Determination of Factors Associated with Critical Weight Loss in Oral Cavity Carcinoma Patients: A Retrospective Cohort Study

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Abstract

Introduction Critical weight loss is defined as an unintentional weight loss of $\geq$ 5% at 1 month or $\geq$ 10% at 6 months from the start of treatment. Critical weight loss leads to deterioration of the immune function and reduced tolerance to treatment (surgery $\pm$ radiochemotherapy) as well as increased complication rates.

Objective Critical weight loss, defined as a weight loss of $\geq$ 5% after 1 month or $\geq$ 10% after 6 months from the start of treatment, is not uncommon in head and neck cancer patients. We aimed to assess the factors associated with critical weight loss during the treatment of oral cavity squamous cell carcinoma patients.

Methods A retrospective cohort study was performed at the Aga Khan University Hospital, in Karachi, Pakistan, on 125 patients. Patients receiving adjuvant therapy were considered exposed, and the outcome was critical weight loss.

Results The mean age of presentation was 46.9 $\pm$ 12.8 years in patients undergoing surgery and adjuvant therapy, with 119 (79.3%) of them being male and 31 (20.7%) female. One hundred and twelve patients (81.3%) developed critical weight loss at 6 months from the start of treatment, and the only significant variable associated with critical weight loss was the stage of the disease ($p = 0.03$).

Conclusion A large proportion of patients with oral cancer developed critical weight loss requiring a need for intervention. The overall stage of the disease is a significant predictor of critical weight loss in patients undergoing treatment.

Keywords
- weight loss
- mouth neoplasm
- radiotherapy
- surgery
- oral

Introduction

Critical weight loss (CWL) is defined as an unintentional weight loss of $\geq$ 5% at 1 month or $\geq$ 10% at 6 months from the start of treatment.[1] Due to the location of the tumor, there is difficulty in mastication, which leads to further weight loss. Critical weight loss is seen in up to 55% of head and neck cancer patients;[1] it leads to deterioration of the immune function and reduced tolerance to treatment (surgery $\pm$ radiochemotherapy) as well as increased complication rates.[1] Finally, CWL also impairs the functional status and worsens the quality of life.[1]

During the treatment, the patients develop acute toxicity, mostly due to radiotherapy.[2] The most common treatment-related toxicity is mucositis that leads to dysphagia and

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further aggravates the problem of weight loss.[2] Malnutrition, that is most commonly assessed by weight loss, is seen in 41–88% of patients receiving radiotherapy.[2] The toxicity of radiotherapy and reduction in weight continue weeks after completion of radiotherapy.[2] Critical weight loss has also shown to be an independent risk factor for disease-free survival in patients undergoing radiotherapy.

Therefore, it is of utmost importance to determine the prevalence and factors associated with CWL in patients receiving treatment (surgery $\pm$ adjuvant therapy) for oral cavity squamous cell carcinoma in our population based in a developing country, which was the aim of this study.

Material and Methods

A retrospective cohort study was conducted from January to December 2014. Institutional ethical review committee exemption was obtained before the beginning of the study. The study site was a tertiary care hospital where the patients were diagnosed and treated. The data was collected via non-purposive consecutive sampling. All patients receiving treatment for oral cavity squamous cell carcinoma from January to December 2014 were included in the study

Inclusion criteria were patients $\geq$ 18 years with confirmed diagnosis of squamous cell carcinoma of oral cavity treated at the tertiary care hospital. Exclusion criteria were patients with histological findings other than squamous cell carcinoma, distant metastasis before the commencement of treatment and patients treated primarily outside Aga Khan University Hospital. Patients with missing data, those who did not complete their treatment and those who were lost to follow-up were excluded from the study. Patients with pT4b (advanced stage) tumors were also excluded as these patients are referred for palliative treatment and are not admitted under our care.

The weight and height were assessed and documented at the time of first reporting to the outpatient clinic and the weight was assessed at the first postoperative visit and at every follow-up visit by the clinic staff using a standardized weighing machine. In this study, CWL was defined as weight loss of more than 10% at 6 months from the commencement of treatment (surgery) At this time, the patients with advanced-stage disease (pT3-T4) had completed their adjuvant therapy and were on a regular 4 weekly follow-up visit schedule. All the patients had a dietitian's input at the time of discharge. The patients were stratified into oral intake and tube feeding. Patients either remained on oral diet intake, if the disease is of early stage and not affecting swallowing after surgery, or tube feeding was instigated if the tumor was of late stage or if the patient was expected to require adjuvant treatment postoperatively, which impedes oral intake. Tube feeding was further stratified into none, nasogastric tube, gastrostomy and per-endoscopic gastrostomy.

The patients were divided into two groups, surgery alone (unexposed) and surgery + adjuvant therapy (exposed). The chemotherapeutic agent used as an adjunct regimen for our patients was cisplatin and 5-fluorouracil. The outcome was dichotomous (yes/no) CWL. The univariate analysis was conducted first ($p = 0.25$). Each significant variable was then added for model building based on the likelihood score. Multiple logistic regression was run on the final model using the software STATA version 12 (StataCorp LLC, College Station, TX, USA). The only statistically significant variable in our final model was the overall stage of the disease.

Results

A total of 150 patients were included in the study, who had undergone treatment for oral cavity squamous cell carcinoma in the year of 2014 at our institute. The data was stratified on the primary exposure variable, which was adjuvant therapy (radiotherapy/chemotherapy/both). Variables having less cell count in the sub-categories (< 5), such as site of tumor (tongue/buccal mucosa/alveolus), pathological T-stage (early = pT1 & 2, late = pT3 & 4), overall stage (early = 1 & 2, late = 3 & 4) and co-morbidities (yes/no), were merged.

There was a total of 111 patients who underwent surgery and adjuvant therapy, and 39 patients who had surgery alone. The mean age of the patients undergoing surgery along with adjuvant therapy was 46.9 $\pm$ 12.77 years. The majority of the patients were males 89 (80.2%), and the remaining 22 (19.8%) were females (►**Table 1**).

The majority of the patients—122 (81.3%)—developed CWL, that is, weight loss of more than 5% at 1 month or more than 10% of the body weight at 6 months from the commencement of treatment (surgery). Of all the variables under consideration, the significant variables at univariate analysis ($p = 0.25$) were overall stage, mode of nutrition (oral/stomach tubes), type of enteral nutrition (PEG/gastrostomy/nasogastric tube), pathological T-stage, adjuvant therapy and comorbidities (►**Table 2**). The multicollinearity (cutoff 0.8) amongst the variables was assessed using ETA. Cramer and Pearson correlation and was not present. The multivariable analysis revealed the overall stage ($p = 0.03$) to be significantly associated with CWL, keeping the primary exposure variable (adjuvant therapy) in the model (►**Table 3**). Goodness-of-fit of the final model was assessed using Pearson Goodness-of-fit, and the final model fit well. (Pearson chi 83.52, $p = 0.99$). The interaction was assessed between biologically plausible variables, but no interaction was seen. The receiver operating characteristic (ROC) curve was plotted after running binary logistic regression on the final model (Area under curve = 0.7825) (►**Fig. 1**).

In conclusion, the risk of developing CWL is 1.73 times higher in patients with advanced stage disease (stages III & IV) when compared with patients in the early stages of the disease (stages I & II) keeping the primary exposure in the model (adjuvant treatment).

Discussion

Cancer anywhere in the body causes cachexia. It is thought that the systemic effects of carcinoma lead to changes in appetite and taste;[1,3] these changes coupled with the location of tumor in the oral cavity causing mechanical

Table 1 Patient demographics and tumor-related variables

Variable		Unexposed (Surgery alone) *n* (%)	Exposed (Surgery + adjuvant therapy) *n* (%)
Age Mean (SD)*		51.48 (10.55)*	46.91 (12.76)*
Gender	Males	30 (76.9)	89 (80.2)
	Females	9 (23.1)	22 (19.8)
Comorbidities	No	30 (76.9)	80 (72.1)
	Yes	9 (23.1)	31 (27.9)
Site	Tongue	14 (35.9)	24 (21.6)
	Buccal mucosa	22 (56.4)	66 (59.5)
	Alveolus	3 (7.7)	21 (18.9)
pT	Early (I & II)	25 (64.1)	46 (41.4)
	Late (III & IV)	14 (34.9)	65 (58.6)
Overall stage	Early (I & II)	21(53.8)	20 (18)
	Late (III & IV)	18 (46.15)	91 (82)
Type of neck dissection	None	3 (7.7)	0 (0)
	Supraomohyoid ND	7 (17.9)	11 (9.9)
	Selective ND	7 (17.9)	21 (18.9)
	Modified radical ND	13 (33.3)	57 (51.3)
	Radical ND	9 (23)	22 (19.8)
Bilateral/unilateral neck dissection	No	28 (71.8)	68 (61.3)
	Yes	11 (28.2)	43 (38.7)
pN stage	N0	26 (66.7)	0 (0)
	N1	2 (5.1)	10 (9)
	N2a	0 (0)	36 (32.4)
	N2b	8 (20.5)	22 (19.8)
	N2c	3 (15.4)	43 (38.7)
Grade of tumor	Well differentiated	17 (43.6)	26 (23.4)
	Moderately differentiated	18 (46.1)	69 (62.2)
	Poorly differentiated	4(10.3)	16 (14.4)
Perineural invasion	No	35 (89.4)	90 (81.1)
	Yes	4 (10.3)	21 (18.9)
Extra capsular spread	No	27 (69.2)	84 (75.7)
	Yes	12 (30.8)	27 (24.3)
Mode of nutrition	Oral	26 (66.7)	95 (85.6)
	Tube feeding	13 (33.3)	16 (14.4)
Type of tube feeding	None	12 (30.7)	15 (13.5)
	Nasogastric tube	2 (5.1)	5 (4.5)
	Gastrostomy	20 (51.2)	60 (54)
	Per-endoscopic gastrostomy	5 (12.8)	31 (27.93)

Abbreviations: ND, neck dissection; pN, pathological assessment of the regional lymph nodes; pT, primary tumor; SD, standard deviation.

obstruction—that is, dysphagia and odynophagia—are thought to cause a further reduction in weight over the course of time.[1] The aim of the present study was to assess weight loss in patients over the course of treatment (surgery ± adjuvant therapy) at a tertiary care setting in a developing country.

Critical weight loss prior to the start of treatment has been reported in 31–57% of patients.[1] This assessment of weight

Table 2 Univariate analysis significance (*p*-value = 0.25)

Serial #	Variable	*p*-value	LR	Unadjusted HR (RR)	Z-test
1	Age	0.61	0.27	0.99	−0.51
2	Gender	0.96	0.00	0.99	−0.05
3	**Comorbidities**	**0.13**	**2.24**	**1.34**	**1.52**
4	Site	0.33	2.24	1.37 1.45	1.34 1.26
5	Neck dissection type	0.79	1.71	2.16	0.75
6	Bilateral/unilateral ND	0.44	0.58	1.15	0.77
7	**Stage**	**0.008**	**6.92**	**1.81**	**2.47**
8	**pT**	**0.01**	**6.32**	**1.59**	**2.47**
9	pN	0.81	1.57	1.24	0.86
10	Grade	0.91	0.2	1.06 0.95	0.29 -0.17
11	Perineural spread	0.56	0.33	0.87	−0.57
12	Extra capsular spread	0.50	0.45	1.14	0.68
13	**Mode of nutrition**	**0.009**	**6.78**	**0.50**	**−2.38**
14	**Source of enteral feeding**	**0.09**	**6.39**	**1.93**	**1.31**
15	**Adjuvant treatment**	**0.15**	**2.02**	**1.36**	**1.38**

Abbreviations: HR, hazard ratio; LR, chi2 Likelihood; ND, neck dissection; pN, pathological assessment of the regional lymph nodes; pT, primary tumor; RR, relative risk.

Table 3 Multivariable analysis significance (*p*-value = 0.05) using cox proportional algorithm

Serial #	Variable	LR	*p*-value	RR	Z-test	*p*-value
1	Adjuvant therapy (primary exposure)	7.23	0.02	1.73	2.17	0.03
2	Stage	7.23	0.02	1.14	0.56	0.58

Abbreviations: LR, chi2 Likelihood; RR, relative risk.

loss of ≥ 5% in 1 month or ≥ 10% in 6 months before the start of treatment could be subjective and may be overestimated owing to the recall bias. We studied CWL over the course of treatment at our center, and the patients' weight was recorded at every follow-up visit starting from the time when the diagnosis was made. Our results show that 81.3% of the patients developed CWL over the course of the treatment, which is a significant number. Where other studies aimed to study CWL in all patients presenting with head and neck cancer,[1,2,4] we focused our study on patients with oral cavity carcinoma due to its high prevalence in our region,[5] which might estimate results close to parameter. Also, previous studies have shown a greater weight loss in patients with oral cavity carcinoma when compared with other sites in the head and neck area, making it a high-risk category.[1]

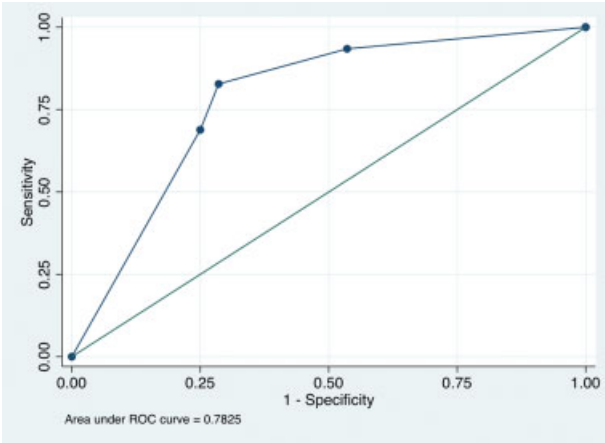

Fig. 1 Receiver Operating Characteristic (ROC) curve of the final model.

Studies have shown various factors to be significantly associated with weight loss at and around the time of radiotherapy, which is known to cause toxicity.[6] Tumor site (oral cavity) is a well-recognized factor that leads to weight loss.[4] In our study, we subcategorized the tumor location within the oral cavity and assessed its significance with CWL. The tumor site within the oral cavity, such as tongue and buccal mucosa, did not show significant association with CWL ($p = 0.33$) in the univariate or multivariable analyses.

Enteral feeding via feeding tubes is still a topic of debate, especially for patients in the early stages of the disease

who undergo postoperative radiotherapy.[4] However, recent studies have shown that tube feeding is not indicated for all patients undergoing radiotherapy; rather, a careful decision should be made, especially for patients in the early stages of the disease.[4] This could be because early-stage patients undergo limited resection of the tumor followed by radiotherapy that may be well tolerated. In our study, the mode of nutrition (oral/feeding tubes) was statistically significant in univariate analysis ($p = 0.009$), and the type of feeding tube used (PEG/gastrostomy/NGT) was also significant ($p = 0.09$) but only in the multivariable analysis. However, none of these factors fit into the final model to predict CWL.

The stages of cancer are generally divided into early (stages I & II) and late (stages III & IV), and a comparison drawn between them shows that patients with advanced-stage disease are more likely to develop weight loss and also to receive enteral nutrition. We categorized our stage accordingly and the stage of disease was significant ($p = 0.03$) on multivariable analysis in the final model. The pathological T-stage was significant ($p = 0.01$) on the univariate analysis but was insignificant on the multivariable analysis. Critical weight loss in advanced-stage disease can be explained by the fact that patients undergo an extensive surgical resection involving the bone and, at times, reconstruction, thereby requiring a longer duration for healing and returning back to the normal physiology. Patients with advanced-stage disease also tend to receive radio and chemotherapy, and each of these modalities have their toxic effects.

Critical weight loss in our cohort was seen in more than 2/3 of the cases, and it could be attributed to the poor economic conditions of a developing country, lack of education and lack of proper dietary follow-up and input. We acknowledge that our study has limitations, which reside in its retrospective design. We had to exclude a significant number of cases due to loss to follow-up and missing data. Although a standardized weighing tool was used to assess weight at every follow-up visit, there could have been a slight variability given that three different clinic staff members had been assessing the weight. Given the limitations, however, our study provides insight into the nutritional status of patients under treatment at a tertiary care center in our population. Our results could be generalized given the wide range of socioeconomic classes our hospital caters to because of availability of welfare funds. Further prospective studies are needed to establish the diet plan patients follow during their course of treatment and its impact on weight loss.

Conclusion

Oral cavity carcinoma patients are at an increased risk of developing CWL over the course of their treatment. Lack of resources and poor economic conditions of a developing country further add to the challenges in maintaining good physical condition during the course of treatment. The final stages of the disease and adjuvant treatment (radio/chemotherapy) are factors that predict CWL. Special attention in terms of dietary input is required for patients with advanced-stage disease receiving adjuvant treatment.

References

1 Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer–prevalence and risk factors at diagnosis: an explorative study. Support Care Cancer 2007;15(09):1045–1050
2 Langius JA, Bakker S, Rietveld DH, et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. Br J Cancer 2013;109(05):1093–1099
3 Laviano A, Meguid MM, Rossi-Fanelli F. Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. Lancet Oncol 2003;4(11):686–694
4 Nourissat A, Bairati I, Samson E, et al. Predictors of weight loss during radiotherapy in patients with stage I or II head and neck cancer. Cancer 2010;116(09):2275–2283
5 Bhurgri Y. Cancer of the oral cavity - trends in Karachi South (1995-2002). Asian Pac J Cancer Prev 2005;6(01):22–26
6 Langius JA, Doornaert P, Spreeuwenberg MD, Langendijk JA, Leemans CR, van Bokhorst-de van der Schueren MA. Radiotherapy on the neck nodes predicts severe weight loss in patients with early stage laryngeal cancer. Radiother Oncol 2010;97(01):80–85