Original Article

The importance of weight loss during definitive radiotherapy in patients with laryngeal carcinoma

ABSTRACT

Background: The aim of this study is to determine the prognostic significance of weight loss (WL) on overall survival (OS) and progression-free survival (PFS) in patients with locally advanced unresectable laryngeal carcinoma undergoing definitive radiotherapy (RT) or chemo-RT (CRT) in a single institution.

Patients and Methods: One hundred and thirty-two patients with newly diagnosed locally advanced laryngeal carcinoma were included in this study retrospectively. All patients were treated with definitive RT or CRT. The tumor and metastatic lymph nodes received 70 Gy. Subclinical disease (low-risk and high-risk area) was irradiated 50–60 Gy prophylactically. Unintentional WL ≥5% was defined as the "critical level." Bodyweight was evaluated on the 1st day of RT and once a week during RT. Caloric needs were calculated as 25–30 kcal/kg/day.

Results: Median follow-up was 17.8 months (range: 2.35–85 months). During treatment, there was a statistically significant WL in patients ($P = 0.004$). WL was ≥5% in 62 (47%) of the patients. There was a statistically significant relationship between WL and tumor differentiation ($P = 0.004$), completion of treatment ($P = 0.004$), WHO performance status ($P < 0.0001$), T stage ($P = 0.003$), N stage ($P = 0.049$), and supraglottic tumor location ($P = 0.005$). In the univariate analysis, WL, WHO performance status, T stage, N stage, tumor localization, and tumor differentiation, were seen to affect OS. Additionally, WL, WHO performance status, N stage, and tumor differentiation were prognostic factors for PFS. In the multivariate analysis, it was observed that only WL and WHO performance status were significant factors for both OS ($P = 0.001$, and $P < 0.01$) and PFS ($P < 0.001$, and $P < 0.001$), respectively. Three-year OS and PFS was 50.3% and 19.5% for patients with WL versus 77.8% and 49.0% for patients without WL.

Conclusions: It is clear that WL has prognostic significance in patients who have undergone definitive RT or CRT due to locally advanced laryngeal carcinoma. In particular, it should be taken into consideration that patients with supraglottic tumor, lymph node involvement, and poor performance status are at greater risk for WL.

KEY WORDS: Laryngeal carcinoma, radiotherapy, weight loss

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INTRODUCTION

Head-and-neck cancer (HNC) has a prevalence of around 3%–4% worldwide. Definitive Radiotherapy (RT) or Concurrent chemo-radiotherapy (CRT) are the main treatment options for patients who do not undergo surgery. Mucositis, taste impairments, dysphagia, odynophagia, and nausea, related to the disease or treatments, are common side effects resulting impaired oral intake, weight loss (WL), and malnutrition.[1] Serious WL, defined as WL ≥5% in the last 1 month or WL ≥10% in the past 6 months, can be seen in 20%–50% of the cases at the beginning of treatment, but the percentage may increase to 88% during treatment.[2-8] Nutritional problems deteriorate patient's quality of life, immunity and treatment compliance, and all these affect the treatment results negatively.[4,9]

Although it has been stated in most studies that WL is one of the important prognostic factors on treatment results of patients with HNC, it is hard to say that there is a malnutrition risk in all subgroups of HNC. In studies conducted, the importance of WL in the oral cavity and oropharyngeal cancer has been evaluated as subgroup.[3,10] The relation

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between WL and progression-free survival (PFS) or overall survival (OS) needs to be further evaluated in different subgroups of HNC patients. In the literature, there is only one study examining the prognostic significance of nutritional status in laryngeal carcinoma, in which the factors affecting malnutrition in early-stage laryngeal carcinomas were evaluated.[5] The aim of the present study was to determine the prognostic significance of and factors affecting WL during treatment in patients with locally advanced unresectable laryngeal carcinoma treated with definitive RT or CRT.

PATIENTS AND METHODS

Between January 2010 and December 2015, 132 patients with newly diagnosed locally advanced laryngeal carcinoma were included in this study and were analyzed retrospectively. The inclusion criteria of the study were as follows: Patients with pathological SCC of larynx who underwent complete staging procedures received definitive RT and obtained nutritional information, including height and pre-treatment body weight. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Radiotherapy

All patients were treated with three-dimensional conformal RT (CRT) or intensity-modulated RT. Whole RT treatment volumes were determined using computed tomography (CT) and/or positron emission tomography (PET)-CT scans. Patients were treated with thermoplastic masks to ensure immobilization and repeatability during treatment. The tumor and metastatic lymph nodes received 70 Gy in five weekly fractions of 1.8–2.0 Gy. Subclinical disease (low-risk and high-risk area) was irradiated 50–60 Gy (1.8–2.0 Gy/fraction) prophylactically.

Chemotherapy

Cisplatin 75–100 mg/m^2 was given with 21-day intervals or 30 mg/m^2 in weekly intervals (with consideration to the age and renal functions) and was administered intravenously during RT treatment.

Nutritional assessments

Bodyweight (kg) was measured in the morning on an empty stomach with light clothes and without shoes on the first day of RT and once a week during RT. WL was calculated based on the equation: (current weight-usual weight)/usual weight × 100%.[11] Caloric needs were calculated as 25–30 kcal/kg/day. Diet counseling was given to all patients at the start of treatment. If patients had insufficient caloric intake, they received oral nutritional supplements (ONS). If the oral intake was not feasible, percutaneous gastrostomy (PEG) or supplemental parenteral nutrition (S-PN) was used for feeding. S-PN 1000 kcal/day was given three times a week by peripheral vascular route. Unintended "critical level" WL was defined as a WL of ≥5% in the past 1 month. Body mass index (BMI) and the cutoff values for BMI were calculated based on the European Society for Clinical Nutrition and Metabolism guidelines. The patients were divided into three groups based on their BMI; underweight (BMI < 20), normal (BMI = 20–25), and overweight (BMI ≥ 25).[12] Nutritional assessment was performed weekly using the Nutritional Risk Screening Score 2002 (NRS-2002).[13]

Follow-up

During RT, patients were seen every week. Acute and delayed toxicities arising from RT were reported according to standard RTOG criteria. Assessment of tumor response was performed according to "Response Evaluation Criteria in Solid Tumors" guideline 3 months after the end of treatment.[14] CT or PET-CT was performed for response evaluation 3 months after the completion of treatment. Following treatment, all patients underwent a complete head and neck examination that included flexible fiberoptic laryngoscopy, head-and-neck CT and chest radiography every 3 months for the first 2 years, every 6 months for years 2–5, and then annually thereafter. The disease detected in the first 6 months after the completion of the treatment in the primary disease area or neck was defined as "persistent disease" and disease detected after >6 months as "recurrent disease," and their radiological extensiveness was verified by biopsy.

Statistical analyses

The primary endpoint of the study was to determine whether WL seen during treatment has an impact on PFS and OS in patients with laryngeal carcinoma who received definitive RT. The secondary endpoint was to determine the clinical factors related to the patient and the disease that may be associated with WL during treatment in these patients. PFS was measured from the first day of treatment until the date of disease progression locally, regionally, or distantly. OS was estimated from the date of diagnosis until the date of death or the last contact date. Clinical and therapeutic factors as well as tumor characteristics were first analyzed using univariate summary tables (absolute and relative frequencies) that were used for descriptive analysis of categorical variables. As central value, average and its 95% confidence intervals (CIs) or median and its min-max values were used for continuous variables. When appropriate, the Chi-square two-tailed test was used for comparative analysis between categorical variables. Factors that seemed determinant were subsequently evaluated using the Kaplan–Meier survival curves and by the log-rank test. Finally, the significant factors in univariate analysis were tested in multivariate analysis using Cox's proportional hazard models. The relationship between WL and clinical factors related to the patient and the disease was determined by Pearson's correlation analysis. WL during treatment was evaluated using the repeated measures ANOVA method. A two-sided 5% significance level was used for the comparisons of the groups.

RESULTS

The median follow-up was 17.8 months (range: 2.35–85 months). Median PFS was 16.2 months (range: 1–81.7

months). By the time of analysis, 62 (64%) patients had died. Patient demographics and baseline disease characteristics are listed in Table 1. All patients received definitive RT. All of the patients underwent biopsy only before initiation of the treatment. The median age was 62.6 (range: 36–84 years). 123 (93.2%) of the patients were male. All of the patients had squamous cell carcinoma, and 86 (65.2%) patients had grade 2–3 malignancy. Seventy-six (57.6%) patients had the WHO performance score 0-1, and the remaining 56 (42.4%) patients had the WHO performance 2. The majority of tumors were in the supraglottic region (77.3%). Seven (5.3%) patients did not complete the treatment. One hundred-three (78%) patients had T3–4 disease, 62 (47%) patients had N(+) disease, 73 (55.3%) patients had Stage IV disease. 113 (85.6%) received concurrent chemotherapy. The median treatment time was 53 days (12–73 days).

All patients received ONS 300 kcalx2–3 to meet their insufficient calorie requirements during treatment. Nasogastric tube was inserted in 4 (3%) patients with insufficient oral intake and PEG was inserted in 6 (4.5%) patients and additional enteral nutritional support was given. The total number of patients who received S-PN was 117 (88.6%) and all patients with Stage IV received S-PN.

During treatment, statistically significant WL occurred in the patients ($P = 0.004$). WL was ≥ 5% in 62 (47%) of the patients. There was a statistically significant relationship between WL and tumor differentiation ($P = 0.004$), completion of treatment ($P = 0.004$), WHO performance status ($P < 0.0001$), T stage ($P = 0.003$), N stage ($P = 0.049$), and supraglottic tumor location ($P = 0.005$). There was no statistically significant relationship between WL and the disease being Stage III versus Stage IV ($P > 0.05$) or the patient receiving simultaneous CT ($P > 0.05$).

Median pre-treatment BMI was 23.7 (17.3–32.7). BMI was <20 in 47 (35.6%) patients at the end of the RT. BMI is not a prognostic parameter affecting PFS ($P > 0.05$) or OS ($P > 0.05$).

In univariate analysis, WL, WHO performance status, tumor differentiation, T stage, N stage, and tumor localization were seen to affect OS [Table 2], whereas just WL, and WHO performance status were significant on PFS [Table 3]. In multivariate analysis, WL and WHO performance status were found prognostic on both OS [Table 2] and PFS [Table 3]. Three-year OS was 50.3% for patients with WL versus 77.8% for patients without WL ($P = 0.001$) [Figure 1]. Three-year PFS was 19.5% for patients with WL versus 49.0% for patients without WL ($P = 0.01$).

Table 1: Patient characteristics

Characteristic	Number of patients (%)
Gender	
Male	123 (93.2)
Female	9 (6.8)
Tumor differentiation	
Grade I	33 (37)
	24 (18.1)
Grade II–III	26 (29)
	86 (65.2)
Unknown	30 (34)
	22 (16.7)
WHO PS	
<2	76 (57.6)
2	56 (42.4)
Tumor localization	
Supraglottic	102 (77.3)
Others	25 (18.9)
Unknown	5 (3.8)
Completion of treatment	
Yes	125 (94.7)
No	7 (5.3)
Weight loss	
<5%	70 (53)
≥5%	62 (47)
T stage	
T2	29 (22)
T3–T4	103 (78)
N stage	
N0	70 (53)
N(+)	62 (47)
Stage	
Stage III	59 (44.7)
Stage IV	73 (55.3)

WHO PS=World Health Organization Performance Status

DISCUSSION

The main findings of the present study were: (i) Critical WL was observed during RT in our patient group consisting only of patients with laryngeal cancer. (ii) Critical WL was an independent adverse prognostic factor in multivariate analysis on both PFS and OS.

When making a treatment decision in HNC patients, TNM stage is taken into consideration and factors that may affect the treatment results such as age, WHO performance status and whether there is malnutrition are overlooked.

Malnutrition is a common problem in patients undergoing definitive RT or CRT. When it occurs during the course of treatment, it adversely affects not only the quality of life of the patient but also treatment compliance as well as the patient's prognosis. However, in studies conducted, HNC patients are frequently evaluated as a whole, while the studies in subgroups are generally limited to the oral cavity and oropharyngeal cancers. Our study differs from the current literature in that it only includes patients with laryngeal cancer.

WL is an important parameter indicating malnutrition. WL seen in patients receiving RT occurs with a process in which many factors such as tumor-related causes, treatment side effects, and factors related to nutritional status are involved. Demographic factors have also been investigated in many recent studies. Studies have reported that WL is mostly seen in oropharyngeal tumors and patients receiving adjuvant chemo-RT. However, the effects of age, cancer stage,

Table 2: Prognostic factors for overall survival

Prognostic factor	Number of patients	Median OS (months)	Univariate analysis (*P*)	Multivariate Cox regression (*P*)
Weight loss				
<5%	70	*	<0.001	0.001
≥5%	62	12±2.6		
WHO PS				
0–1	76	62.7±4.8	<0.001	<0.001
2	56	13.9±1.3		
T stage				
T2	29	*	0.001	>0.05
T3–T4	103	15.4±2.5		
N stage				
N0	70	23±2	<0.001	>0.05
N (+)	62	6.2±0.6		
Tumor localization				
Supraglottic	102	16.9±2.5	0.023	>0.05
Others	30	*		
Tumor differentiation				
Grade I	24	*	<0.001	>0.05
Grade II-III	88	11.3±1.1		
Unknown	22	16.7±3.7		

*Median OS didn't reach 0.5. WHO PS: World Health Organization Performance Status, OS=Overall survival

Table 3: Prognostic factors for progression-free survival

Prognostic factor	Number of patients	Median PFS (months)	Univariate analysis (*P*)	Multivariate Cox regression (*P*)
Weight loss				
<5%	70	15.4 ± 5.3	<0.001	0.01
≥5%	62			
WHO PS				
0–1	76	*	<0.001	<0.001
2	56	15 ± 2.1		
N stage				
N0	70	24 ± 4.4	0.04	>0.05
N(+)	62	3.6 ± 0.7		
Tumor differentiation				
Grade I	24	*	<0.001	>0.05
Grade II-III	88	22.4 ± 3.5		
Unknown	22	13.2 ± 2.9		

*Median PFS didn't reach 0.5. PFS = Progression free survival, WHO PS: World Health Organization Performance Status

pre-treatment WL and total RT dose on WL are not consistent.[15] In our study, the factors affecting WL during definitive RT or CRT of laryngeal carcinomas and its prognostic significance were evaluated. It was found that WL during treatment was affected by tumor differentiation, WHO performance at the beginning of treatment, localization of the tumor, T, and N stage.

In HNC patients, malnutrition may be related to treatment-related toxicity (e.g., xerostomia or dysphagia), or it may develop secondary to inflammation caused by the tumor itself or treatments.[1,2] Malnutrition rates of 20%–50% at the start of treatment can increase to 88% during treatment.[1,5] In our study, WL ≥5 was seen in 62% (47%) patients during treatment ($P = 0.004$). In the study by Langius *et al*. involving laryngeal carcinomas as well, the rate of WL during treatment was 57%.[5] Compared to the series that includes all HNC patients, the rate in our study was acceptable. The results may be heterogeneous since the same WL criteria were not used in all studies.[16] All of our patients were given ONS to meet their insufficient calorie needs, and 10 (7.5%) patients with insufficient oral intake were given enteral nutritional support. Nutritional supportive therapy was given to 117 (88.6%) patients with insufficient oral and/or enteral intake with S-PN. The continued WL, despite the nutritional supplement we provided caused us to review the nutritional policy of our clinic.

Subgroup analysis of the current literature shows that patients with laryngeal tumors experience less WL.[17] The probable reason for this is that cases with laryngeal cancer are relatively in the early stages. Thus, early-stage tumors have less negative effects on nutrition, and treatment-related WL is less common because they are treated from a more limited area. We think that the reason we saw significant WL in our patients is that, unlike other studies, there is a significant proportion of advanced-stage patients in our patient group (78% of patients had T3–4 disease, and 47% of patients had N (+) disease). Moreover, the majority of tumors were in the supraglottic region (77.3%), and there is a statistically significant relationship between WL and supraglottic localization. In the study of Jager-Wittenaar *et al*., WL was

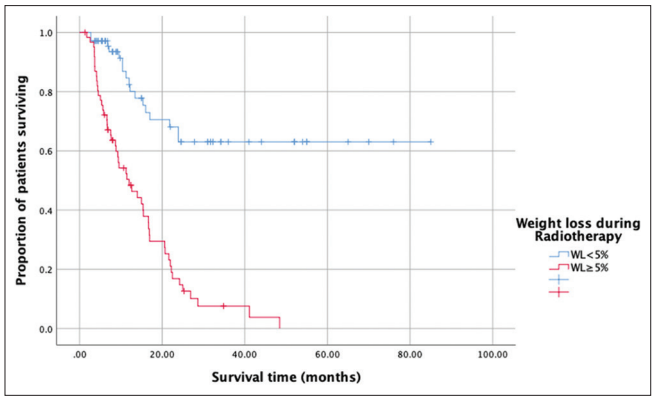

Figure 1: Weight loss was a statistically significant prognostic factor for OS ($P = 0.001$). Kaplan–Meier curves for OS. OS=Overall survival

most frequently seen in patients with laryngeal carcinoma whose tumors were located in the supraglottic area. The fact that the tumor is supraglottic and advanced in the majority of patients significantly impairs oral intake.[18]

The effects of WL resulting from malnutrition on survival have been reported in many studies. It was first reported by Regueiro *et al*. that pre-treatment WL affects disease-related survival in patients with head-and-neck cancer.[19] In that study, it was determined that pre-treatment WL in patients with oropharynx cancer is an independent predictor of disease-specific survival with 2.3 hazard ratio.

There are several studies with those investigating the survival effect of WL during RT. While WL was observed to affect disease-free survival in all of these studies, no effect on OS was detected. In the study of Cho *et al*., in patients with oral cavity and oropharynx cancer, WL of >10% during and 1 year after treatment was seen to be an independent factor on disease-free survival (hazard ratio 2.2), but its effect on OS was not detected.[20] Similarly, in the study of Langius *et al*., it was seen in the univariate analysis that severe WL during RT led to worse 5-year survival, but this significance was lost in multivariate analysis.[21] However, it was observed that severe WL was an independent prognostic factor on 5-year disease-free survival, and persisted in the multivariate analysis. The reason behind the fact that WL leads to worse disease-free survival outcomes maybe that treatment is less effective in this patient group. Another factor that strengthens RT to cause cell death by causing DNA damage is the antitumor immune response. In malnourished patients with insufficient nutritional intake, this antitumor immune response may be impaired.[21] In our study, WL during treatment was found to be a significant independent prognostic factor on both OS and PFS in multivariate analysis. With this result, our study differs from the literature. One reason for this may be that our study only included patients with laryngeal cancer. It is well known that unlike other head-and-neck tumors, the most important factor determining OS in laryngeal cancer is the success of treatment on local disease. In our study, we think that a factor such as WL that negatively affects the success of local disease treatment may have also negatively affected OS. Nevertheless, it would be beneficial for us to consider this significance with caution regarding the OS found in this study. This is because our retrospective study is limited both in terms of the number of patients and the short follow-up period.

BMI is one of the frequently used measures for evaluating nutritional disorders.[12] The importance of BMI in HNC patients at the start of RT was analyzed in a few studies. Ottosson *et al*., found that patients with higher BMI had higher 5-year survival rates at the start of RT (58.8% and 56.7%, respectively; $P < 0.001$).[22] Another study by McRackan showed that the recurrence rate increased ($P = 0.026$) and OS decreased ($P = 0.043$) in patients with a BMI ≤25.[23] However, Platek *et al*. reported that pretreatment BMI was not a statistically significant prognostic factor for disease progression.[9] BMI affected neither disease progression nor OS in our study.

Pre-treatment performance status is one of the most important prognostic factors in HNC patients treated with RT or CRT. Mangar *et al*. determined that pre-treatment performance status was a significant prognostic factor in determining enteral nutritional status during treatment.[24] In the study of Langius *et al*., however, no prognostic significance of the WHO performance status was found in determining the nutritional status in the laryngeal carcinoma subgroup.[5] In this study, there was a statistically significant relationship between the WHO performance status and WL. We believe that the finding may be associated with the fact that patients with locally advanced disease were evaluated, unlike Langius's study, although only laryngeal carcinoma patients were evaluated in both studies.

Many studies have shown that giving concurrent CRT was a strong risk factor that increases the risk of developing malnutrition.[7,25] Combined modality treatment increases WL by increasing treatment toxicity. In this study, concurrent chemotherapy was not a factor that increased WL. We think that this finding may be associated with the fact that 113 (85.6%) patients had received concurrent chemotherapy.

Our study has some limitations. First, the study was retrospective, the number of cases was small and follow-up time relatively short. Second, neck irradiation was not the same in every patient because the N stage was different although all patients had locally advanced disease. Therefore, dysphagia may show heterogeneity among patients due to dose distribution. Third, ONS compliance was 30% on average and patients may have hidden the fact that they were not following their therapy.

CONCLUSIONS

It is clear that the effect of RT or CRT is inadequate, and the prognosis of the patient is poor in patients with insufficient

nutrition. WL is a common symptom in laryngeal carcinomas due to dysphagia and similar side effects. Performance status, supraglottic involvement, and tumor extensiveness are risk factors for malnutrition. Critical WL was an independent adverse prognostic factor in multivariate analysis on both PFS and OS.

Therefore, all patients should be monitored regularly for nutritional aspects at the beginning and during treatment. Further prospective studies are strongly needed to assess the impact of WL on survival in patients with head and neck cancer.

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Conflicts of interest
There are no conflicts of interest.

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