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"Rare Head and Neck Tumors"

Retrospective Study

Corresponding author
Gus J. Slotman, MD
Director of Clinical Research
Inspira Health Network
1505 West Sherman Avenue
Suite B, Vineland, NJ 08360, USA
Tel. 856-641-8635
Fax: 856-641-8636
E-mail: SlotmanG@ihn.org

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Survival is Increased in Patients Developing Severe Weight Loss During Concommitant Chemotherapy and Radiation Therapy for Advanced Operable Stage III and IV Squamous Cell Carcinoma of the Head and Neck

Casey Sheck, DO; Jessica Tyrrell, BS; Michael Davis, DO; Paul Boulos, DO; Jeffrey Emrich, DO; Janette Gomez, DO; Jill Darminio, MD; Leon Kushnir, MD; Gus J. Slotman, MD*

Department of Surgery, Inspira Health Network, Vineland, NJ 08360, USA

ABSTRACT

Background: Severe malnutrition is common during chemo-irradiation for advanced squamous cell carcinoma of the head and neck (SCCHN).
Objective: To determine whether or not severe weight loss during chemo-irradiation adversely affects outcomes.
Methods: Records of 49 patients with SCCHN who underwent chemo-irradiation with fractionated cisplatin (CTRT) were examined in two groups: <7.5% weight loss (Non-Severe CTRT Weight Loss (NSCWL); n=9) and >7.5% loss (severe CTRT weight loss (SCWL); n=40). Statistics were by Chi-squared, ANOVA, and Kaplan-Meier.
Results: SCWL *versus* NSCWL weight loss was -17.23%±7.90% *vs*. -2.11%±4.04%, (p< 0.0001). Toxicity, tumor response and the need for radical surgery did not vary significantly. Overall and disease-free survival (DFS) favored SCWL (p=0.002). Median overall survival was 12.5 and 83.8 months for NSCWL and SCWL, respectively.
Conclusion: Severe weight loss during CTRT for advanced SCCHN does not increase morbidity but rather increases overall and DFS. These findings suggest a biologic interaction between CTRT-related host weight loss and SCCHN outcomes.

KEY WORDS: Head and Neck Cancer; Cisplatin; Radiation therapy; Squamous cell carcinoma; Malnutrition; Weight loss.

ABBREVIATIONS: SCCHN: Squamous Cell Carcinoma of the Head and Neck; CTRT: Chemo-irradiation with fractionated cisplatin; SCWL: Severe CTRT Weight Loss; CAC: Cancer Associated Cachexia; PEG: Percutaneous Endoscopic Gastrostomy; OS: Overall Survival; DFS: Disease-Free Survival.

INTRODUCTION

The nutritional support of SCCHN patients provides a challenge unique to this population, as weight loss is often multifactorial.[1-3] Nausea, vomiting, and altered taste sense commonly preclude adequate nutritional intake in cancer patients.[4] Cancer associated cachexia (CAC), a dysregulation of host inflammatory responses, leads to marked and rapid decrease in skeletal muscle and white adipose tissue mass.[5] While these issues face nearly all cancer patients, dysphagia is a well-recognized cause of malnutrition in those being treated for SCCHN.[6,7]

Previous investigations have associated weight loss prior to initiation of treatment for SCCHN with decreased overall survival.[8-11] However, whether or not weight loss during si-

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multaneous chemotherapy and radiation therapy in the treatment of SCCHN adversely influences outcomes is unknown. Some large studies have reported poor cancer specific survival, overall survival, and disease-free survival (DFS) with severe weight loss during chemo-irradiation.[11-13] Others, however, observed no statistically significant association between weight loss during multi-modality cancer therapy and survival; however, a trend towards improved response to therapy with patients losing >5% of their starting body weight has been reported.[8] One recent study has shown improved outcomes with the objective of this study to evaluate the effects of severe weight loss during uniform CTRT in patients with advanced, operable Stage III and IV SCCHN.

PATIENTS AND METHODS

With the approval of the Inspira Health Network's Institutional Review Board (IRB), records of 49 patients with Stage III and IV, clinically operable SCCHN who underwent high-dose radiotherapy and concomitant chemotherapy (CTRT). Those patients with pre- and post-CTRT weights as well as percutaneous endoscopic gastrostomy (PEG) placement, nutritional consultation/follow-up were included in the study.

Patients were divided into either the Severe CTRT Weight-Loss (SCWL) group if they lost >7.5% of pre-treatment weight at the conclusion of CTRT or the Non-Severe CTRT Weight-Loss (NSCWL) group if the lost <7.5% per NIH/Academy/ASPEN malnutrition and weight-loss definitions.[14] It is from here that the two groups were compared. Data were examined retrospectively. Study variables included age at diagnosis, pre-treatment weight, posttreatment weight, tumor site, grade, and stage, CTRT toxicity, clinical response, post-CTRT biopsy result, recurrence, overall survival (OS), DFS, surgeries performed, and disease status upon expiration. Clinical staging was by the classification of the American Joint Committee on Cancer Staging.[15] Toxicity to treatment was determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events. After CTRT, panendoscopy with biopsy was performed. Clinical complete response (CCR) was defined as the resolution of visible tumor while histologically complete response (HCR) was defined by negative biopsy results.

CTRT chemotherapy consisted of preoperative cisplatin, 20 mg/M^2 for four consecutive days during weeks 1, 4, and 7 of radiotherapy. Over the course of the study (2001-2011), the radiation therapy technique varied as the technology changed. In the earlier portion of the study, patients were treated with a regimen consisting of single daily fractionation with 6 MV photons and 3D treatment planning followed by a boost, in which they were treated with a hyperfractionated (two fractions/day) regimen with concurrent chemotherapy. In 2006, patients were treated with normal fractionation to a higher total dose, between 70-74 Gy. In the latter part of the treatment study, the patients were treated with a field-within-a-field technique utilizing head and neck intensity modulated radiotherapy (IMRT). Planning target volumes (PTVs) were treated between 70-74 Gy. Most treatment regimens were delivered with 6 MV photons with either customized blocks or multi-leaf collimator generated blocks. Verification was performed using port films and later changed to stereoscopic imaging followed by cone beam computed tomography (CT).

Statistical analysis was performed using the chi-square equation, ANOVA, and Kaplan-Meier logarithmic rank test. (SAS/STAT(R) 9.22 User's Guide).

RESULTS

Pre-CTRT data is displayed in Table 1. As per study design, % weight loss was significantly greater in the SCWL group than NSCWL (-17.23%±2.45% *vs.* -2.11%±2.64%, CI 95%, p<0.0001). Pre-CTRT age in years, stage, tumor grade, and

Table 1: Pretreatment Demographics.

	NSCWL (σ)	SCWL(σ)	*p* value
Mean Age at Diagnosis (yrs)	61.20 (11.04)	60.10 (10.37)	NS (0.79)
Mean Starting Weight (lbs)	145.00 (34.75)	182.55 (42.38)	< .05
Mean Weight Change (lbs)	-3.67 (6.18)	-32.20 (19.68)	<.0001
Mean Weight Change (%)	-2.11% (4.04)	-17.23% (7.90)	<.0001
	NSCWL (%)	**SCWL(%)**	
Clinical Stage			
III	3/9 (33.3%)	14/40 (35.0%)	NS (0.17)
IVa	5/9 (55.6%)	19/40 (47.5%)	
IVb	1/9 (11.1%)	6/40 (15.0%)	
IVc	0/9 (0.0%)	1/40 (2.5%)	
Primary Location			
Oral/Pharynx	4/9 (44.4%)	9/40 (22.5%)	NS (0.40)
Tongue/Hypopharynx	4/9 (44.4%)	25/40 (62.5%)	
Larynx	1/9 (11.1%)	6/40 (15.0%)	

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Table 2: Response to Pre-Operative Treatment.

	NSCWL (%)	SCWL(%)	*p* value
Toxicity to CTRT			
NCI toxicity grade			
1	4/9 (44.4%)	17/40 (42.5%)	NS (0.18)
2	3/9 (33.3%)	11/40 (27.5%)	
3	2/9 (22.2%)	12/40 (30.0%)	
4	0	0	
5	0	0	
Tumor response	**NSCWL (%)**	**SCWL(%)**	***p* value**
Clinical response			
Clinically complete	5/9 (55.6%)	30/40 (75.0%)	NS(0.25)
Partial	4/9 (44.4%)	10/40 (25.0%)	
Biopsy result			
Histologically complete	5/9 (55.6%)	30/40 (75.0%)	NS(0.25)
Residual disease	4/9 (44.4%)	10/40 (25.0%)	
Recurrence			
Reoccured	4/9 (44.4%)	12/40 (30.0%)	NS (0.45)
No reoccurance	5/9 (55.6%)	28/40 (70.0%)	

toxicity to CTRT did not vary significantly as of between NSCWL and SCWL. Primary tumor site for NSCWL *vs*. SCWL, Oral cavity/pharynx (44.4% *vs*. 22.5%), Tongue/Hypopharynx (44.4% *vs*. 62.5%), and Larynx (11.1% *vs*. 15.0%) did not vary significantly.

Results of CTRT treatment regimen and follow-up are listed in Table 2. CCR was achieved in 30/40 (75%) of SCWL and in 5/9 (56%) of NSCWL patients. HCR was identified in 30/30 SCWL and 5/5 NSCWLCCR patients who underwent post-CTRT biopsy. Major cancer operations were required in 2/40 (5%) of SCWL, and in 1/9 (11%) of NSCWL patients. SCCHN recurred in 12/40 (30%) of SCWL and 4/9 (44%) of NSCWL patients. All recurrences were local/regional. Raw survival was 25/40 (62.5%) of SCWL and 4/9 (44%) of NSCWL patients.

Figures 1 and 2 display the Overall and Disease-Free Kaplan-Meier survival curves, respectively. Median overall survival time was 12.5 months for NSCWL patients and 83.8 months for SCWL patients ($p<0.002$). DFS also was increased among SCWL patients, with <50% expired, *versus* median survival time of 38.7 months for NSCWL.

DISCUSSION

The results of this study indicate that developing severe weight loss and malnutrition during CTRT for Stage III and IV SCCHN not only has no detrimental effects on CTRT toxicity, tumor response, or the need for radical surgery, but is associated also

Figure 1: Overall Survival Kaplan Curve for Severe Treatment Weight Loss (STWL) and Non-Severe Treatment Weight Loss (NSTWL) groups. SCCHN=Squamous Cell Carcinoma of the Head and Neck.

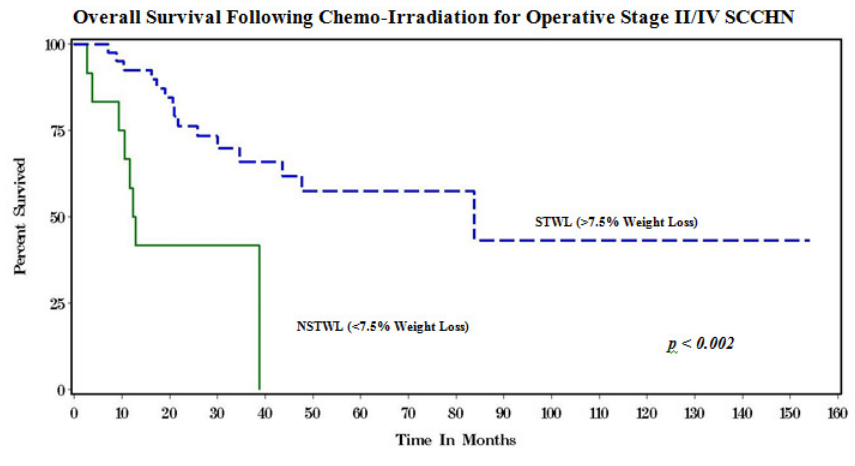

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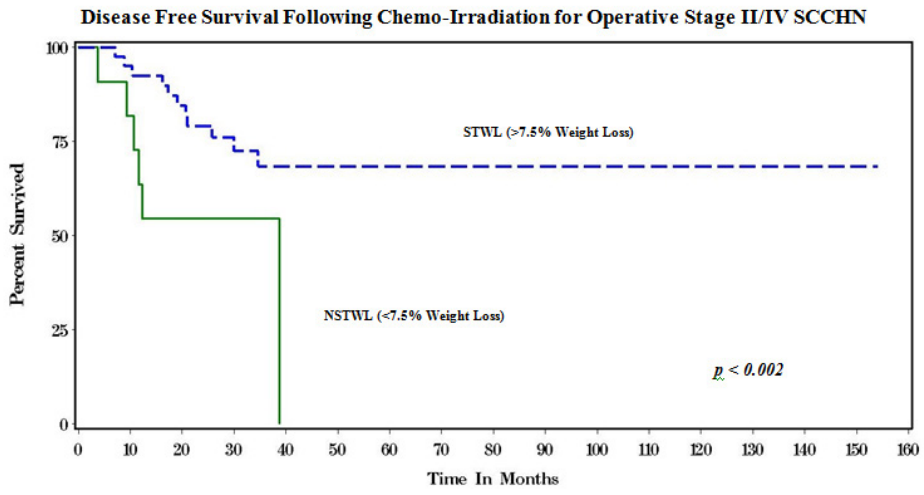
Figure 2: Disease Free Survival Kaplan Curve for Severe Treatment Weight Loss (STWL) and Non-Severe Treatment Weight Loss (NSTWL) groups. SCCHN=Squamous Cell Carcinoma of the Head and Neck.



with increased overall DFS. Toxicity to chemo-irradiation was not significantly different between SCWL and NSCWL. While not statistically significant, tumor response to CTRT was numerically superior in SCWL compared to NSCWL, with CCR responses of 75% *vs*. 56%, respectively, and HCR 75% *vs*. 56%. The need for radical surgery was not increased among SCWL patients compared with NSCWL (8% *vs*. 11%). Recurrence was numerically decreased in SCWL *vs*. NSCWL (30% *vs*. 44%). All recurrences were local/regional, including one patient in the SCWL group who developed a metachronous metastasis to the left neck from the left pyriform sinus. These outcomes were not related to unequal distribution of primary tumor sites, as anatomic location did not differ, but not significantly between SCWL and NSCWL. Both overall survival and DFS were increased greater than 6-fold for SCWL compared with NSCWL with median survival time for disease free and overall at 83.8 months *vs.* 12.5 months (p<0.002) respectively. Our review of the literature indicates that the increased survival of patients who became severely malnourished during CTRT, without concomitant excessive toxicity or need for radical surgery, has not been reported previously and is a significant finding of this study.

Both the SCWL and NSCWL groups had equivocal events graded by NCI toxicity with Grade 1 (42.5% *vs.* 44.4%), Grade 2 (27.5% *vs.* 33.3%) and Grade 3 (30% *vs.* 22.2%) respectively. Neither group experienced Grade 4 or Grade 5 events. These findings contrast witha retrospective study by Meyer et al[16] who reported significant increased toxicity in patients with SCCHN who lost weight during radiotherapy. The majority of toxicities reported in SCCHN patients results from radiotherapy and its sequelae. With our patient population, all had PEG placement, which could reduce the reporting of toxicity related complications that can be overcome with utilization of alternate pathway enteral feeding, i.e., mucositis, and dysphagia.

Primary tumor location did not vary significantly between SCWL and NSCWL groups. Primary tumor locations were found in the SCWL group and NSCWL group to be: Oral cavity/pharynx (44.4% *vs*. 22.5%), Tongue/Hypopharynx (44.4% *vs*. 62.5%), and Larynx (11.1% *vs*. 15.0%). This is important as previous investigations observed that tumors located in the tongue/hypopharynx tended to be more aggressive and had poorer outcomes overall.[17] In addition, tumors of the oropharynx port end a more drastic weight loss.[18] The absence of variation in primary tumor site among the patients examined here indicates that the results were related more directly to their nutritional response during CTRT.

One might have speculated that severe weight loss during CTRT would result in poor tumor response and increased recurrent disease; however, in this investigation SCWL patients did not fare worse than NSCWL, but had numerically superior CCR and HCR (75% *vs*. 25%), and recurrence (30% *vs*. 44%) rates. Significant results have been seen with pre-treatment weight loss groups by Ghadjar et al, who reported that pre-treatment weight loss >10% body weight for SCCHN increased the rate of local or regional treatment failure with a hazard ration of 2.5 (p=0.002).[8] As seen in our study Ghadjar et al also reported weight loss during treatment was associated with slightly but not significantly improved outcomes for weight loss of >10%[8] in regards to local or nodal progression or recurrence or death as a result from tumor. Those investigators also reported significantly decreased distant metastasis free survival with weight loss before treatment of >5-10% and >10% as well as a non-significant survival benefit in the weight loss during treatment groups of >5-10% and >10%.

The most significant finding from this study was increased OS and DFS among the SCWL patients compared with the less malnourished NSCWL group. This was manifested in an overall median survival time of 83.6 months for SCWL patients *versus* 12.5 months in the NSCWL group (p<0.002). This finding is clinically significant as our review of the literature did not

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identify any other investigation that reported increased OS or DFS in patient groups who experienced significant weight loss during chemo-irradiation or radiotherapy alone. In fact, previous papers described either decreased OS or DFS for patients with critical weight loss or at least no significant difference. Langius et al. reported 5 year OS and disease specific survival for patients with >5-10% weight loss during radiotherapy at 62% and 82% compared to 70% and 89% for patients without critical weight loss.[17] Ghadjar et al report no significant effects of weight loss during chemo-irradiation treatment on OS or cancer-specific survival.[8]

With this significant and unique finding the mechanism of weight loss in SCCHN patients, nutrition, and the impact on survival must be analyzed. Malnutrition and cachexia are associated with poor response to treatment, and increased morbidity and mortality rates in SCCHN patients,[19-22] affecting as many as 63% before initiation of treatment[23-28] and significant weight loss is seen in 38% to 82% of those with advanced disease.[4] To combat these findings PEG are placed in select patients. The University of Michigan Oncology, General Surgery and Nutritional services in 1996 noted increased admissions for dehydration, weight loss and malnutrition of HNC patients which lead to PEG protocols for these patients.[29] It has been shown that after weight loss in HNC patients placement and use of PEG can arrest weight loss.[29] With these findings it is interesting that PEG placement and tube feeding use in HNC patients varies greatly from 4-60%.[30]

With such drastic improvement of weight loss after PEG placement reported[29] it is interesting that severe weight loss developed in 40 of 49 patients evaluated in this study, the SCWL group, as all 49 patients underwent PEG placement and had access to nutritional support at home. Of the 49 patients only 6 (12%) reported not using any tube feeds or having the PEG tube removed and of these only 1 patient who did not use a PEG did not use oral nutritional supplementation. With such access to enteral nutrition it is intriguing that the effort not only did not allay malnutrition during treatment and yet the excessive weight loss still resulted in better OS and DFS.

It is known that metabolically hyperactive tumors produce an inflammatory cascade resulting in a hypermetabolic patient state. It is hypothesized from the result in this study that this may be causing increased weight loss despite adequate nutritional intake efforts. However, while these tumors may have inherent resistance to radiation therapy, they may be more susceptible to the radiation and chemotherapeutic treatment studied here. The rapidly dividing tumor cells may have increased uptake of chemotherapeutic agents compared to the senescent native cells resulting in improved outcomes and decreased too.

Limitations of this study must be acknowledged. Firstly, pre-treatment weight loss data was not universally available on each patient. The first documented data point of weight for each patient was at time of diagnosis. The patients were not asked to recall weight 6 months prior to the diagnosis. The patients home use of enteral nutritional support can only be self-reported causing possible over-estimation of how often tube feeds were used. Pre-CTRT comorbidity scores (i.e., Charleston scores) were not calculated for this study, precluding the analysis of performance factors in comparing the study group results. Although, all patients in this study received the same CTRT regimen, the data still carries the inherent limitations of a retrospective study. Nevertheless, the observations here are a new contribution to the literature.

CONCLUSIONS

Improved overall survival and DFS in clinically malnourished patients who lost a severe percentage of pre-treatment weight is a new contribution to the literature. Patients in the SCWL group not only had improved OS and DFS but also had no increased rates or severity of toxicity to treatment. The local/regional control and recurrence data in our study mirrors published data of improved control and decrease recurrence in patients losing significant amounts of weight during treatment, however both of us fell short of being statistically significant. From this it is evident that further research into the mechanisms of weight loss in patients with SCCHN undergoing chemo-irradiation is needed. This is especially true in a population of patients with PEG placement prior to treatment, as a large hurdle in the way of opportunity for nutritional supplementation has been removed.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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