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Swallowing Dysfunction is a Common Sequelae After Chemoradiation for Oropharynx Carcinoma

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Abstract

Introduction: A retrospective review of all patients with advanced oropharynx cancer from a single institution was performed.

Methods: Sixty-seven patients with stage III/IV oropharynx cancer were treated with definitive radiotherapy with or without concurrent chemotherapy from 1990 to 2004. Follow-up ranged from 6 to 91 months with a median of 32 months.

Results: Patients treated with concurrent chemotherapy had a statistically significant benefit for control above the clavicles, primary control, disease-free survival, and overall survival but no difference in distant control at 3 years. Cox proportional regression model demonstrated the use of concurrent chemotherapy to be the only independent variable that reached significance for control above the clavicles, primary control, and overall survival. Complete dysphagia for solids and/or gastrostomy tube dependence was observed in more patients who were treated with chemoradiation than those treated with radiation alone; 18% and 0%, respectively ($P = 0.04$).

Conclusions: Concurrent chemotherapy decreases the recurrence at the primary site and above the clavicles. The most notable difference in sequelae between the 2 groups was the increase in swallowing dysfunction with concurrent chemotherapy.

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Keywords

oropharynx cancer; chemoradiation; swallowing dysfunction; sequelae; radiation therapy

Treatment for advanced stage oropharynx cancer has been evolving over the last decade from treatment with radiation therapy alone toward treatment with concurrent chemotherapy and radiation therapy. Randomized trials have suggested a survival advantage with a combined modality approach.[1,2] Other head and neck sites have failed to find a survival advantage with chemotherapy but have suggested an improvement in local regional control.[3] Sequelae after treatment have been incompletely documented. To determine future avenues of investigation, a retrospective review of all patients with stages III and IV oropharynx cancer from a single institution was performed.

METHODS AND MATERIALS

Sixty-seven patients with stage III/IV oropharynx cancer were treated with definitive radiotherapy at Wake Forest University Medical Center from 1990 to 2004. Retrospective chart review was performed after Institutional Review Board approval. Demographics of these patients can be seen in Table 1. Radiation alone was given using hyperfractionation (9) or standard fractionation (19), and radiation with concurrent chemotherapy was given using hyperfractionation (4) or standard fractionation (35). Radiation treatments were given with opposed lateral head and neck fields that encompassed the primary and nodal areas. Intensity modulated radiation therapy was not used. Patients treated with radiation alone received daily fractionation of 180 (2 patients) or 200 (17 patients) for a total dose of 66 to 70 Gy. Concomitant boost radiotherapy was delivered in 9 patients for a total dose of 72 Gy. Patients treated with concurrent chemotherapy were treated with concomitant boost radiotherapy for 72 Gy total (4 patients) or 200 cGy per fraction for a total dose of 66 to 70 Gy (35 patients).

Concomitant chemotherapy consisted of cisplatin 100 mg/M2 given every 3 weeks (11 patients) with most patients receiving 2 cycles. Weekly cisplatin or carboplatin with paclitaxel was given to 27 patients with number of cycles ranging from 2 to 7 and a median of 4.

Patients treated with chemotherapy and radiation tended to have more advanced tumors: T3/4 (62% vs. 50%) and nodal disease > N1 (87% vs. 68%). Table 2 provides patient characteristics comparing these 2 groups.

Follow-up without death or recurrence ranged from 16 to 126 months with a median of 42 months. Patients were assessed as controlled at the primary site or above the clavicles if there was no evidence of residual or recurrent tumor. Distant metastasis refers to recurrence of disease below the clavicles. Statistical analyses were performed using SAS Version 9. Kaplan-Meier curves were estimated using the LIFETEST procedure in SAS.[4] Overall curves and curves stratified by different factors of interest (chemotherapy use, tumor stage, and nodal stage) were estimated and comparisons between strata were made using the log-rank test statistic. Next, Cox proportional hazards regression models were used to determine

independent risk factors for each outcome (local control, primary control, overall survival, disease free survival, and distant recurrence).[5] In these models, a stepwise selection procedure was used to identify potential predictors with an entrance criteria for each variable set at $P = 0.05$. Seven potential predictors were considered in these models. These variables were tumor stage, nodal stage, chemotherapy (yes/no), gender, age, race (African-American or white), and neck dissection.

RESULTS

Overall control above the clavicles (CC), control at the primary site (CP), and disease-free survival rates (DFS) for all patients at 3 years were 78%, 86%, and 66%, respectively, and can be seen in Figure 1. Patients treated with concurrent chemotherapy had a statistically significant benefit for CC (87% vs. 69%, $P = 0.04$); CP (95% vs. 74%, $P = 0.02$); DFS (77% vs. 49%, $P = 0.05$); and overall survival (81% vs. 56%, $P = 0.03$) but no detectable difference in distant control at 3 years as seen in Table 3. Of the 38 patients with T3/4 tumors, CP was 92% with concurrent chemotherapy and 64% with radiotherapy alone ($P = 0.04$). This is demonstrated in Figure 2. Patients with T1/2 tumors had a 3-year CP of 100% with chemoradiation and 82.5% with radiation alone ($P = 0.12$).

Stepwise Cox Proportional regression models were performed with a selection criteria for $P = 0.05$. Only treatment with chemotherapy entered the model for control above the clavicles ($P = 0.04$), control at the primary site ($P = 0.02$), and overall survival ($P = 0.04$). For distant control and DFS there were no variables that reached significance.

Six (21%) patients treated with radiation alone required support with feeding tubes during or after treatment. Thirty patients (77%) treated with chemoradiation required support with feeding tubes during and/or after treatment. Eight patients required extended use of feeding tubes ranging from 3 to 9 months after completion of chemoradiation. Seven patients treated with chemoradiation had complete dysphagia for solids or were gastrostomy tube dependent. Differences in late sequelae for the radiation alone and concurrent chemotherapy groups included trismus in 4% and 13%, and complete dysphagia for solids and/or gastrostomy tube dependence in 0% and 18% ($P = 0.04$), respectively. Figure 3 demonstrates a comparison of sequelae between patients treated with chemoradiation or radiation alone. Complete dysphagia was associated with stages T3/4 compared with T1/2 ($P = 0.01$), use of chemotherapy compared with no chemotherapy ($P = 0.01$), and use of paclitaxel compared with nonpaclitaxel regimens ($P = 0.056$). Swallowing dysfunction was not related to the use of a feeding tube during radiation. Patients developed complete dysphagia with similar frequency when comparing those who did not receive a feeding tube during treatment and those who did have a feeding tube during treatment, 2/9 (22%) and 5/30 (16%), respectively.

DISCUSSION

In the last decade concurrent chemoradiation has become a standard therapy for locally advanced oropharynx cancers.[6] Multivariate analysis from published literature has demonstrated that the most important independent factor for locoregional control has been T stage with other authors showing that use of hyperfractionated radiation, use of

chemotherapy, and race have been significant as well.[7-9] The most common independent factor predictive of survival is nodal stage.[9]

At our institution, concurrent chemotherapy improved local control at the primary site, control above the clavicles, disease free survival, and overall survival in patients with advanced oropharynx cancer, which is similar to published randomized trials.[1,2] No statistical difference in distant metastasis was observed for these patients.

We found that patients treated with concurrent chemoradiation had more documented toxicity including complete dysphagia, trismus, and hypothyroidism. As with any retrospective report, documentation of sequelae was frequently incomplete. Because there was a higher frequency of larger tumors treated with chemoradiation compared with radiation alone, more destruction of normal tissues could have existed before instituting therapy. In addition, even patients who were not termed gastrostomy tube dependent may have had some component of swallowing dysfunction that could not be documented in this retrospective study.

Sequelae after treatment of oropharyngeal cancers have been incompletely documented. Most documentation is based on aspiration and gastrostomy tube dependence. In a randomized study comparing radiation fractionation, Horiot et al[9] documented no difference in functional sequelae. Mendenhall et al[10] documented that of patients treated for tonsillar cancer primarily with radiation alone, 9% developed serious late complications including 4% who required permanent gastrostomy. Of patients treated for base of tongue cancer primarily with radiation, 7% required permanent gastrostomy.[7] In contrast, Bensadoun et al[1] reported no significant difference between radiation and chemoradiation arms with no dysphagia observed in either arm. However, several smaller reports have documented significant swallowing dysfunction after concurrent chemoradiation. Shiley et al[11] documented 31% gastrostomy tube dependence after chemoradiation for advanced stage oropharyngeal cancers. Base of tongue lesions tended to have worse swallowing dysfunction than other oropharynx primaries. A multicenter trial reported by Garden et al[12] documented that 6% to 22% of patients treated with 3 different chemoradiation regimens required gastrostomy tubes at last follow-up.

Eisbruch et al[13] noted that the structures whose damage may cause dysphagia and aspiration after intensive chemotherapy and radiotherapy (RT) include the pharyngeal constrictors and the glottic and supraglottic larynx. They found that compared with 3D-RT, moderate sparing of these structures was achieved by intensity-modulated RT (IMRT). No clinical validation has been done. Another manuscript noted that after intensive chemoradiotherapy, significant objective swallowing dysfunction is prevalent. Reduced base-of-tongue retraction with reduced contact to the posterior pharyngeal wall and incomplete cricopharyngeal relaxation resulted in pooling in the pyriform sinuses and vallecula of residue, which was frequently aspirated after the swallow.[14] A recent report documented differing types of swallowing disorders depending on the site of the lesion. The most frequent occurring disorders were reduced tongue base retraction, reduced tongue strength, and delayed vestibule closure.[15]

Recommendations of early swallowing therapy and exercises have been recommended to maximize good swallowing outcomes in these patients.[16] However, there is absence of data concerning the optimum timing and duration of these exercises. As more information is obtained regarding the influence of the size and location of the tumor, doses and location of the radiation distribution, types of chemotherapy, and other patient and treatment related variables, better comparisons can be made between chemoradiation regimens and/or surgical therapies. Systematic evaluation of patients before and after treatment should be performed to gain better understanding of functional outcomes. In addition, reduction of the volume of normal tissue with more targeted radiation techniques may be helpful in decreasing normal tissue toxicity.

In this retrospective review, chemoradiation improved the disease control above the clavicles for patients with oropharynx cancer compared with radiation alone. Distant recurrences remain the predominant pattern of recurrence. Optimizing systemic agents will be necessary to improve distant and disease-free survival rates. The most notable difference in sequelae between the 2 groups was the increase in swallowing dysfunction with concurrent chemotherapy. Future investigations should focus on the role of pretreatment and posttreatment swallowing evaluation and/or therapy. Reduction in the volume of normal tissue with more targeted radiation techniques may be helpful in decreasing normal tissue toxicity. Only large-scale trials with systematic assessment will determine the concurrent agents or fractionation schemes that may result in optimal locoregional control and function.

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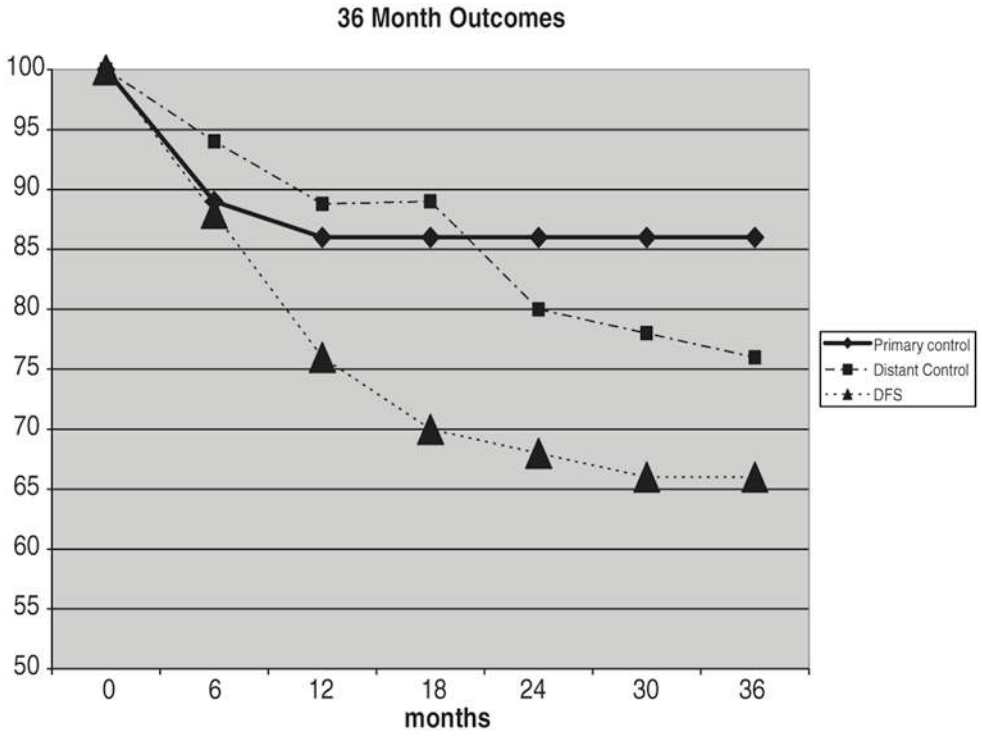

FIGURE 1.
Disease-free survival, distant control, and primary control for all patients.

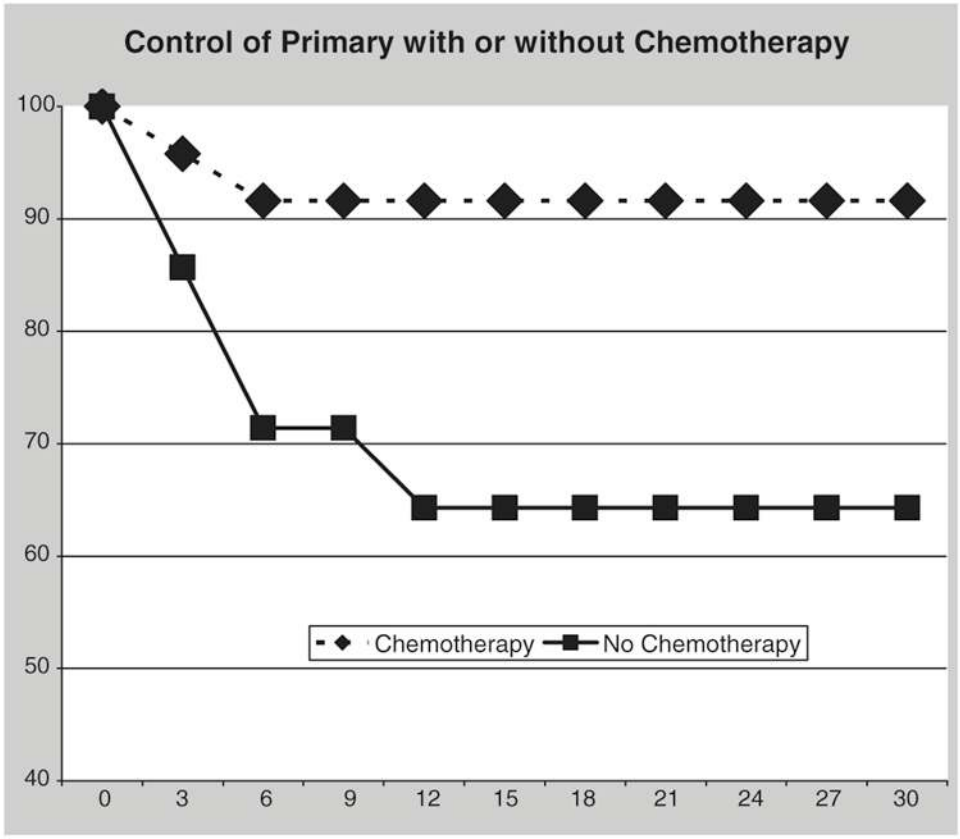

FIGURE 2.
Control of the primary for patients with T3/4 tumors with or without chemotherapy.

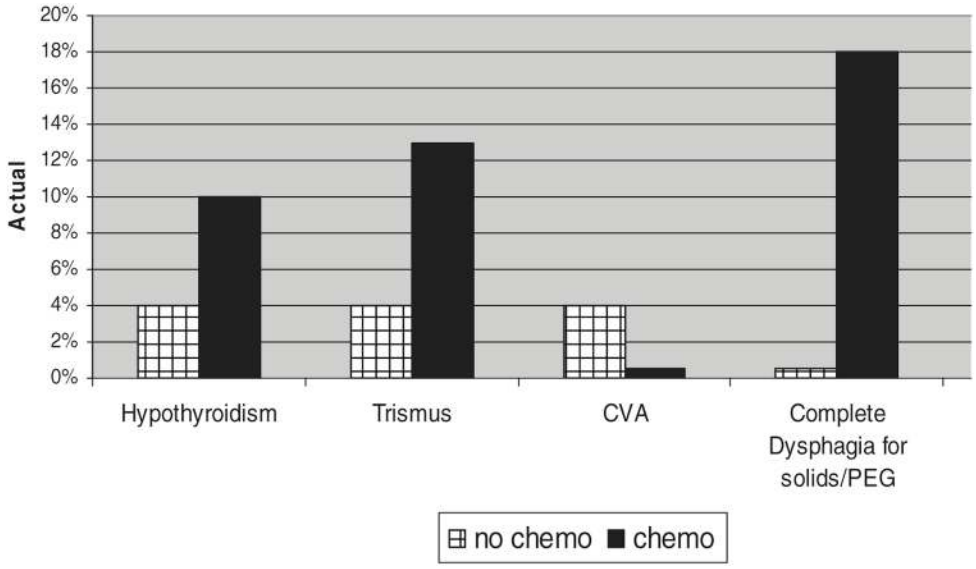

FIGURE 3.
Comparison of sequelae in patients treated with chemoradiation or radiation alone.

TABLE 1.

Patient Demographics

	No. Patients	%
Race		
Black	14	21
White	53	79
Sex		
Female	14	21
Male	53	79
Chemo R_x		
No	28	42
Yes	39	58
T stage		
3/4	38	57
1/2	29	43
N stage		
0/1	14	21
2/3	53	79

TABLE 2.

Comparison of Characteristics

	Concurrent CRT (n = 39)	RT Alone (n = 28)
% Non-white	21	21
Age range (median)	37–76 (55)	41–84 (54)
% Female	15	29
T 3/4 (%)	62	50
N 2/3 (%)	87	68
Fractionation	200 cGy	200 cGy
Total dose	7000 Gy	7000 cGy

TABLE 3.

Disease Outcomes at 36 mo for All Patients

	No Chemo (%)	Chemo (%)	*P*
Primary control	74	95	0.02
Control above clavicles	69	87	0.04
Distant control	73	77	0.85
Disease-free survival	49	77	0.05
Survival	56	81	0.03