INTENSITY-MODULATED RADIOTHERAPY OF HEAD AND NECK CANCER AIMING TO REDUCE DYSPHAGIA: EARLY DOSE–EFFECT RELATIONSHIPS FOR THE SWALLOWING STRUCTURES

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Purpose: To present initial results of a clinical trial of intensity-modulated radiotherapy (IMRT) aiming to spare the swallowing structures whose dysfunction after chemoradiation is a likely cause of dysphagia and aspiration, without compromising target doses.

Methods and Materials: This was a prospective, longitudinal study of 36 patients with Stage III–IV oropharyngeal (31) or nasopharyngeal (5) cancer. Definitive chemo-IMRT spared salivary glands and swallowing structures: pharyngeal constrictors (PC), glottic and supraglottic larynx (GSL), and esophagus. Lateral but not medial retropharyngeal nodes were considered at risk. Dysphagia endpoints included objective swallowing dysfunction (video-fluoroscopy), and both patient-reported and observer-rated scores. Correlations between doses and changes in these endpoints from pre-therapy to 3 months after therapy were assessed.

Results: Significant correlations were observed between videofluoroscopy-based aspirations and the mean doses to the PC and GSL, as well as the partial volumes of these structures receiving 50–65 Gy; the highest correlations were associated with doses to the superior PC ($p = 0.005$). All patients with aspirations received mean PC doses $>60$ Gy or PC $V_{65} > 50\%$, and GSL $V_{50} > 50\%$. Reduced laryngeal elevation and epiglottic inversion were correlated with mean PC and GSL doses ($p < 0.01$). All 3 patients with strictures had PC $V_{70} > 50\%$. Worsening patient-reported liquid swallowing was correlated with mean PC ($p = 0.05$) and esophageal ($p = 0.02$) doses. Only mean PC doses were correlated with worsening patient-reported solid swallowing ($p = 0.04$) and observer-rated swallowing scores ($p = 0.04$).

Conclusions: These dose–volume-effect relationships provide initial IMRT optimization goals and motivate further efforts to reduce swallowing structures doses to reduce dysphagia and aspiration.

IMRT, Dysphagia, Aspiration, Head and neck cancer, Radiotherapy.

INTRODUCTION

Intensification of the therapy for head and neck cancer, by altered fractionated radiotherapy (RT) or the addition of concurrent chemotherapy, has resulted in improved tumor control rates. The main late sequela following treatment intensification has been increasing rates and severity of long-term dysphagia (1). For example, Radiation Therapy Oncology Group (RTOG) study 91-11 randomized patients between RT alone or RT concurrent with cisplatin and demonstrated improved tumor control rates in the chemo-RT arm. However, 1 year after therapy 23% of the patients in the chemo-RT arm could eat only soft/liquid food, compared with 9% in the RT-alone arm (2). Studies in which the chemo-RT regimens were intensified even further in an effort to improve tumor control rates reported 1-year rates of feeding-tube dependence of 20% in the experimental regimens (1). Evidence has recently emerged that aspiration pneumonia is associated with dysphagia after chemo-RT, constituting an underreported sequela of therapy (3, 4).

Improvements in target dose conformity may reduce the rate and severity of dysphagia following intensive therapy.

Conflict of interest: none.

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if these improvements can sufficiently reduce the doses delivered to the anatomic structures whose malfunction after intensive chemo-RT causes dysphagia and aspiration. We have recently initiated studies to investigate this issue. The first step in these studies was the identification of the most important swallowing-related structures. The pharyngeal constrictors (PC) and the glottic and supraglottic larynx (GSL) were found to change anatomically after intensive chemo-RT, and their malfunction explained the posttherapy abnormalities observed in objective assessments of swallowing (5). Certain intensity-modulated radiotherapy (IMRT) strategies (dysphagia/aspiration-specific IMRT) achieved improved sparing of these swallowing structures, without compromising target irradiation, compared with “standard” IMRT (5). We have subsequently initiated a prospective trial aiming to assess the clinical benefits gained by these strategies. Initial results of this trial are presented here, focusing on the relationships between the doses delivered to the swallowing structures that we aimed to spare (PC, GSL, and esophagus) and the changes in the objective and subjective measures of swallowing dysfunction and aspiration from before to 3 months after therapy.

**METHODS AND MATERIALS**

This is a prospective, longitudinal study of chemo-IMRT for head-and-neck cancer approved by the Institutional Review Board of the University of Michigan; all patients signed a study-specific informed consent form. Eligible patients were those with Stage III/IV squamous cell carcinoma of the head and neck who had not received prior therapy, had a Karnofsky performance status ≥60, and who were recommended to receive primary therapy with chemo-RT. The main study objective was assessing treatment-related effects on dysphagia measures. To reduce tumor-related effects on these endpoints, we excluded patients with laryngeal or hypopharyngeal cancer, owing to their high prevalence of pre-existing swallowing abnormalities and aspiration (6), and because tumor response to therapy might have affected the results in these patients.

**Radiotherapy**

The principles of target selection and definition have been detailed elsewhere (7, 8). The targets in the low neck were outlined and included in the IMRT plans; anterior low-neck fields abutting the upper neck IMRT plans were not used in any patient. Of particular importance for this study was the delineation of the retropharyngeal (RP) nodes. These nodes were defined as targets for all nasopharyngeal and almost all oropharyngeal cancers, particularly if these improvements can sufficiently reduce the doses delivered to the anatomic structures whose malfunction after intensive chemo-RT causes dysphagia and aspiration. We have recently initiated studies to investigate this issue. The first step in these studies was the identification of the most important swallowing-related structures. The pharyngeal constrictors (PC) and the glottic and supraglottic larynx (GSL) were found to change anatomically after intensive chemo-RT, and their malfunction explained the posttherapy abnormalities observed in objective assessments of swallowing (5). Certain intensity-modulated radiotherapy (IMRT) strategies (dysphagia/aspiration-specific IMRT) achieved improved sparing of these swallowing structures, without compromising target irradiation, compared with “standard” IMRT (5). We have subsequently initiated a prospective trial aiming to assess the clinical benefits gained by these strategies. Initial results of this trial are presented here, focusing on the relationships between the doses delivered to the swallowing structures that we aimed to spare (PC, GSL, and esophagus) and the changes in the objective and subjective measures of swallowing dysfunction and aspiration from before to 3 months after therapy.

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The planning target volumes (PTVs) were created by uniform expansions of the CTVs by 0.3 cm. These margins were set according to our findings that by using daily on-line imaging and correction of the systematic setup errors, setup errors were reduced to a mean (± SD) of 1 ± 1.5 mm (unpublished data).

Contouring of the swallowing structures, including the PC and the GSL, has been detailed previously (5). In brief, the three parts of the PC (upper, middle, and lower) were outlined as a single structure for which the cranial-most extent was the caudal tips of the pterygoid plates and the caudal-most extent was the inferior border of the cricoid cartilage. For purposes of analysis, the constrictors were considered as one structure and were also schematically divided into three parts: the superior PC was defined from the cranial-most extent through the upper edge of the hyoid bone, the middle PC was defined from the upper through the lower edge of the hyoid, and the inferior PC was defined from below the hyoid through the inferior edge of the cricoid. Caudal to the inferior border of the cricoid, the esophagus was contoured, with its caudal-most extent corresponding to the caudal-most extent of the low neck targets. The GSL was contoured as a single structure.

The prescribed doses were 70 Gy at 2.0 Gy per fraction to gross disease PTVs and 59–63 Gy at 1.7–1.8 Gy per fraction to low- and high-risk subclinical PTVs, respectively, delivered concomitantly. Inverse-planned beamlet IMRT was planned using an in-house optimization system, and target dose homogeneity (≤1% of the PTV could receive <99% or >107% prescribed dose) was achieved using previously detailed methods (21). The optimization cost functions aimed at reducing maximal mandibular dose (<72 Gy), mean parotid gland (≤26 Gy), and mean noninvolved oral cavity dose (≤30 Gy).
Dosimetric goals for the swallowing structures outside the PTVs were arbitrarily set at a maximal dose of 50 Gy, with an additional lightly weighted penalty for any dose above zero, to lower their doses as much as possible (rather than being set at the allowed maximum). In all patients, the plans addressed target prescription goals as the highest priority, whereas critical organ dosimetric goals (apart from maximal spinal cord dose) were secondary. Optimization strived to spare the parts of the swallowing structures, major salivary glands, and oral cavity that were outside the PTVs. This was achieved by subtracting the PTVs from each structure, yielding the noninvolved structures for optimization. For purposes of dosimetric correlations with outcome, it was assumed that the doses to the whole structures were clinically meaningful. Dose–volume histogram analyses were, therefore, performed and reported for the whole structures, including the parts that overlapped with the PTVs.

Chemotherapy and supportive care
For patients with non-nasopharyngeal cancer, chemotherapy was given once per week during the 7-week RT course: carboplatin (AUC 1) i.v. over 30 min and paclitaxel 30 mg/m² i.v. over 1 h. Patients with nasopharyngeal cancer received cisplatin 100 mg/m² every 3 weeks during RT, starting on the first RT day. Antiemetics and pre- and postchemotherapy hydration were delivered according to standards of care. Percutaneous endoscopic gastrostomy feeding tubes were inserted before or during therapy in patients who were malnourished or if weight loss during therapy approached 10%. Intravenous hydration was delivered routinely once or twice weekly.

Evaluation of dysphagia
Swallowing dysfunction and dysphagia were evaluated before therapy and 3 months after therapy with objective, patient-reported, and observer-assessed instruments. The study endpoints were the changes in these measures from before to 3 months after therapy.

Objective evaluation was performed using videofluoroscopy (VF) including modified barium swallow study and esophagogram. Each patient was viewed in the lateral and anteroposterior planes and asked to swallow multiple trials of various food consistencies. A timer was activated at the start, and the examinations were monitored and recorded. Abnormal timing or duration of each swallowing phase was defined when it was beyond the range found in normal controls (22). Aspiration was defined as occurring once the bolus passed the level of the vocal folds and entered the subglottic region (22). Posttherapy worsening ("aspirators") was defined in patients who either developed new-onset aspiration or whose frequency of aspirations worsened after compared with before therapy. Base of tongue motion causes its contact with the posterior pharyngeal wall and is essential for the propulsion of the bolus. Loss of contact due to reduced motion was recorded. Pharyngeal residue was defined as any portion of the bolus remaining in the vallecula or pyriform sinuses after the swallow, with the potential risk of aspiration after the swallow. Laryngeal elevation and anterior movement during the swallow facilitates closure of the airway and opening of the upper esophageal sphincter, essential for airway protection. It was determined by measuring the extent of maximal laryngeal rise during swallow. Epiglottic function was measured as the degree of movement of the epiglottis from vertical to horizontal during swallowing: normal, reduced, and nonfunction were defined as full movement to the horizontal position, incomplete movement, and no observed movement, respectively. Cricopharyngeal muscle dysfunction was defined as prominence (indentation of the cricopharyngeal muscle into the lumen of the hypopharynx), incomplete relaxation (narrowing of the contrast bolus column, resulting in reduced contrast after the swallow), and premature closure. Each VF was evaluated simultaneously by two speech pathologists (T.L. and M.H.), who summarized and scored the findings after reaching a consensus.

Patient-reported dysphagia was assessed with two validated head-and-neck cancer–related quality-of-life questionnaires given to patients before therapy and 3 months after the completion of therapy. They included the Head and Neck Quality of Life (HNQOL) instrument (23) and the University of Washington Head and Neck–related Quality-of-Life (UWQOL) instrument (24). The HNQOL questionnaire contains two questions related to dysphagia ("How much are you bothered by swallowing liquids?" and "How much are you bothered by swallowing solids?") each having five possible answers ("not at all", "slightly", "moderately", "a lot", and "extremely"). The UWQOL contains one swallowing question with five possible answers ("I swallow normally", "I cannot swallow certain solid food", "I can only swallow soft food", "I can only swallow liquid foods", and "I cannot swallow").

Observer-assessed dysphagia was included in the recording of acute toxicity, made weekly during therapy and 1 month after therapy using the Common Terminology Criteria for Adverse Events (CTCAE), and in the recording of late toxicity, made 3 months after the completion of therapy using the RTOG/European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scale.

Statistical analysis
Pair-wise relationships of doses and function were assessed using Pearson correlation coefficients. Doses received by the swallowing structures in patients with and without aspiration were compared using the Wilcoxon rank-sum test. Tests for change in function from before therapy to 3 months after therapy were performed using McNemar’s test for dichotomous outcomes, Wilcoxon signed-rank test for continuous parameters, and generalized linear model with logit link and generalized estimating equation for ordinal category parameters, such as "epiglottic function". The dose–response relationships between each of the dysphagia outcome measures and dose measures were modeled using multiple regression analyses, with change-of-score of dysphagia measure from before therapy to 3 months after therapy as the dependent variable. Statistical significance was determined at \( p \leq 0.05 \) (two-tailed).

RESULTS
Patient characteristics and dysphagia assessments
The study included 36 subjects with oropharyngeal (31) or nasopharyngeal (5) cancer. Patient and tumor characteristics are detailed in Table 1.

The mean doses and the partial volumes receiving specified doses (Vₚₘₛ) to the swallowing structures are detailed in Table 2. For each swallowing structure, highly significant correlations were noted between the mean dose (calculated for the whole structure) and the percentage of the volume of the structure that lies inside the PTVs, with Spearman correlation coefficients of 0.9, 0.8, and 0.5 for the PC, GSL, and esophagus, respectively \((p < 0.001\) in all cases). Additional analysis demonstrated a strong correlation between the mean dose and each of the Vₚₘₛ receiving 40, 50, 60, and 65 Gy for each of the swallowing structures, with correlation coefficients \(\geq 0.8\) in all cases \((p < 0.001\). Therefore, further
analyses emphasized the relationships between the dysphagia endpoints and the mean doses to the swallowing structures. The results of the VF studies are detailed in Table 3. Three patients (8%) aspirated according to the pretreatment VF, and 16 (44%) aspirated 3 months after treatment ($p = 0.002$). Other statistically significant VF changes after treatment compared with before therapy included decreases in normal epiglottic function, laryngeal elevation, and base of tongue function, and increases in pharyngeal transit time (for liquids) and in vallecular residue after swallowing. No patient had strictures before therapy, whereas three (8%) developed strictures at 3 months ($p = 0.25$).

All patient-reported dysphagia scores, assessed by the HNQOL and UWQOL questionnaires, were significantly worse at 3 months compared with before therapy (Table 4).

The observer-reported acute CTCAE and late RTOG/EORTC esophageal/pharyngeal and mucosal toxicity scores are detailed in Table 5. The median of the highest acute
esophageal/pharyngeal toxicity was 2; 13 patients (36%) had feeding tubes inserted either before therapy (2) or during therapy (11). Three months after the completion of therapy, the median late toxicity score was 1.0, with 3 patients (8%) still dependent on gastric feeding (late Grade 3 toxicity), 8 (22%) requiring soft/liquid food (Grade 2), 9 (25%) with mild dysphagia but able to eat a regular diet (Grade 1), and 16 (44%) with no dysphagia.

**Swallowing structure doses vs. VF-based aspiration**

The mean doses to the entire PC, to each of the individual constrictors, and to the GSL (but not to the esophagus), as well as the V_{50} for the PC and GSL, were significantly higher in aspirators than in non-aspirators (Table 6 and Fig. 2). The mean doses to the entire PC, and to the superior PC in particular, had the strongest correlations with aspiration, with estimated increase in odds of 1.38 (p < 0.01) and 1.53 (p < 0.01), respectively, in the risk of aspiration associated with a 1-Gy increase of mean dose. Of the 9 patients receiving mean PC doses ≤60 Gy, none aspirated, whereas 16 aspirated out of 26 patients who received PC mean doses >60 Gy (Fig. 2). Dose–volume histograms (Fig. 3a) for the PC showed the presence of thresholds below which aspiration did not occur: V_{40} = 90%, V_{50} = 80%, V_{60} = 70%, and V_{65} = 50%. Of the individual constrictors (Figs. 3b–d), dose–volume thresholds were most significant statistically and could be most easily defined for the superior PC, including V_{40} = 95%, V_{50} = 90%, V_{60} = 80%, and V_{65} = 70%. Although similar dose–volume thresholds were more difficult to establish for the GSL, no aspiration was noted when the GSL V_{50} was <50%, with the exception of one outlier (Fig. 3e). No dose–volume thresholds were apparent for the esophageal doses (Fig. 3f), consistent with the odds ratio analysis detailed in Table 6.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Question</th>
<th>Scale*</th>
<th>Before therapy, median (range)</th>
<th>3 mo after therapy, median (range)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNQOL</td>
<td>Difficulty swallowing liquids</td>
<td>0–4</td>
<td>0 (0–3)</td>
<td>1 (0–3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HNQOL</td>
<td>Difficulty swallowing solids</td>
<td>0–4</td>
<td>0 (0–3)</td>
<td>2 (0–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UWQOL</td>
<td>Difficulty swallowing overall</td>
<td>10–50</td>
<td>10 (10–30)</td>
<td>20 (10–50)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 5. Observer-rated toxicity scores

<table>
<thead>
<tr>
<th>Observer-rated toxicities</th>
<th>Scale*</th>
<th>Median (range)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest acute mucosal toxicity</td>
<td>0–4</td>
<td>3 (2–3)</td>
<td>2.6 (0.5)</td>
</tr>
<tr>
<td>Highest acute esophageal/pharyngeal toxicity</td>
<td>0–4</td>
<td>2 (2–3)</td>
<td>2.3 (0.5)</td>
</tr>
<tr>
<td>Late esophageal/pharyngeal toxicity (at 3 mo)</td>
<td>0–4</td>
<td>1 (0–3)</td>
<td>1.0 (1.1)</td>
</tr>
</tbody>
</table>

* See Methods and Materials for definitions of scale categories. Lower scores reflect less toxicity.

There were no significant differences in age, gender, T stage, N stage, gross tumor volume, primary tumor site, or chemotherapeutic regimen between aspirators and non-aspirators. However, there was a trend toward larger GTVs in aspirators (p = 0.08).

**Swallowing structure doses vs. VF-based strictures**

Analysis of the relationships between the swallowing structure doses and the development of strictures was limited owing to the small number of patients (3) with strictures (all were located in the hypopharynx), which precluded statistical significance. Patients with strictures received a mean (± SD) PC dose of 67 ± 2.0 Gy, compared with 63 ± 5 Gy for stricture-free patients (p = 0.25). Dose–volume histograms of the PC suggest thresholds below which strictures did not develop, including a mean dose of 66 Gy, as well as dose volume thresholds of V_{50} = 85%, V_{60} = 70%, and V_{65} = 60% (Fig. 4). Neither GSL mean doses (60 ± 12 Gy vs. 56 ± 10 Gy) nor esophageal mean doses (41 ± 13 Gy vs. 42 ± 6 Gy) showed any trend for differences between patients with and without strictures.

**Swallowing structure doses vs. other VF parameters**

In addition to aspiration and stricture, examination of the relationships between the pre- to posttreatment changes in other VF parameters, detailed in Table 3, and the swallowing structure doses, revealed that the mean doses to the PC and GSL were significantly higher in patients with worsening epiglottic function and decreased laryngeal elevation than in patients whose function did not worsen (p < 0.01). No significant relationships were noted between the dose variables and worsening in base of tongue function, pharyngeal transit time, pharyngeal residue, vallecular stasis, pyriform sinus stasis, or cricopharyngeus dysfunction.

**Swallowing structure doses vs. patient-reported dysphagia**

Both mean esophageal (p = 0.02) and PC (p = 0.05) doses were significantly associated with the HNQOL assessment of difficulty swallowing liquids, with the superior PC mean dose having the strongest relationship (p = 0.01) among the individual constrictors. Mean PC dose (p = 0.04), but not mean esophageal or GSL doses, was correlated with worsening of HNQOL scores of solid food swallowing, with mean superior PC dose (p = 0.003) showing the strongest association among the individual constrictors. For the UWQOL scores, the patient-reported decrease in swallowing ability
was significantly associated only with the mean PC dose ($p = 0.04$), with the superior PC mean dose having the highest correlation ($p = 0.03$) among the individual constrictors.

Swallowing structure doses vs. observer-assessed dysphagia

Table 7 details the correlations between the mean swallowing structure doses and the acute and 3-month toxicities. No significant correlation was observed between the mean dose to any structure and the severity of acute mucositis (which was Grade 3 in the majority of patients). Esophageal mean dose was significantly correlated with the highest acute pharyngeal/esophageal toxicity observed in each patient ($p = 0.04$), whereas the mean PC dose was significantly associated with the 3-month late esophageal/pharyngeal toxicity ($p = 0.01$).

**DISCUSSION**

In this clinical study of IMRT aiming at reducing dysphagia, we have found statistically significant, and potentially clinically important, dose–volume effect relationships for dysphagia and aspiration, which can serve as initial dosimetric goals for IMRT. These relationships support the hypothesis that reducing the doses to the swallowing structures may reduce the prevalence and severity of dysphagia; however, they do not yet prove this hypothesis because they do not establish a cause–effect association. In any case, our findings motivate efforts to further reduce these doses, without compromising target doses. The limiting factor in this regard is the percentage of the volume of each of the swallowing structures that is encompassed by the PTVs, found in our study to correlate highly with the mean doses to the whole structure. The first step in the efforts to improve the sparing of the swallowing (and other) structures in this series has been made by daily on-line imaging and correction of setup deviations, which facilitated reducing PTV margins to 3 mm. Future efforts at our institution include the elimination of PTV margins and the construction of IMRT plans that cover the CTVs and their known distribution of setup uncertainties (25). Additional potential strategies like proton beam IMRT or structure and target assessments and adaptation during therapy should be evaluated.

We have found significant dose–volume effect relationships regarding aspiration for the PCs as a whole and also

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**Table 7. Relationships between doses to the swallowing structures and VF-based aspiration**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Median (range) of mean doses (Gy)</th>
<th>Median (range) of $V_D$ (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-aspirators</td>
<td>Aspirators</td>
<td>Non-aspirators</td>
<td>Aspirators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSL</td>
<td>54 (22–69)</td>
<td>61 (45–69)</td>
<td>—</td>
<td>—</td>
<td>1.12</td>
</tr>
<tr>
<td>Esophagus</td>
<td>36 (17–58)</td>
<td>46 (15–61)</td>
<td>—</td>
<td>—</td>
<td>1.05</td>
</tr>
<tr>
<td>PC</td>
<td>62 (51–70)</td>
<td>66 (61–72)</td>
<td>—</td>
<td>—</td>
<td>1.38</td>
</tr>
<tr>
<td>Superior</td>
<td>65 (58–74)</td>
<td>70 (65–74)</td>
<td>—</td>
<td>—</td>
<td>1.53</td>
</tr>
<tr>
<td>Middle</td>
<td>62 (53–72)</td>
<td>66 (59–75)</td>
<td>—</td>
<td>—</td>
<td>1.17</td>
</tr>
<tr>
<td>Inferior</td>
<td>49 (30–66)</td>
<td>56 (43–70)</td>
<td>—</td>
<td>—</td>
<td>1.11</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI = confidence interval. Other abbreviations as in Table 2.

$V_D$ = percentage structure volume receiving $\geq D$ dose.

Odds ratio estimates the odds of aspiration associated with a 1-Gy increase in mean dose or 1% increase in $V_D$.

Fig. 2. Distribution of swallowing structure mean doses in aspirators versus non-aspirators. Median values represented by a horizontal bar. PC = pharyngeal constrictors; GSL = glottic and supraglottic larynx.
for each of their parts: the superior, middle, and inferior constrictors. These relationships were statistically strongest for the superior constrictor. The importance of the superior PC doses may be explained by the details of the swallowing mechanism. Elevation of the larynx and pharynx during the swallow is essential for airway protection and bolus propulsion. This elevation is facilitated by the contraction of longitudinal muscles (glossopharyngeus, stylopharyngeus, salpingopharyngeus, and palatopharyngeus), which blend with the circular fibers of the superior constrictor (26). As the larynx and pharynx are pulled up and forward by these muscles, they are pulled away from the lower posterior pharyngeal wall and facilitate opening of the upper esophageal sphincter at the cricopharyngeus level (27). These
mechanisms of swallowing and protection from aspiration, as well as our VF-based results, suggest that the benefits from efforts to spare the swallowing structures are likely to be maximized if they include the superior constrictors rather than being confined to the esophagus and its upper inlet. Our findings that patient-reported dysphagia was also highly correlated with the doses to the superior PC serve as an independent validation of the importance of sparing this structure. In addition, a recently presented study in which brachytherapy was found to reduce dysphagia, concluded that the doses to the upper and middle constrictors were the most significant predictors of patient-reported dysphagia (28).

We have also found significant correlations between the dose–volume parameters in the GSL and dysphagia. Several recently presented studies examined various dysphagia endpoints after conventional radiotherapy and found significant correlations with the doses to the supraglottic (29, 30) or glottic (29) larynx. In general, these correlations were similar to those reached by our longitudinal study, in which the endpoints were the differences between the pre- and the postradiation dysphagia measures (rather than the postradiation dysphagia alone). In aggregate, these studies affirm the potential benefits in reducing the doses to both glottic and supraglottic larynx.

The dose–volume effect relationships for the swallowing structures may depend on the intensity of the chemo-RT regimen. In the present study, no strictures were observed in patients receiving mean PC dose <66 Gy. In comparison, we have previously found that after an intensive gemcitabine-RT regimen, the minimal dose associated with strictures was 50 Gy (3). The differences are likely related to the severity of acute mucositis and its consequential effect on pharyngeal tissue. Chemo-RT regimens that do not differ markedly in the rate and severity of the acute mucositis seem to cause similar types and rates of swallowing abnormalities (6). We therefore anticipate that the dose–volume effect relationships found in the present study, which used a moderate-intensity chemo-RT regimen, will be reproduced after other commonly used regimens of chemo-RT. The site of the primary tumor also affects dose–response relationships, because different primary tumor sites were found to be associated with different rates of both pre- and posttherapy swallowing abnormalities (6). The relative homogeneity of the patient population in our study, most of whom had oropharyngeal cancer, may have facilitated identifying the dose–response relationships for the swallowing structures. The 3-months posttherapy swallowing results reported here, as well as the dose–volume effect relationships, may change over longer observation time. Swallowing seems to reach a steady state after approximately 12 months, as edema subsides and long-term fibrosis develops (31). This issue will be addressed as we continue to collect swallowing endpoints at 12 and 24 months.

Swallowing-related laryngeal and pharyngeal motion during treatment may change dose distributions in these structures compared with those observed in the simulation CT. A detailed study of these effects found that the incidence and duration of swallowing during RT is very low, averaging 0.45% (range, 0–1.5%) of the total irradiation time (32). Also, the mean doses to the swallowing structures were found in our study to be highly correlated with the percentages of the structure volumes inside the PTVs. In a previous study, we found that these percentages did not change significantly when expansion of the swallowing structures to produce planning organ-at-risk volumes was made, compared with the non-expanded structures (5). These data suggest that expanding the swallowing structures to obtain their respective planning organ-at-risk volumes would not alter substantially the planning, optimization, or results of our study. This issue deserves further investigation.

As detailed in Methods and Materials, only the lateral RP nodes, and not the medial ones, were included in the CTVs

Table 7. Observer-rated mucosal and esophageal/pharyngeal toxicities (CTCAE and RTOG scales) vs. swallowing structure mean doses

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Mean ± SD (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC</td>
</tr>
<tr>
<td>Highest acute esophageal/pharyngeal toxicity</td>
<td></td>
</tr>
<tr>
<td>0–2 (mild to moderate)</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>3 (severe)</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>p</td>
<td>0.64</td>
</tr>
<tr>
<td>Highest acute mucosal toxicity</td>
<td></td>
</tr>
<tr>
<td>0–2 (mild to moderate)</td>
<td>65 ± 6</td>
</tr>
<tr>
<td>3 (severe)</td>
<td>62.8 ± 5</td>
</tr>
<tr>
<td>p</td>
<td>0.19</td>
</tr>
<tr>
<td>Esophageal/pharyngeal toxicity at 3 months</td>
<td></td>
</tr>
<tr>
<td>0–1 (none to mild)</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>2–3 (moderate to severe)</td>
<td>67 ± 4</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; RTOG = Radiation Therapy Oncology Group. Other abbreviations as in Table 2.

The toxicity grades were grouped according to the medians (see Table 5).
when the RP nodes were judged to be at risk (unless the lateral RP nodes were grossly involved). This decision facilitated partial sparing of the pharyngeal constrictors and the upper parts of the GSL. We have previously described several RP nodal failures in patients receiving IMRT; all occurred in the lateral RP space, medial to the carotid artery (8). McLaughlin et al. (10) stated that the medial RP nodes have not often been recognized as sites of cancer metastases. Our literature search found several series of head-and-neck cancer that detailed involvement of the lateral and medial RP nodes (11–20). These series demonstrated a very low risk of involvement of the medial RP nodes, as detailed in Table 8: in 10 series reporting a total of 603 patients with RP nodal enlargement or involvement, lateral nodal involvement was found in 98% of the patients, whereas medial nodal involvement was noted in 2%. One of these studies detailed the results of dissections of 11 cadavers and found lateral RP nodes in 9 and medial ones in 1 (20). The afferent lymphatics from the nasopharynx and oropharynx were found in this study to flow to the lateral RP nodes, whereas the medial RP nodes received afferent flow only from the posterior pharyngeal wall. These series suggest that in almost all cases in which the RP nodes are at risk, only the lateral ones are at substantial risk (except for tumors involving the posterior pharyngeal wall). However, some lymphatic channels do traverse the medial RP space, and the consequences of reducing the doses delivered to this space are not yet known. Also, sparing of the swallowing structures results in steeper dose fall-off near the targets in the vicinity of these structures, compared with IMRT plans that do not include such sparing (5). Therefore, outlining the targets requires a high degree of caution, taking into account the lack of certainty in defining the mucosal extent of the gross tumor using current imaging modalities (33). Thus far, at a median follow-up of 20 months, 3 local-regional failures (8%) were observed in the present study; all occurred within the previous GTVs that had received the full prescribed doses.

The IMRT plans in this series included the whole neck. An alternative approach is abutting an IMRT plan for the primary tumor and upper neck with an anterior low-neck field, matched at the thyroid notch, with a small mid-line laryngeal block. This technique reduces the dose to the glottic larynx compared with whole-neck IMRT (34, 35). However, this technique should be used with caution in cases in which the risk to the low/posterior neck is high, because it may result in underdosage of deep-lying parts of these targets. This might have been the reason for some reported low-neck nodal failures (36, 37).

In conclusion, this study has demonstrated that IMRT aiming at sparing the swallowing structures is feasible. Significant relationships were found between dose–volume parameters for these structures and objective and subjective measures of swallowing dysfunction and dysphagia. These relationships can now serve to define optimization goals, and they motivate efforts to reduce these doses as much as possible. Longer follow-up is clearly necessary. Most importantly, care in the outlining of targets in the vicinity of these structures, avoiding target underdosing, and determining and reporting the locations of locoregional recurrences, are essential to ensure that the rates of local recurrences do not increase compared with the rates observed previously after IMRT.

### REFERENCES


