Intensity-Modulated Chemoradiotherapy Aiming to Reduce Dysphagia in Patients With Oropharyngeal Cancer: Clinical and Functional Results

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ABSTRACT

Purpose

To assess clinical and functional results of chemoradiotherapy for oropharyngeal cancer (OPC), utilizing intensity-modulated radiotherapy (IMRT) to spare the important swallowing structures to reduce post-therapy dysphagia.

Patients and Methods

This was a prospective study of weekly chemotherapy (carboplatin dosed at one times the area under the curve [AUC, AUC 1] and paclitaxel 30 mg/m²) concurrent with IMRT aiming to spare noninvolved parts of the swallowing structures: pharyngeal constrictors, glottic and supraglottic larynx, and esophagus as well as the oral cavity and major salivary glands. Swallowing was assessed by patient-reported Swallowing and Eating Domain scores, observer-rated scores, and videofluoroscopy (VF) before therapy and periodically after therapy through 2 years.

Results

Overall, 73 patients with stages III to IV OPC participated. At a median follow-up of 36 months, 3-year disease-free and locoregional recurrence-free survivals were 88% and 96%, respectively. All measures of dysphagia worsened soon after therapy; observer-rated and patient-reported scores recovered over time, but VF scores did not. At 1 year after therapy, observer-rated dysphagia was absent or minimal (scores 0 to 1) in all patients except four: one who was feeding-tube dependent and three who required soft diet. From pretherapy to 12 months post-therapy, the Swallowing and Eating Domain scores worsened on average ($\pm$ standard deviation) by 10 ± 21 and 13 ± 19 , respectively (on scales of 0 to 100), and VF scores (on scale of 1 to 7) worsened from 2.9 ± 1.5 (mild dysphagia) to 4.1 ± 0.9 (mild/moderate dysphagia).

Conclusion

Chemoradiotherapy with IMRT aiming to reduce dysphagia can be performed safely for OPC and has high locoregional tumor control rates. On average, long-term patient-reported, observer-rated, and objective measures of swallowing were only slightly worse than pretherapy measures, representing potential improvement compared with previous studies.

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INTRODUCTION

Concurrent chemoradiotherapy (CRT) for head and neck (HN) cancer has improved tumor-related outcomes compared with radiotherapy (RT) alone, at the expense of increased toxicity, primarily long-term dysphagia.¹⁻³ We have previously identified the pharyngeal constrictors (PCs) and the glottic and supraglottic larynx (GSL) as anatomic structures in which dysfunction after CRT causes long-term dysphagia and aspiration.⁴ Several subsequent studies demonstrated statistically significant relationships between the doses delivered to these structures and

dysphagia.⁵⁻¹¹ Therefore, we⁴ and others^{7,12} hypothesized that sparing the parts of the swallowing structures not involved by tumor and not at risk of subclinical disease might reduce dysphagia without reducing tumor control rates. We have previously demonstrated that intensity-modulated RT (IMRT) allowed significant partial sparing of the noninvolved swallowing structures if such sparing was included in the objectives of the IMRT plans.⁴ Sparing of the swallowing structures, especially the PCs, which are part of the posterior pharyngeal wall, must take into account the retropharyngeal nodes (RPNs), which are important sites of metastases in

advanced HN cancer. The RPNs consist of lateral and medial groups, and the medial RPNs are close to the center of the PCs. However, the medial RPNs have rarely been involved with metastasis in HN cancer, according to multiple radiologic and surgical series, summarized elsewhere.⁵ We, therefore, anticipated that, if we included only the lateral RPNs in the targets and if we excluded the medial ones, we would be able to spare substantial parts of the PCs without risking an increased rate of local tumor recurrence.⁵

To assess whether sparing the swallowing structures is safe and whether it achieves functional gains, we conducted a prospective study of chemotherapy concurrent with IMRT. The aim was to reduce the radiation doses to these structures in patients with advanced oropharyngeal cancer.

PATIENTS AND METHODS

This was a prospective, longitudinal study of chemotherapy plus IMRT for HN cancer and was approved by the institutional review board of the University of Michigan. All patients signed study-specific informed consent. Eligibility included stages III to IV squamous cell carcinoma of the oropharynx, no prior therapy, Karnofsky performance status ≥ 60 , and primary therapy with CRT. Patients with tumors involving the posterior pharyngeal wall (medial to the carotid arteries) or with radiologic evidence of involvement of the RPNs were excluded, because the PCs would be encompassed completely within the targets, which would prevent partial sparing.

Details of therapy have been published elsewhere.⁵ In brief, all patients required treatment of the bilateral neck. The swallowing-related structures were outlined, as previously detailed.^{4,5} IMRT planning objectives included the dosimetric sparing of the parts of the swallowing structures (ie, PCs, esophagus, and GSL), as well as the major salivary glands and oral cavity, which were outside the targets. Targets included the lateral, but not medial, RPNs in all patients. The gross tumor volumes (GTVs) and subclinical disease (clinical target volumes [CTVs]) were each expanded uniformly by 3 mm to yield the planning target volumes (PTVs). For IMRT, 70 Gy and 59 to 63 Gy were delivered to the gross and subclinical PTVs, respectively, in 35 daily fractions. Achieving adequate target doses superseded sparing of any organ except the spinal cord. Whole-neck-field IMRT was used in all patients. Assurance of correct patient set-up was made by online imaging and correction before each treatment. An example of an IMRT plan is provided in Figure 1.

Concurrent chemotherapy. Carboplatin (dosed at one times the area under the curve [AUC; AUC 1]) and paclitaxel 30 mg/m² once weekly. Antiemetics and hydration were delivered according to standards of care. Feeding tubes (FTs) were inserted if weight loss during therapy approached 10%. Post-therapy follow-up included clinical examination every 6 to 8 weeks during the first 3 years and positron emission tomography (PET) – computed tomography (CT) scans at 3 and 12 months.

Objective assessment of swallowing was made by videofluoroscopy (VF).¹ VFs were performed pretherapy and at 3, 12, and 24 months post-therapy, as previously described.¹³ VF summary score was calculated and presented by using the Swallowing Performance Scale.¹⁴ A score of 1 indicated normal swallowing; scores of 2 to 3, mild swallow dysfunction; a score of 4, mild/moderate dysfunction; a score of 5, moderate dysfunction that required modified diet and swallowing precautions to minimize risk of aspiration; and scores of 6 to 7, significant dysfunction that required enteral feeding. VF-based aspiration was defined once the bolus passed the vocal folds and entered the subglottis.¹⁵ Instructions on safe swallowing, including maneuvers deemed beneficial during VF, were given to aspirating patients.¹⁵

Patient-reported dysphagia (PRD) was assessed with the Eating Domain of the Head and Neck Quality of Life questionnaire (HNQOL)¹⁶ and the Swallowing Question from the University of Washington Head and Neck-Related QOL questionnaire (UWQOL).¹⁷ Observer-rated dysphagia (ORD) was scored on a scale of 0 to 4 at each follow-up visit on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, version

Fig 1. Example of intensity-modulated radiotherapy plan. Dose distributions (Gy) are labeled. Blue (long arrow), pharyngeal constrictor; purple (short arrows), lateral retropharyngeal nodal sites; yellow, planning target volumes. The medial retropharyngeal nodes are not included in the targets, and the medial parts of the constrictor are outside the high doses.

2.0. Details of the PRD and ORD are provided in the Data Supplement (online only).

Statistics

Kaplan-Meier estimates were calculated for overall survival, recurrence rates, and locoregional control rates. Before assessing post-therapy clinical and functional outcomes, we tested indirectly if dropout (ie, missing 24 months data) depended on the unobserved health status. We used logistic regression to test if dropout was associated with the various observed outcome values as well as the baseline clinical covariates.

Changes from pretherapy to specific post-therapy time points were assessed for statistical significance by using two-tailed, paired *t* tests. To test for longitudinal trends in outcomes, the data were first graphically explored, then linear mixed-effects models were used to assess the longitudinal outcome trends. The specific parameterization of the mixed-effects model was based on the results of the visualization. For example, if the visualized trends showed improvements in outcomes up to month 12, followed by no notable change beyond, the model used post-therapy outcome scores from months 1 to 12 as the response variable and included as independent variables the baseline values of the response variable, as well as time in months to test for and estimate the rate of improvement.¹⁸ To test whether the outcomes stabilized beyond 12 months, we fit another model by using the entire 24-month data, and we tested for a change in slopes from up to 12 months to beyond 12 months.

To assess the unadjusted influence of baseline parameters on the dysphagia outcomes (ie, worsening aspiration relative to baseline, VF scores, HNQOL Eating Domain, and UWQOL swallowing scores), we evaluated the relationship between each pretherapy parameter with each outcome variable by using the linear mixed-effects model, adjusted only for time since therapy. To assess

the covariate-adjusted (ie, multivariate) influence of baseline parameters on outcomes, we added other covariates to this model. Factors tested in the longitudinal analyses for association with the dysphagia outcomes included PC, GSL, esophagus mean doses, GTV size, baseline dysphagia scores, T stage, N stage, smoking status, age, sex, tumor location (tonsil v base of the tongue), and whether the patient had planned neck dissection.

RESULTS

From October 2003 to February 2008, 125 consecutive patients with stages III to IV oropharyngeal cancer were treated at our institution. Twenty-one of these patients (17%) were not eligible because of involvement of the posterior pharyngeal wall or gross involvement of the RPNs. Of the remaining 104 patients, 73 agreed to participate in the study. Summaries of baseline patient and tumor characteristics are provided in Table 1. Human papillomavirus status is detailed in the Data Supplement (online only). Median follow-up was 36 months (range, 2 to 73 months) for all patients and was 36 months (range, 13 to 73 months) for surviving patients. Six patients were lost to follow-up, two before 2 years (at 13 and 20 months) and four after 2 years (range, 35 to 47 months).

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	Patients	
	No.	%
Age, years		
Median	55	
Range	50-78	
Sex		
Male	65	89
Female	8	11
Tumor location		
Tonsil	35	48
Base of tongue	38	52
Gross tumor volume, mL		
Median	110	
Range	19-378	
T stage		
1	9	12
2	29	40
3	17	23
4	18	25
N stage		
0	6	8
1	6	8
2	55	75
3	6	8
AJCC stage		
III	9	12
IVA	58	80
IVB	6	8
Smoking status		
Never*	26	36
Previous	31	42
Current	16	22

Abbreviation: AJCC, American Joint Committee on Cancer.

*Patients who never smoked reported less than one pack-year cigarettes or equivalent life-time tobacco use.

Fig 2. Kaplan-Meier estimates of overall survival, freedom from recurrence, and locoregional control.

Sixty-eight patients (93%) received at least six of the planned seven cycles of concurrent chemotherapy, and the remaining five patients (7%) received five cycles. All patients received the prescribed total RT dose with no interruptions apart from holidays. Average $\pm$ standard deviation mean doses to the PCs, GSL, and esophagus were 58 ± 8 Gy, 48 ± 14 Gy, and 34 ± 13 Gy, respectively; minimal doses were 24 ± 15 Gy, 23 ± 16 Gy, and 19 ± 16 Gy, respectively; and mean doses delivered to the parts of the swallowing structures outside the PTVs were 48 ± 6 Gy, 42 ± 12 Gy, and 32 ± 12 Gy, respectively, all delivered in 35 fractions. The doses to the sites of the medial RPNs were similar to outside-PTVs PC doses. Average and standard deviation partial PC volumes receiving 60 Gy was $61\% \pm 22\%$, and partial GSL volume average and standard deviation receiving 50 Gy was $48\% \pm 33\%$.

Twenty-four patients (30%) underwent elective neck dissection 10 to 14 weeks after the completion of therapy as planned (in the early years of the study) or because of persistent neck mass or suspicious post-therapy PET scan, and seven patients (29%) had microscopic residual disease in the resection specimens.

Overall survival, freedom from recurrence, and locoregional control are demonstrated in Figure 2. Three patients (4%) had locoregional failure (two within ipsilateral level II CTVs and one within the GTV of a locally advanced tonsil cancer). There were no failures within or near the spared swallowing structures. Five patients (7%) developed distant metastases. Two patients died without disease as a result of unknown causes at 2 and 24 months, and five died as a result of disease at 11 to 50 months.

Hematologic toxicities of grade 2 or greater consisted of seven occurrences of grade 2 and one occurrence of grade 4 neutropenia, as well as one occurrence of grade 2 thrombocytopenia. Maximal observer-rated toxicities of grade 2 or greater included acute mucositis (44%, grade 2; 55%, grade 3), acute dermatitis (62%, grade 2; 18%, grade 3), and skin fibrosis/induration (9%, grade 2; one patient, grade 3). Xerostomia of grades 0 to 1 and 2 were observed in 84% and 16%, respectively, at 12 months.

Long-term observer-rated dysphagia is detailed in Table 2. During therapy, 21 patients (29%) required FTs because of acute dysphagia. At 3 to 6 months after treatment, 6% to 7% of the patients still required supplemental enteral feeding (dysphagia grade 3). By 12

Table 2. Observer-Rated Dysphagia

Event Grade	Time Period (months)											
	Pre-therapy (n = 73)		3 (n = 72)		6 (n = 62)		12 (n = 68)		18 (n = 58)		24 (n = 51)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	71	97	36	50	32	52	39	58	36	62	30	59
1	1	2	25	35	22	35	25	37	19	33	19	37
2	1	2	6	8	4	6	3	4	2	3	1	2
3	0	0	5	7	4	6	1	1	1	2	1	2

months or later, one patient required supplemental enteral feeding, three required modified diet (grade 2), and all other patients (94%) had dysphagia grade 0 to 1 (eating regular diets). Weight loss peaked at 1 to 3 months (70% and 40% had weight loss > 10% and > 15%, respectively, compared with pretherapy) and then gradually improved (50% and 10% had weight loss > 10% and > 15%, respectively, at 24 months compared with pretherapy).

Analysis of missing data showed that dropouts did not depend on any of the observed prior outcome values, including the baseline, 3-, 6- or 12-month outcome values, or any of the baseline covariates; thus, missing data appeared to be completely at random. Patient-reported dysphagia assessed by the HNQOL Eating Domain and UWQOL Swallowing Question are detailed in Table 3 and Appendix Figure 1. Both questionnaires demonstrated acute worsening at 1 month post-treatment followed by significant improvement over time. Eating Domain scores improved (ie, decreased) through 12 months ($P < .001$; on the basis of the test of significance of linear trend over time in the mixed-effects model with data up to 12 months), and then stabilized through 24 months ($P = .33$ for a test of no change in rate of improvement beyond 12 months). In comparison, UW swallowing scores improved (ie, decreased) through 6 months ($P < .001$ for test of linear change on the basis of a mixed-effects model) and then stabilized through 24 months ($P = .57$ for a test of no change in rate of improvement beyond 6 months). Neither patient-reported domain scores returned to the pretherapy levels. On average ($\pm$ standard deviation), the UW swallowing scores worsened by 10 ± 21 on the 0 to 100 scale from pretherapy to 12 months post-therapy. Typically, worsened scores represented a change from no dysphagia to not swallowing certain solid foods. The HNQOL Eating Domain scores showed a similar pattern; at 12 months, the mean and standard deviation difference compared with pretherapy was 13 ± 19 on the 0 to 100 scale.

Table 4 lists VF-based aspiration rates and summary VF scores. Objective swallowing function assessed by VF summary scores worsened moderately at 3 months after CRT (mean and standard deviation score, 4.3 ± 1.1 compared with 2.9 ± 1.5 pretherapy; $P = .001$ on the basis of paired t test; $n = 68$) without significant improvement from 3 to 24 months ($P = .31$ for test of linear change on the basis of a linear mixed-effects model). The lack of significant improvement in the VF scores over time was due to stability of many of the anatomic/functional changes observed on VF, notably aspirations. When compared with pretherapy, 12-month scores improved in 8% and worsened in 55% of the patients. The median score at 12 months for the patients whose scores worsened compared with pretherapy was 4 (range, 3 to 7), representing mild/moderate dysfunction.

VF-based aspirations were observed pretherapy in eight patients (11%). Of the patients who had not aspirated pretherapy, 16% to 26% demonstrated aspiration at various post-therapy times (Table 4). During VF-observed aspirations, 60% of the aspirating patients either elicited no cough or the cough was not effective in ejecting the aspirate. Eight patients (11%) developed pneumonia post-therapy. All eight had demonstrated aspirations on VFs, and almost all demonstrated no effective cough response during aspiration. VF-based hypopharyngeal strictures were observed in five patients (7%). Of these, two were symptomatic and required dilation, after which dysphagia improved to grade 0 to 1.

Analyses of factors associated with the post-therapy dysphagia outcomes (ie, aspiration, VF scores, Eating Domain and UW swallowing scores) revealed statistically significant correlations for all outcomes with PC, laryngeal, and esophageal mean doses, GTV sizes, the pretherapy outcome scores, T stage, current smoking for aspiration, VF scores, and neck dissection for Eating Domain scores. In multivariate analyses, the mean doses (PC, laryngeal or esophageal) were statistically significantly associated with all end points ($P \leq .001$). After adjusting for the mean doses and time since therapy, T stage and pretherapy outcome scores remained significantly associated with most outcome scores. In addition, neck dissection was significantly associated with the Eating Domain scores ($P = .02$), and current smoking was significantly associated with the VF scores ($P = .01$).

DISCUSSION

The results of this study suggest that the high locoregional control rates reported recently after chemotherapy with IMRT of oropharyngeal cancer¹⁹⁻²⁴ have not been compromised by the efforts to spare the parts of the swallowing structures outside the PTVs. Specifically, the

Table 3. Patient-Reported Swallowing Scores

Variable	Time Period (months)													
	Pretherapy (n = 73)		1 (n = 67)		3 (n = 72)		6 (n = 61)		12 (n = 67)		18 (n = 59)		24 (n = 50)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HNQOL eating domain*	10	16	43	19	36	20	33	20	24	17	24	18	22	16
UWQOL swallowing*	8	16	39	24	27	22	19	18	18	18	18	17	17	15

Abbreviations: HNQOL, Head-Neck Quality of Life Questionnaire; UWQOL, University of Washington Head-Neck Quality of Life questionnaire.

*Scores are in a scale of 0 to 100; higher scores denote worse symptoms.

Table 4. Videofluoroscopic-Measured Aspiration Rates and Summary Swallow Scores

Time, months	No. of Patients With VF Studies	Patients With VF-Based Aspiration (%)		Patients Who Aspirated After Therapy but Did Not Aspirate Before Therapy		VF Score*	
		No.	%	No.	%	Mean	SD
Pretherapy	72	8	11			2.9	1.5
3	68	22	32	18	26	4.3	1.1
12	66	16	24	13	20	4.1	0.9
24	44	10	22	7	16	4.2	0.9

Abbreviations: VF, videofluoroscopy; SD, standard deviation.

*VF scores reported on a scale of one to seven. Higher scores denoted worse function.

decision to exclude the medial RPNs from the targets, which facilitated efforts to spare parts of the PCs, did not result in any recurrence near the spared structures (notwithstanding incidental doses, averaging 48 Gy at 1.4 Gy/fraction, received by the medial RPNs because of their proximity to targets). Seventeen percent of the patients with oropharyngeal cancer seen at our institution during the time of the study were not eligible to participate because of gross involvement of the RPNs or the posterior pharyngeal wall, which would not allow partial sparing of the PCs. Gross involvement of the RPNs is a poor prognostic factor,²⁵ and the exclusion of these patients may have contributed to the high tumor control rates in our series. Also, 36% of the patients were nonsmokers, similar to other recent series, so these patients likely had human papillomavirus-related cancer that was associated with good prognosis.²⁶ Nevertheless, our results provide clinical affirmation to the lack of anatomic or radiologic evidence of involvement of the medial RPNs and support the target selection strategy employed in patients eligible for this study. Additional confirmatory studies are required, as the one-sided 95% CI for 0 of 73 recurrences near the spared structures is between 0% and 4%.

Evaluation of dysphagia and its comparison with other trials are complicated by multiple patient-reported instruments²⁷; multiple end points for interpretation and summary of VF results¹⁵; poor reproducibility in interpreting the results of VF²⁸; and low correlations between observer, patient, and objective measures, for which observers tend to underestimate dysphagia.^{29,30} Notwithstanding these limitations, the longitudinal results of this study are compatible with mild long-term worsening of dysphagia compared with the pretherapy baseline.

Both observer-rated and patient-reported dysphagia scores worsened significantly early after therapy, followed by gradual improvement through 12 months and subsequent stabilization during the second year. At 12 months, almost all observer-rated scores were 0 or 1, with a score of 1 denoting mild dysphagia without a need for modified diet. It is often difficult to differentiate this grade from the effect of xerostomia affecting patient perception of dysphagia of dry food.³¹ Some series suggest that oropharyngeal tumors are associated with worse dysphagia after CRT compared with other sites.^{12,32,33} Our observer-rated results compare favorably with other series, which reported rates of abnormal diet of 20% to 42% at 12 months^{2,34} and long-term feeding-tube dependency of 12% to 31%.^{2,35-37} It should be noted, however, that clinical factors, such as those identified in this study and in other studies,^{12,38} affect long-term dysphagia and com-

plicate direct comparisons. Also, the exclusion from our study of patients with gross RPNs or posterior pharyngeal wall involvement could have affected the functional results of the study.

The average and standard deviation differences in the patient-reported dysphagia domain scores of the UWQOL and HNQOL at 12 months, compared with pretherapy, were 10 ± 21 and 13 ± 19 , respectively, on 0 to 100 scales. These differences were statistically significant; however, an important issue is their clinical meaningfulness. A difference of one half of the standard deviation is associated with minimal clinically important differences in QOL instruments.^{39,40} According to these criteria, the differences from pretherapy to 12 months in the UWQOL swallowing scores were slightly below threshold, and the differences in the HNQOL Eating Domain (which covers broader aspects like mouth opening, taste, xerostomia, and chewing in addition to swallowing) were slightly greater than threshold. Thus, on average, long-term worsening of patient-reported scores did occur but was clinically mild.

VF scores worsened from mild dysfunction pretherapy to mild-moderate dysfunction soon after therapy, and they did not subsequently improve. Some of the worsening was due to aspirations, which occurred soon after therapy and remained throughout 2 years. Most aspirations were silent; that is, they did not elicit cough response and were not detected by the patients. The 24% rate of VF-based aspiration at 12 months in our series, including 5% who aspirated pretherapy, is at the lower range of the 18% to 81% aspiration rate reported after chemoradiation of all HN sites^{2,11,13,41-44} or 18% to 54% after chemoradiation of oropharyngeal cancer.^{32,44,45} The association between VF-based aspirations and clinical pneumonia, observed in this study and others,^{13,41,46} motivates additional efforts to reduce aspiration rates. The reported correlations between doses to the swallowing structures and aspirations^{5,6} suggest that additional reduction of swallowing structures doses may improve these rates. Additional dose reductions may be achieved via improved IMRT planning, potentially by split-field IMRT compared with the whole-field IMRT used in this study^{47,48} and potentially by better future technology. However, it is unlikely that technology alone will completely eliminate dysphagia. Additional strategies like customization of treatment intensity to predictors of tumor control, improved cytoprotection, better targeted radiosensitization, and prompt swallow therapy when indicated are required for additional progress.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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