ORIGINAL ARTICLE

Predictors of Gastrostomy Placement and Dependence in Oropharyngeal Cancer Patients Treated with Chemoradiotherapy*

[1]Edward D McCoul, [2]Gady Har-El, [3]Krishnamurthi Sundaram

[1]Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York, USA

[2]Department of Otolaryngology—Head and Neck Surgery, Lenox Hill Hospital New York and Department of Otolaryngology SUNY Downstate Medical Center, Brooklyn, New York, USA

[3]Department of Otolaryngology, Long Island College Hospital, Brooklyn, New York, USA

Correspondence: Krishnamurthi Sundaram, Department of Otolaryngology, Long Island College Hospital, 339 Hicks Street Brooklyn, New York 11201, USA, Phone: (718) 780-1498, e-mail: krishsun@aol.com

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Abstract

Introduction: Treatment of oropharyngeal cancer (OPC) with primary chemoradiotherapy (CRT) may necessitate placement of a gastrostomy tube (GT). We sought to identify factors that may predict GT placement and dependence.

Materials and methods: A retrospective review of 61 consecutive patients receiving primary CRT for OPC over a 10-year period at a tertiary referral center. Patients with prior head and neck malignancy, distant metastasis, incomplete treatment course, or inadequate follow-up were excluded. Forty-four patients were included for analysis.

Results: Sixty-one percent of tumors were located in the tonsil and 62% were stage IV disease at presentation. Complete response to CRT occurred in 36 patients, among whom GT placement was more likely when weight loss occurred before the start of CRT than after CRT ($p = 0.028$). Continued GT dependence was more likely in patients with GT placement after the start of CRT ($p = 0.019$). Multivariate analysis showed significant associations of GT placement with post-treatment dysphagia and mucositis. Advanced tumor stage was a significant predictor of GT dependence.

Conclusions: Prophylactic GT placement may be advisable in patients receiving CRT for OPC who have pretreatment weight loss. Conversely, GT may be withheld from asymptomatic patients.

Keywords: Squamous cell carcinoma, oropharynx, gastrostomy, radiotherapy, chemotherapy.

INTRODUCTION

Treatment of oropharyngeal carcinoma (OPC) may involve primary chemoradiotherapy (CRT), with or without surgical management. Because of its central location in the aerodigestive tract, OPC is associated with significant functional impairment, which may include dysphagia, odynophagia and airway edema. Such deficits may necessitate the placement of gastrostomy tube (GT), either before, during or after treatment. Although this intervention may reduce morbidity in the short-term, prolonged dependence may contribute to decreased quality of life.[1,2] In addition, management of complications may introduce delays to the treatment of malignant disease.

High rates of GT placement and dependence have been described in association with treatment of OPC,[3-8] although it remains unclear what factors are most likely to predict these complications. Identification of patients who may be at higher risk prior to the start of treatment would assist with patient counseling and potentially decrease the incidence of unplanned treatment breaks. We sought to identify potential predictors of GT placement and dependence in a cohort of patients with OPC treated with primary CRT.

PATIENTS AND METHODS

A retrospective review was conducted of all patients diagnosed with squamous cell carcinoma of the oropharynx between January 1997 and December 2006 from the institutional registry at a university-affiliated teaching hospital (Othmer Cancer Center of Long Island College Hospital). A consecutive sample of 61 patients who received CRT with curative intent, with or without adjunctive surgical

Table 1: Patient characteristics (N = 44)

Characteristic	*No (%)*
Sex	
Male	34 (77.3)
Female	10 (22.7)
Race	
White	16 (36.7)
Black	21 (47.7)
Hispanic	7 (15.9)
Age	
Mean (SD)	60.7 (9.0)
Range	42, 83
Subsite	
Base of tongue	9 (20.5)
Tonsil	27 (61.4)
Palate	6 (13.6)
Pharyngeal wall	2 (4.5)
Local disease	
T1	8 (18.2)
T2	14 (31.8)
T3	14 (31.8)
T4	8 (18.2)
Regional disease	
N0	10 (22.7)
N1	9 (20.5)
N2	20 (45.5)
N3	5 (11.4)
Distant disease	
M0	44 (100)
M1	0 (0)
AJCC stage	
I	2 (4.5)
II	4 (9.1)
III	9 (20.5)
IV	30 (68.2)
Chemotherapy	
Concurrent with radiotherapy	44 (100)
Induction chemotherapy	5 (11.4)
Targeted biologic agent	5 (11.4)
Surgery	
None	24 (54.5)
Pre-treatment neck dissection	16 (36.4)
Post-treatment neck dissection	1 (2.3)
Definitive resection	2 (4.5)
Salvage resection	1 (2.3)
Degree of response	
Partial	8 (18.1)
Complete	36 (81.9)
Duration of radiotherapy (weeks)	
Median (SD)	9.0 (1.3)
Range	7, 12
Length of follow-up (months)	
Median (SD)	22 (9.8)
Range	4, 43

AJCC—American Joint Committee on Cancer

management, were selected for inclusion. Patients were excluded if they had a history of prior treatment for malignancy of the head and neck, metastatic disease beyond the head or neck region present at the time of diagnosis, incomplete course of radiation therapy, or a post-treatment follow-up period less than 4 months. After applying exclusion criteria, 44 patients remained in the study. Approval was obtained from the Institutional Review Board prior to the start of data collection.

The primary outcome of interest was GT placement. The secondary outcome was GT dependence, defined as either exclusive use of the GT for nutritional needs, or daily use to supplement insufficient oral intake. Dependence was determined based on patient status at the time of the last recorded follow-up visit.

Charts were reviewed for patient-related and tumor-related characteristics, including gender, race, age at diagnosis, duration of follow-up, site of primary tumor, tumor-node-metastasis (TNM) staging, and American Joint Committee on Cancer (AJCC) stage. Treatment-related data of interest included dose and duration of radiation, type of chemotherapeutic agent, type of surgical management (if any), duration of follow-up, and date of the last follow-up visit. When applicable, GT placement was noted as occurring either before or after initiation of therapy. By convention, significant weight loss was defined as a history of 10% reduction in body weight over a 6-month period.[9] Symptoms and signs of note included dysphagia, odynophagia, trismus, laryngopharyngeal edema. Symptoms were designated as pre-treatment or post-treatment factor with respect to the start of CRT. Additional treatment-related complications of interest included mucositis, xerostomia, thrush, trismus, dermatitis, radionecrosis, cytopenias, aspiration, stenosis and velopharyngeal reflux (VPI).

External beam radiation therapy was performed at the Department of Radiation Oncology at the Long Island College Hospital. In general, the head and neck region was treated using 6 MV photons via parallel opposed lateral fields at 180 cGy per day for a dose of 4140 cGy. The field was decreased for off-cord treatment with 6 MV photons at 180 cGy per day for an additional 3060 cGy. The minimum planned total dose to the primary was typically 7200 cGy. Treatment was given to the bilateral supraclavicular fossae using a single anterior field of 6 MV photons at 180 cGy per day for a total dose of 4500 cGy. The posterior cervical

chains received a boost with 9 MV photons in an enface fashion at 200 cGy per day for a total dose of 5540 cGy. A hyperfractionation scheme was incorporated for treatment of tumors of the base of tongue, using 6 MV photons at 110 cGy twice daily for a dose of 3880 cGy to the primary field, with additional boosts twice daily to a minimum planned total dose of 7200 cGy. No planned breaks were incorporated in the schedule.

Chemotherapy was administered during weeks 1 and 4 of radiation therapy on an inpatient basis. Patients received prophylactic hydration and antiemetics. Cisplatin was given as a rapid infusion of 75 to 100 mg/m^2 on day 1 of each cycle. Fluorouracil and cetuximab were administered at the discretion of the treating oncologist using standardized dosing. There were no provisions for reduction in the doses of chemotherapy.

Statistical analysis was conducted using SPSS 16.0 (SPSS Corporation, Chicago, Illinois). Sample size estimation using Cohen's power calculation determined the included cohort to be adequate for analysis.[10] Univariate exact logistic regression was used to model GT placement and tracheostomy as separate outcomes. Covariates included patient characteristics, treatment factors, and treatment-related complications. Predictors that were statistically significant at the 0.05 level were entered simultaneously into a multivariate exact logistic regression model. Odds ratios with 95% confidence intervals and midpoint probability test *p*-values were reported. Two-way frequency tables were generated for categorical predictors against outcomes, and compared using the Fisher exact test. Life-table analysis was performed using the Kaplan-Meier technique, with significance determined by the log-rank test.

RESULTS

Forty-four patients receiving CRT for OPC were included for analysis. Patient characteristics are shown in Table 1. The tonsil accounted for 61.4% of tumors, and 68.2% of patients had stage IV disease at presentation. All patients received concurrent CRT, with 5 patients receiving induction chemotherapy and 5 patients receiving additional treatment with a targeted-biologic agent (cetuximab). Sixteen patients (36.4%) were treated prior to CRT with a therapeutic neck dissection. The median (standard deviation, SD) duration of CRT was 9.0 (1.3), and the median (SD) follow-up period was 22 (9.8) months.

Thirty-six patients (81.9%) demonstrated a complete response to CRT. Within this group, 66.7% of patients who experienced significant weight loss before the start of CRT required GT placement, compared to 44.4% of patients with weight loss after the start of CRT (p = 0.028, Fisher exact test). GT placement did not occur in any patients who did not have dysphagia, odynophagia or weight loss. Continued GT dependence, either partially or totally, at last follow-up was reported in 55.6% of patients who had GT placement after treatment, compared to 25.0% who had GT placement before treatment (p = 0.019, Fisher exact test; Table 2). The median (SD) duration of GT dependence was 18.5 (9.3) months. Survival analysis of duration of GT dependence showed no significant difference with regard to the timing of GT placement (Fig. 1).

Multivariate analysis identified post-treatment dysphagia and mucositis as predictive factors for GT placement (Table 3). Advanced AJCC stage was a significant predictor for GT dependence on multivariate analysis. There were no reported occurrences of radionecrosis, stenosis, aspiration, or velopharyngeal insufficiency.

DISCUSSION

Organ preservation protocols have gained popularity in the management of OPC on the strength of studies that favorably compare survival rates with CRT vs primary surgical resection.[11-13] Although nonsurgical management of OPC may result in better cosmetic and speech outcomes compared with primary surgery, the incidence of severe dysphagia following treatment is not reduced.[8,14]

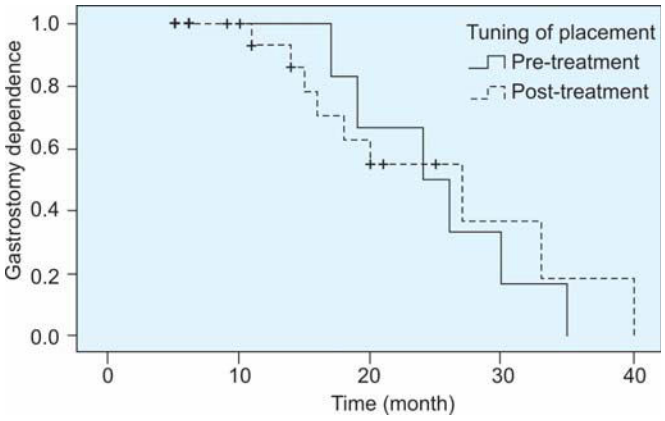

Fig. 1: Survival analysis comparing the frequency of weaning from tube feeding for all patients receiving gastrostomy prior to treatment versus those receiving gastrostomy after treatment. There was no significant difference in frequency of weaning (p = 0.775).

Table 2: Patient factors and treatment factors relating to gastrostomy placement

Characteristic	*Total patients*	*Gastrostomy placement (%*)*	*Gastrostomy dependent (%†)*
Sex			
Male	34	20 (58.8)	10 (50.0)
Female	10	6 (60.0)	2 (33.3)
Race			
White	16	11 (68.8)	6 (54.5)
Black	21	11 (52.4)	4 (36.4)
Hispanic	7	4 (57.1)	2 (50.0)
Subsite			
Base of tongue	9	6 (66.7)	1 (16.7)
Tonsil	27	16 (59.3)	9 (56.2)
Soft palate	6	3 (50.0)	1 (33.3)
Pharyngeal wall	2	1 (50.0)	1 (100)
T-stage			
T1, T2	22	11 (50.0)	3 (27.3)
T3, T4	22	15 (68.1)	9 (60.0)
AJCC Stage			
I, II	6	2 (33.3)	0 (0)
III, IV	38	24 (63.2)	12 (50.0)
Weight loss			
None	6	0 (0)	–
Pre-treatment	26	16 (61.5)	6 (38.5)
Post-treatment	12	10 (83.3)	6 (60.0)
Dysphagia			
None	13	0 (0)	–
Pre-treatment	14	12 (85.7)	5 (41.7)
Post-treatment	17	14 (82.4)	7 (50.0)
Odynophagia			
None	10	0 (0)	–
Pre-treatment	3	3 (100)	1 (33.3)
Post-treatment	31	23 (74.2)	11 (47.8)
Laryngopharyngeal edema			
None	27	14 (51.9)	–
Pre-treatment	12	8 (66.7)	2 (25.0)
Post-treatment	5	4 (80.0)	3 (66.7)
Trismus			
None	35	20 (57.4)	–
Pre-treatment	7	5 (71.4)	2 (40.0)
Post-treatment	2	1 (50.0)	0 (0)
Mucositis	30	23 (76.7)	10 (47.6)
Xerostomia	23	12 (52.2)	4 (33.3)
Thrush	13	8 (61.2)	3 (37.5)
Neck dissection	17	11 (64.7)	6 (54.6)
Complete response	36	22 (61.1)	10 (45.5)
Timing of placement			
pre-treatment	–	8 (18.2)	2 (25.0)
post-treatment	–	18 (40.9)	10 (55.6)
Total	**44**	**26 (59.1)**	**–**

AJCC—American Joint Committee on Cancer
*Percentage of all patients in study
†Percentage of patients receiving gastrostomy who remained dependent at last follow-up visit

Table 3: Selected results for independent multivariate analysis of gastrostomy placement and tracheostomy

Characteristic	Gastrostomy placement		Gastrostomy dependence	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Dysphagia				
Pre-treatment	0.350 (0.058, 2.096)	0.25	1.825 (0.458, 7.273)	0.19
Post-treatment	0.076 (0.016, 0.365)	0.001*	1.800 (0.470, 6.898)	0.19
Odynophagia				
Pre-treatment	0.343 (0.027, 4.399)	0.41	1.364 (0.112, 16.578)	0.45
Post-treatment	1.450 (0.236, 8.924)	0.69	1.450 (0.236, 8.924)	0.69
Laryngopharyngeal edema				
Pre-treatment	0.800 (0.177, 3.618)	0.77	0.440 (0.81, 2.390)	0.20
Post-treatment	0.490 (0.115, 2.089)	0.33	0.955 (0.234, 3.889)	0.28
Trismus				
Pre-treatment	0.469 (0.075, 2.945)	0.42	1.080 (0.180, 6.490)	0.35
Post-treatment	0.667 (0.098, 4.541)	0.68	1.933 (0.281, 13.295)	0.30
Mucositis	0.170 (0.040, 0.726)	0.017*	3.889 (0.731, 20.682)	0.075
Xerostomia	0.629 (0.713, 10.178)	0.14	0.342 (0.0850, 1.377)	0.085
Thrush	0.659 (0.164, 2.620)	0.56	0.733 (0.163, 3.304)	0.27
Neck dissection	0.688 (0.180, 2.620)	0.58	1.909 (0.497, 7.337)	0.17
AJCC stage	0.192 (0.032, 1.137)	0.17	0.205 (0.049, 0.854)	0.038*
Complete response	1.601 (0.906, 2.829)	0.11	1.154 (0.199, 6.698)	0.34

AJCC—American Joint Committee on Cancer; OR—odds radio;CI—confidence interval
*$p < 0.05$

The present study suggests that the need for GT placement may be increased in the presence of certain treatment-related symptoms or signs. Dysphagia is common and may be attributed either to the disease process or treatment-related toxicity. Moreover, the absence of dysphagia, odynophagia or weight loss in the present study essentially excluded the necessity of GT placement. This underscores the importance of a careful functional assessment prior to embarking on CRT.

Weight loss is frequently encountered among head and neck cancer (HNC) patients.[15] Lees et al reported a mean weight loss of 6.5 kg in 57% of patients, corresponding to approximately 10% of body weight.[16] Mick et al determined that pre-treatment weight loss was the strongest independent predictor of survival in patients with advanced-stage HNC.[17] Our findings indicate that pre-treatment weight loss may predict the necessity of eventual GT placement in patients receiving CRT. This is of particular interest in patients who otherwise demonstrate a favorable response with regard to disease eradication following treatment.

Factors identified by multivariate analysis as predicting GT placement include mucositis and post-treatment dysphagia. Mucositis is a well-known complication of CRT, and may account for at least some of the incidence of dysphagia during and after treatment. Notably, pre-treatment dysphagia was not a significant predictor of GT placement, which suggests that tumor-related dysphagia may be less severe than treatment-related dysphagia.

The benefits of prophylactic GT placement have been previously described. Lee et al reported decreased weight loss and reduced hospitalizations for patients with advanced HNC receiving CRT who had pre-treatment GT placement.[18] The maintenance of adequate dietary intake is essential to the treatment of HNC, including OPC. The loss of oral intake may result from tumor-related anorexia, loss of sense of taste, radiation-related xerostomia, the effects of prior surgery, and treatment-related mucositis.[19] Unplanned treatment breaks or hospitalizations resulting from malnutrition or dehydration can adversely impact treatment efficacy. To this end, prophylactic GT placement is a potentially valuable adjunct to the management of OPC.

Under optimal conditions, removal of GT is considered once treatment is completed and eradication of disease has been demonstrated. However, a subset of patients remains dependent on GT for part or all of their nutritional needs. Published reports of GT dependence following CRT range from 13 to 64% at short-term follow-up (6 months),[3,6,7] and 13 to 33% at long-term follow-up (>12 months).[5,6] In our study, GT dependence at last follow-up was 25% in patients with pre-treatment GT, versus 55.4% in patients with

post-treatment GT. These findings may support a recommendation for prophylactic GT in patients with OPC.

GT placement can have a significant effect on patient quality of life, both in terms of physical discomfort and social anxiety, as well as placing the patient at risk for wound infection and other complications. A previous study of HNC patients used validated instruments to show significant quality-of-life deficits in patients with GT.[1] A randomized trial of malnourished HNC patients showed improved quality of life for patients with GT, although this benefit was lost at 6 months after treatment.[2] Our study suggests that patients receiving CRT for OPC are less likely to remain dependent on enteral feeding when GT placement occurs prior to the start of treatment. Moreover, patients with a good prognosis following complete response to CRT may suffer a reduced quality-of-life as a result of prolonged GT dependence. Prophylactic GT placement may obviate this circumstance.

This study has several limitations. Because of the retrospective design, historical bias may be present, as some aspects of the treatment course may be incomplete from the available data. Second, determining the basis of selection for CRT *vs* surgical management was often not possible. Thirdly, a larger sample size may have provided additional power in regression analysis. Finally, the use of regression analysis identifies association between study variables but does not determine causation. The technique of radiation delivery did not change substantially during the study period, which presumably kept bias from secular changes at a minimum.

CONCLUSIONS

Treatment of OPC with CRT may be complicated by GT placement, which may occur more frequently in patients with pre-treatment weight loss. This may be particularly important in those who have complete response to treatment in terms of tumor eradication. Prolonged GT dependence is associated more often with GT placement after the start of treatment, which suggests the importance of prophylactic GT placement. We recommend offering prophylactic GT placement to patients with significant weight loss prior to treatment of OPC, although determination of additional risk factors will require further study.

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