with low WL ( $P=0.047$ ).

These findings of improved survival with high WL contrast with several existing reports in the literature. Cho *et al.* reported, among 226 oral squamous cell cancer patients treated with RT, high WL (≥10%) had lower disease-free survival (52.5% *vs.* 77.1%,  $P<0.01$ ) (18). Langius *et al.*, in a cohort of 1,340 HNC patients adjusted for potential confounding variables (age, gender, primary tumor site, TNM stage, treatment modality, etc.), found 57% incidence of high WL (defined as >5% WL from start of RT until week 8 or >7.5% WL until week 12) which was significantly associated with worse disease-specific survival

**Table 1** Baseline characteristics of patients before matching

Characteristics	Low weight loss		High weight loss		P
	N	%	N	%	
Gender					0.54
Male	320	76	329	78	
Female	101	24	93	22	
Total	421	100	422	100	
Age (years)					0.02
<61	190	45	225	53	
≥61	231	55	197	47	
Total	421	100	422	100	
Pre-RT weight (kg)					<0.001
Median	75.7		83.5		
IQR	62.3–87.2		70.7–97.7		
Smoker					0.93
Never	97	23	102	24	
Former	216	51	213	50	
Current	108	26	107	25	
Total	421	100	422	100	
HPV					<0.001
Negative	91	22	82	19	
Positive	77	18	161	38	
NA	253	60	179	42	
Total	421	100	422	100	
Comorbidity (No.)					0.15
0	68	16	83	20	
1	110	26	127	30	
2	124	29	101	24	
3	119	28	111	26	
Total	421	100	422	100	
T stage					<0.001
X	2	0	3	1	
0–2	196	47	217	51	
3–4	189	45	194	46	
NA	34	8	8	2	
Total	421	100	422	100	
N stage					<0.001
0–1	211	50	146	35	
2–3	175	42	267	63	
NA	35	8	9	2	
Total	421	100	422	100	

**Table 1** (continued)

**Table 1** (continued)

Characteristics	Low weight loss		High weight loss		P
	N	%	N	%	
M stage					<0.001
0	368	87	405	96	
1	13	3	7	2	
NA	40	10	10	2	
Total	421	100	422	100	
Primary site					<0.001
NA	87	21	50	12	
Oral cavity	84	20	34	8	
Nasopharynx	11	3	9	2	
Oropharynx	88	21	189	45	
Hypopharynx	21	5	25	6	
Glottis	62	15	47	11	
Salivary	24	6	8	2	
Other	11	3	4	1	
Unknown	16	4	34	8	
Multiple	17	4	22	5	
Total	421	100	422	100	
Histology					<0.001
Squamous	355	84	400	95	
Others	66	16	22	5	
Total	421	100	422	100	
Laterality					<0.001
Unilateral	69	16	69	16	
Bilateral	88	21	167	40	
NA	264	63	186	44	
Total	421	100	422	100	
RT type					<0.001
Definitive	253	60	345	82	
Post-operative	168	40	77	18	
Total	421	100	422	100	
RT total dose (Gy)					<0.001
Median	67.5		70		
IQR	65.3–70.0		70.0–70.0		
RT duration (days)					<0.001
<46	215	51	131	31	
≥46	205	49	291	69	
NA	1	0	0	0	
Total	421	100	422	100	

**Table 1** (continued)

Table 1 (continued)

Characteristics	Low weight loss		High weight loss		P
	N	%	N	%	
RT start year					0.55
<2011	138	33	130	31	
≥2011	283	67	292	69	
Total	421	100	422	100	
RT complete					<0.001
No	29	7	10	2	
Yes	353	84	398	94	
NA	39	9	14	3	
Total	421	100	422	100	
Treatment response					0.003
None	27	6	17	4	
Partial	285	68	333	79	
Complete	61	14	44	10	
NA	48	11	28	7	
Total	421	100	422	100	
Surgery					<0.001
No	253	60	342	81	
Yes	168	40	80	19	
Total	421	100	422	100	
Chemo					<0.001
No	159	38	37	9	
Yes	262	62	385	91	
Total	421	100	422	100	
Chemo type					<0.001
None	175	42	45	11	
Cis q21d	101	24	182	43	
Cis wkly	76	18	113	27	
Cetux wkly	23	5	14	3	
NA	5	1	3	1	
Carbo wkly	23	5	26	6	
Pt regimen NOS	10	2	17	4	
Crossover to cetux	7	2	13	3	
Crossover to carbo	1	0	9	2	
Total	421	100	422	100	
Chemo frequency					<0.001
Weekly	135	32	170	40	

Table 1 (continued)

Table 1 (continued)

Characteristics	Low weight loss		High weight loss		P
	N	%	N	%	
Q21d	104	25	196	46	
NA	182	43	56	13	
Total	421	100	422	100	
Nutrition support					<0.001
No	221	52	167	40	
Yes	199	47	254	60	
NA	1	0	1	0	
Total	421	100	422	100	
Hospitalized					0.006
No	351	83	317	75	
Yes	68	16	103	24	
NA	2	0	2	0	
Total	421	100	422	100	
Hemoglobin (g/dL)					<0.001
<12	161	38	301	71	
≥12	85	20	78	18	
NA	175	42	43	10	
Total	421	100	422	100	
WBC count					<0.001
Normal	208	49	337	80	
Low	7	2	8	2	
High	31	7	34	8	
NA	175	42	43	10	
Total	421	100	422	100	

RT, radiotherapy; IQR, interquartile range; HPV, human papilloma virus; NA, not available; Chemo, chemotherapy; Cis, cisplatin; Q21d, every 21 days; wkly, weekly; cetux, cetuximab; Carbo, carboplatin; Pt, platinum; NOS, not otherwise specified; WBC, white blood cell.

**Table 2** UVA-MVA Cox regression analysis of survival outcome

Variables	OS						CSS					
	UVA			MVA			UVA			MVA		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Weight loss												
Low	1	Ref		1	Ref		1	Ref		1	Ref	
High	0.67	0.55–0.81	<0.001	0.75	0.61–0.93	0.01	0.62	0.49–0.78	<0.001	0.71	0.55–0.93	0.01
Pre-RT weight (kg)												
<80	1	Ref		1	Ref		1	Ref		1	Ref	
≥80	0.6	0.49–0.74	<0.001	0.88	0.70–1.11	0.27	0.58	0.45–0.75	<0.001	1.01	0.75–1.34	0.97
Gender												
Male	1	Ref					1	Ref				
Female	1.07	0.86–1.35	0.53				1.09	0.83–1.43	0.52			
Age												
<61	1	Ref		1	Ref		1	Ref		1	Ref	
≥61	1.52	1.25–1.84	<0.001	1.45	1.17–1.80	<0.001	1.47	1.16–1.86	0.001	1.41	1.09–1.84	0.009
Smoker												
Never	1	Ref		1	Ref		1	Ref		1	Ref	
Former	1.49	1.14–1.95	0.004	1.16	0.88–1.54	0.30	1.45	1.05–2.00	0.02	1.07	0.76–1.50	0.70
Current	2.12	1.59–2.83	<0.001	1.84	1.36–2.49	<0.001	2.07	1.47–2.92	<0.001	1.66	1.16–2.39	0.006
HPV												
Negative	1	Ref		1	Ref		1	Ref		1	Ref	
Positive	0.5	0.37–0.67	<0.001	0.85	0.62–1.17	0.32	0.52	0.37–0.74	<0.001	1.02	0.66–1.56	0.94
Comorb (No.)												
0	1	Ref					1	Ref				
1	0.84	0.62–1.14	0.25				0.84	0.59–1.19	0.33			
2	1.13	0.84–1.52	0.41				0.96	0.68–1.36	0.81			
3	1.31	0.98–1.75	0.07				1.03	0.73–1.46	0.85			
T stage												
0–2	1	Ref		1	Ref		1	Ref		1	Ref	
3–4	2.1	1.71–2.58	<0.001	1.9	1.52–2.36	<0.001	2.52	1.96–3.26	<0.001	2.19	1.67–2.88	<0.001
X	1.6	0.40–6.46	0.51				1.22	0.17–8.78	0.84			
N stage												
0–1	1	Ref					1	Ref				
2–3	1	0.82–1.22	0.97				1.18	0.92–1.50	0.20			

**Table 2** (continued)

Table 2 (continued)

Variables	OS						CSS					
	UVA			MVA			UVA			MVA		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
M stage												
0	1	Ref		1	Ref		1	Ref		1	Ref	
1	3.78	2.35–6.08	<0.001	1.7	0.99–2.91	0.052	3.94	2.29–6.76	<0.001	1.51	0.81–2.82	0.2
Primary site												
NA	1	Ref		1	Ref		1	Ref		1	Ref	
OC	0.97	0.71–1.33	0.86				1.05	0.73–1.51	0.8			
NP	0.85	0.44–1.64	0.63				1.05	0.52–2.11	0.9			
OP	0.45	0.34–0.60	<0.001	0.97	0.68–1.38	0.86	0.42	0.30–0.60	<0.001	1.03	0.67–1.59	0.88
HP	1.09	0.72–1.65	0.68				1.05	0.64–1.74	0.83			
Glottis	0.69	0.49–0.98	0.04	0.83	0.57–1.21	0.33	0.63	0.41–0.97	0.04	0.86	0.54–1.38	0.53
Salivary	0.61	0.36–1.03	0.07				0.81	0.46–1.44	0.48			
Other	0.48	0.20–1.19	0.11				0.56	0.20–1.53	0.26			
Unk	0.4	0.24–0.69	<0.001	0.93	0.51–1.69	0.81	0.33	0.16–0.66	0.002	0.95	0.43–2.08	0.89
Mult	1.19	0.77–1.83	0.43				1.08	0.64–1.83	0.77			
Histo												
SCC	1	Ref		1	Ref		1	Ref		1	Ref	
Others	1.4	1.05–1.86	0.02	0.73	0.49–1.10	0.14	1.53	1.10–2.13	0.01	0.74	0.45–1.21	0.23
RT total dose (Gy)												
<70	1	Ref		1	Ref		1	Ref		1	Ref	
≥70	0.81	0.66–0.99	0.04	1	0.75–1.34	0.99	0.75	0.58–0.95	0.02	0.83	0.61–1.13	0.23
RT start year												
<2011	1	Ref					1	Ref				
≥2011	0.82	0.67–1.01	0.06				0.86	0.68–1.09	0.22			
RT compl												
No	1	Ref		1	Ref		1	Ref		1	Ref	
Yes	0.23	0.16–0.33	<0.001	0.59	0.39–0.89	0.01	0.2	0.13–0.30	<0.001	0.57	0.36–0.89	0.01
Resp												
None	1	Ref		1	Ref		1	Ref		1	Ref	
Partial	0.14	0.10–0.19	<0.001	0.12	0.08–0.18	<0.001	0.08	0.06–0.12	<0.001	0.07	0.05–0.11	<0.001
Compl	0.67	0.46–0.98	0.04	0.59	0.40–0.88	0.01	0.58	0.39–0.86	0.006	0.5	0.33–0.77	0.001

Table 2 (continued)

Table 2 (continued)

Variables	OS						CSS					
	UVA			MVA			UVA			MVA		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Surgery												
No	1	Ref					1	Ref				
Yes	0.96	0.77–1.18	0.68				0.99	0.77–1.27	0.93			
Chemo type												
None	1	Ref		1	Ref		1	Ref		1	Ref	
Cis q21d	0.6	0.46–0.78	<0.001	0.5	0.34–0.74	<0.001	0.52	0.38–0.72	<0.001	0.49	0.30–0.80	0.004
Cis wkly	0.8	0.61–1.05	0.11				0.87	0.64–1.19	0.38			
Cetux wkly	1.78	1.17–2.73	0.007	0.85	0.51–1.39	0.51	1.66	1.00–2.77	0.05	0.82	0.45–1.48	0.51
NA	2.52	1.17–5.40	0.02	0.74	0.32–1.72	0.49	2.77	1.21–6.36	0.02	0.75	0.30–1.89	0.54
Carbo wkly	0.87	0.58–1.31	0.51				0.83	0.50–1.36	0.45			
Pt reg NOS	1.04	0.61–1.77	0.9				1.18	0.65–2.16	0.59			
CO to cetux	0.77	0.43–1.37	0.37				0.69	0.32–1.50	0.35			
CO to carbo	0.6	0.22–1.63	0.32				0.44	0.11–1.80	0.25			
Nut support												
No	1	Ref		1	Ref		1	Ref		1	Ref	
Yes	1.3	1.06–1.58	0.01	1.34	1.06–1.70	0.02	1.33	1.05–1.69	0.02	1.39	1.04–1.85	0.03
Hosp												
No	1	Ref		1	Ref		1	Ref		1	Ref	
Yes	1.58	1.26–1.98	<0.001	1.61	1.26–2.06	<0.001	1.49	1.13–1.96	0.004	1.45	1.07–1.95	0.02
Hgb (g/dL)												
≥12	1	Ref		1	Ref		1	Ref		1	Ref	
<12	2.4	1.90–3.03	<0.001	1.27	0.98–1.65	0.07	2.57	1.95–3.40	<0.001	1.2	0.87–1.65	0.27
WBC count												
Normal	1	Ref		1	Ref		1	Ref		1	Ref	
Low	2.4	1.31–4.39	0.005	2.03	1.09–3.78	0.02	2.77	1.42–5.43	0.003	2.34	1.17–4.67	0.02
High	1.96	1.43–2.68	<0.001	1.19	0.85–1.68	0.31	2.28	1.59–3.27	<0.001	1.28	0.86–1.90	0.23

UVA, univariate analysis; MVA, multivariate analysis; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; Ref, reference; RT, radiotherapy; HPV, human papilloma virus; Comorb, comorbidity; NA, not available; OC, oral cavity; NP, nasopharynx; OP, oropharynx; HP, hypopharynx; Unk, unknown; Mult, multiple; Histo, histology; SCC, squamous cell carcinoma; Compl, complete; Resp, response; Chemo, chemotherapy; Cis, cisplatin; Q21d, every 21 days; Wkly, weekly; cetux, cetuximab; Carbo, carboplatin; Pt, platinum; Reg, regimen; NOS, not otherwise specified; CO, crossover; Nut, nutrition; Hosp, hospitalized; Hgb, hemoglobin; WBC, white blood cell.



**Table 3** Baseline characteristics of matched pairs

Variables	Low weight loss		High weight loss		P
	N	%	N	%	
Gender					0.29
Male	206	80	195	76	
Female	52	20	63	24	
Total	258	100	258	100	
Age (years)					0.38
<61	124	48	135	52	
≥61	134	52	123	48	
Total	258	100	258	100	
Pre-RT weight (kg)					0.05
Median	76.8		82.8		
IQR	66.7–91.2		68.5–96.8		
Smoker					0.29
Never	50	19	65	25	
Former	139	54	129	50	
Current	69	27	64	25	
Total	258	100	258	100	
HPV					0.70
Negative	61	24	56	22	
Positive	69	27	77	30	
NA	128	50	125	48	
Total	258	100	258	100	
Comorbidity (No.)					0.72
0	45	17	40	16	
1	73	28	83	32	
2	67	26	60	23	
3	73	28	75	29	
Total	258	100	258	100	
T stage					0.73
X	1	0	3	1	
0–2	113	44	118	46	
3–4	134	52	129	50	
NA	10	4	8	3	
Total	258	100	258	100	
N stage					0.78

Table 3 (continued)

**Table 3** (continued)

Variables	Low weight loss		High weight loss		P
	N	%	N	%	
0–1	106	41	101	39	
2–3	142	55	149	58	
NA	10	4	8	3	
Total	258	100	258	100	
M stage					0.47
0	238	92	243	94	
1	10	4	5	2	
NA	10	4	10	4	
Total	258	100	258	100	
Primary site					0.48
NA	36	14	44	17	
Oral cavity	33	13	29	11	
Nasopharynx	10	4	6	2	
Oropharynx	75	29	95	37	
Hypopharynx	19	7	17	7	
Glottis	44	17	28	11	
Salivary	8	3	8	3	
Other	5	2	3	1	
Unknown	15	6	16	6	
Multiple	13	5	12	5	
Total	258	100	258	100	
Histology					1
Squamous	241	93	240	93	
Other	17	7	18	7	
Total	258	100	258	100	
RT complete					0.23
No	15	6	7	3	
Yes	233	90	239	93	
NA	10	4	12	5	
Total	258	100	258	100	
Treatment response					0.13
None	20	8	13	5	
Partial	175	68	198	77	

Table 3 (continued)

Table 3 (continued)

Variables	Low weight loss		High weight loss		P
	N	%	N	%	
Complete	36	14	24	9	0.76
NA	27	10	23	9	
Total	258	100	258	100	
Surgery					0.76
No	190	74	194	75	
Yes	68	26	64	25	
Total	258	100	258	100	0.28
Chemotherapy type					
None	51	20	40	16	
Cis q21d	86	33	101	39	
Cis wkly	62	24	64	25	
Cetux wkly	20	8	11	4	
NA	4	2	2	1	
Carbo wkly	20	8	15	6	
Pt regimen NOS	7	3	12	5	
Crossover to cetux	7	3	9	3	
Crossover to carbo	1	0	4	2	
Total	258	100	258	100	
Nutrition support					0.59
No	107	41	100	39	
Yes	151	59	158	61	
Total	258	100	258	100	0.39
Hospitalized					
No	208	81	199	77	
Yes	50	19	58	22	
NA	0	0	1	0	
Total	258	100	258	100	0.52
Hemoglobin (g/dL)					
<12	150	58	158	61	
≥12	69	27	58	22	
NA	39	15	42	16	
Total	258	100	258	100	

Table 3 (continued)

Table 3 (continued)

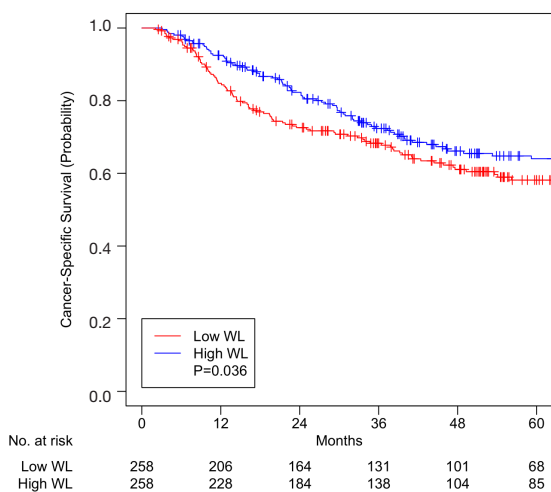
Variables	Low weight loss		High weight loss		P
	N	%	N	%	
WBC count					0.81
Normal	188	73	191	74	
Low	7	3	7	3	
High	24	9	18	7	
NA	39	15	42	16	
Total	258	100	258	100	

RT, radiotherapy; IQR, interquartile range; HPV, human papilloma virus; NA, not available; Cis, cisplatin; Q21d, every 21 days; Wkly, weekly; Cetux, cetuximab; Carbo, carboplatin; Pt, platinum; NOS, not otherwise specified; WBC, white blood cell.

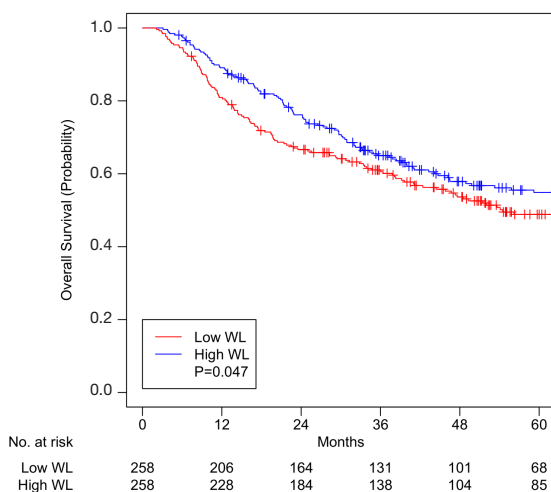
(HR 1.7; 95% CI, 1.2–2.4; P=0.004) (19).

Other studies have reported no association between WL during RT and survival. Ghadjar *et al.* prospectively randomized 224 HNC patients to either RT alone or concurrent chemoradiotherapy (CCRT) and compared patient weights 6 months before RT, at start of RT, and at end of RT (20). After close to 10 years of median follow-up, WL before RT was found to be associated with worse CSS and OS, but WL during RT did not show to influence survival outcomes (20). Pai *et al.* also reported lack of association between WL during RT and survival outcomes in 1,562 HNC patients; however, lower pre-RT body mass index (BMI) was associated with poorer CSS and OS (21).

Despite such varied findings, to identify patients for assessment of malnutrition, studies continue to investigate predictors of WL during RT (22–25). Zhao *et al.* performed a systematic review of 22 observational studies including 6,159 HNC patients undergoing RT and found advanced tumor stage, higher pre-RT BMI, and use of CCRT to be independent risk factors for WL (22). Lønbro *et al.* also found advanced tumor stage (III–IV, P=0.03) and higher pre-RT BMI (>25, P<0.001), as well as primary tumor site (pharyngeal, oral cavity, supraglottic tumors; P<0.001) to be predictors of WL (>5%) during RT (23). Mallick *et al.* retrospectively analyzed 103 HNC patients treated with RT and identified total planning target volume (PTV) >615 cc, prescription dose PTV >235 cc, and CCRT *vs.* RT alone as predictors of WL (>5%) during RT (24). Langius *et al.* more recently investigated a cohort of 910 HNC patients, about half of whom experienced WL (>5%), and identified RT on neck lymph nodes (P<0.001),



**Figure 1** Overall survival for patients with high or low weight loss (WL) after matching.



**Figure 2** Cancer-specific survival for patients with high or low weight loss (WL) after matching.

higher RT dose (>65 Gy,  $P<0.001$ ) on primary tumor, use of three-dimensional conformal RT *vs.* intensity-modulated RT ( $P=0.001$ ), and younger age (per 10 years,  $P=0.01$ ) to be predictors of WL (>5%) (25).

In our study, all patients were treated with intensity-modulated RT to the lymph nodes and had dose of >65 Gy to the primary; age was controlled by matching. We found that patients with higher baseline hemoglobin levels were more likely to experience high WL (OR 1.81; 95% CI, 1.33–2.47;  $P<0.001$ ) while patients with no treatment

response were less likely to have high WL (OR 0.18; 95% CI, 0.05–0.67;  $P=0.03$ ).

### Caveats

Although WL has shown to be more prevalent and significant during RT than before treatment (19,20), our study did not investigate pre-RT WL or pre-RT BMI, both of which have shown to be poor prognostic markers (5-8,19-21). Patients who had WL before RT may have lost comparatively less weight during RT; these patients may have contributed to the poorer prognosis of patients with low WL (<5.8%) based on significant pre-RT WL. In fact, patients with low WL had significantly lower pre-RT weight (75.7 kg, IQR 62.3–87.2) than patients with high WL (83.5, IQR 70.7–97.7) prior to matching (Table 1,  $P<0.001$ ), raising the possibility that our low WL cohort might have had pre-RT WL that contributed to worse outcome. Although our matched pairs were well-balanced, the median pre-RT weight between the two WL cohorts showed a non-significant difference of 6 kg (Table 3,  $P=0.054$ ). Nevertheless, pre-RT weight showed no association with OS ( $P=0.11$ ) or CSS ( $P=0.51$ ). On the other hand, patients with greater pre-RT BMI may have benefited from WL during RT due to reduced adiposity and inflammatory markers that aided treatment response and disease course (9,12,14); these patients may have contributed to the better prognosis of patients with high WL ( $\geq 5.8\%$ ).

### Future directions

Preclinical studies show promising effects of calorie restriction in not only stunting the growth of tumors but also potentiating response of cancer cells to treatment including RT (9-14). The results of our study suggest that WL may not be directly proportional to the level of malnutrition; WL without causing malnutrition may produce some of the beneficial effects of calorie restriction. Thus, WL during RT may not be a reliable prognostic marker in HNC patients.

WL alone may not fully capture dynamic changes in the nutritional status of cancer patients, potentially resulting in heterogeneous findings of its association with survival outcomes in current literature. WL also may need to be interpreted individually in the context of one's clinical and nutritional status.

A comprehensive, multidisciplinary method to evaluate

malnutrition in HNC patients undergoing RT is needed. Though the efficacy of nutrition support in improving outcomes remains controversial (26-28), we fully support evaluation of all head and neck patients by a registered dietician (RD). Unfortunately, there are far too few RDs in the country to meet the need (29). Moreover, we do not endorse calorie restriction or any other intentional or otherwise sanctioned WL during RT except on clinical trial.

## Conclusions

This study mitigates the concern for poor prognosis in HNC patients experiencing WL during RT. On matched-pair analysis, greater than or equal to the median WL ( $\geq 5.8\%$ ) predicted better 5-year OS and CSS. Further research on specifics of patient nutritional status and effects on survival is warranted.

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