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# CAN IMRT OR BRACHYTHERAPY REDUCE DYSPHAGIA ASSOCIATED WITH CHEMORADIOTHERAPY OF HEAD AND NECK CANCER? THE MICHIGAN AND ROTTERDAM EXPERIENCES

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## Abstract

**Purpose—**Dysphagia is a major late complication of intensive chemoradiotherapy of head and neck cancer. The initial clinical results of intensity-modulated radiotherapy (IMRT), or brachytherapy, planned specifically to reduce dysphagia are presented.

**Patients and Methods—**Previous research at Michigan University has suggested that the pharyngeal constrictors and glottic and supraglottic larynx are likely structures whose damage by chemo-RT causes dysphagia and aspiration. In a prospective Michigan trial, 36 patients with oropharyngeal (*n* = 31) or nasopharyngeal (*n* = 5) cancer underwent chemo-IMRT. IMRT cost functions included sparing noninvolved pharyngeal constrictors and the glottic and supraglottic larynx. After a review of published studies, the retropharyngeal nodes at risk were defined as the lateral, but not the medial, retropharyngeal nodes, which facilitated sparing of the swallowing structures. In Rotterdam, 77 patients with oropharyngeal cancer were treated with IMRT, three dimensional RT, or conventional RT; also one-half received brachytherapy. The dysphagia endpoints included videofluoroscopy and observer-assessed scores at Michigan and patient-reported quality-of-life instruments in both studies.

**Results—**In both studies, the doses to the upper and middle constrictors correlated highly with the dysphagia endpoints. In addition, doses to the glottic and supraglottic larynx were significant in the Michigan series. In the Rotterdam series, brachytherapy (which reduced the doses to the swallowing structures) was the only significant factor on multivariate analysis.

**Conclusion—**The dose–response relationships for the swallowing structures found in these studies suggest that reducing their doses, using either IMRT aimed at their sparing, or brachytherapy, might achieve clinical gains in dysphagia.

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**Keywords**

Intensive-modulated radiotherapy; Brachytherapy; Dysphagia; Head and neck cancer; Chemoradiotherapy

## 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 after treatment intensification has been increasing rates and severity of long-term dysphagia (1). Dysphagia after chemo-RT of head-and-neck cancer is associated with aspiration, an underreported complication of therapy (2).

A previous study at the University of Michigan found that the pharyngeal constrictors (PCs) and the glottic and supraglottic larynx (GSL) changed anatomically after intensive chemo-RT, and their malfunction explained the post-therapy abnormalities observed in the objective assessments of swallowing (3). Intensity-modulated RT (IMRT) plans whose cost function included sparing these structures without compromising target irradiation achieved significantly reduced doses to the swallowing structures compared with “standard” IMRT (3). A prospective trial aiming to assess the clinical benefits gained by these strategies was subsequently initiated at Michigan.

At Erasmus Medical Center in Rotterdam, brachytherapy (BT) has been used for many years as a tool to facilitate the delivery of a high tumor dose (4,5). BT substantially reduces the doses delivered to neighboring tissues, specifically the neighboring swallowing structures, compared with conventional RT.

Both IMRT aimed at the sparing of the swallowing structures at Michigan and BT at Rotterdam produced a wide dose range in these structures. This has allowed studies of dose–response relationships, whose initial results are summarized in this report.

## PATIENTS AND METHODS

### Patients and therapy

At Michigan, all 36 patients with oropharyngeal ($n$ = 31) or nasopharyngeal ($n$ = 5) cancer received IMRT, which included cost functions for sparing the PCs, GSL, and esophagus, without under-dosing the targets, according to previously detailed methods (3). Treatment was delivered in 35 fractions, with the gross disease (clinical target volume [CTV]1), high-risk (CTV2), and low-risk (CTV3) targets receiving 70, 63, and 59 Gy at 2.0, 1.8, and 1.7 Gy/fraction, respectively, concurrent with weekly carboplatin and Taxotere (oropharynx) or cisplatin (nasopharynx). At Rotterdam, 77 patients were treated with IMRT ($n$ = 37), three-dimensional conformal RT ($n$ = 22), or computed tomography-based parallel-opposed beam techniques. In 52% of the patients, BT was used according to previously detailed methods (4,5). Additional details regarding the treatment methods used in Rotterdam have been previously published (6).

### Target and structure delineation

Of particular importance to target delineation for IMRT at Michigan was the delineation of the retropharyngeal (RP) nodes. These nodes were defined as targets for all nasopharyngeal and almost all oropharyngeal cancers, particularly in patients with other clinically involved nodes. The RP nodes are divided into the lateral and medial RP nodal chains. The lateral RP nodes (“nodes of Rouviere”) lie medial to the carotid arteries and lateral to the longus coli and capitis muscles, and the medial RP nodes are intercalated along the lymphatics near the midline. Only the lateral RP nodes were defined as targets, and their CTVs were contoured in the spaces medial to the carotid arteries. The medial RP nodes were not defined as targets (unless radiologic evidence was present for gross lateral RP involvement), because they have been reported to be very rarely involved as metastatic sites (7,8). Additional details regarding RP target delineation for this study, and its rationale, have been previously published (9). The inclusion in the CTVs of only the lateral RP nodes, and the exclusion of the medial ones, facilitated the sparing of the swallowing structures.

Contouring of the swallowing structures, including the PCs and GSL, has been previously detailed (3). In brief, the three parts of the PCs (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 the purposes of analysis, the PCs 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 cartilage. Caudal to the inferior border of the cricoid, the esophagus was contoured, and its caudal-most extent corresponded to the caudal-most extent of the low neck targets. The GSL was contoured as a single structure.

### Evaluation of dysphagia

At Michigan, dysphagia was evaluated before and periodically after therapy with videofluoroscopy, quality-of life (QOL) instruments, including the HN-QOL questionnaire and the University of Washington HN-QOL Questionnaire, and the observer-rated Radiation Therapy Oncology Group late toxicity, scored by the treating physicians. At Rotterdam, dysphagia was assessed by three QOL instruments: the performance status questionnaire assessing “eating in public” and “normalcy of diet,” the European Organization for Research and Treatment of Cancer head-and-neck 35-item “swallowing” and “aspiration” questionnaire, and the M.D. Anderson dysphagia inventory–dysphagia-specific QOL questionnaire for head-and-neck cancer.

## RESULTS

In the Michigan study, at 3 months after therapy, video-fluoroscopy-based strictures were observed in 3 patients (8%) and aspirations (passage of barium past the vocal cords) in 16 (44%). The mean ± SD dose to the PC, GSL, and esophagus was 64 ± 5, 56 ± 10, and 41 ± 13 Gy, respectively. Significant correlations were observed between video-fluoroscopy-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 greatest correlations were associated with doses to the superior PC ($p = 0.005$). All patients with aspirations had received a mean PC dose of >60 Gy or PC $V_{65}$ >50%, and GSL $V_{50}$ >50%. Reduced laryngeal elevation and epiglottic inversion correlated with the mean PC and GSL doses ($p < 0.01$). All 3 patients with strictures had received a PC $V_{70}$ >50%. Worsening patient-reported liquid swallowing was correlated with the mean PC ($p = 0.05$) and esophageal ($p = 0.02$) doses. Only the mean PC doses correlated with worsening patient-reported solid swallowing ($p = 0.04$) and observer-rated swallowing scores ($p = 0.04$). Of the individual PCs, the mean dose to the superior PC had the greatest correlation with the observer-rated and patient-reported dysphagia scores. Additional details of the results at Michigan have been previously published (9).

In the Rotterdam study, of 77 patients, 60 were alive and without evidence of disease. The locoregional relapse-free survival rate was 92% at a mean follow-up of 41 months (range 4–72). On univariate analysis, a significant correlation was observed between the doses delivered to the superior or middle PC, and the performance status scores, dysphagia scores of the European Organization for Research and Treatment of Cancer Head-and-Neck 35-item questionnaire, and M.D. Anderson dysphagia inventory–dysphagia-specific QOL questionnaire for head-and-neck cancer. In each QOL instrument, BT was associated with better outcome ($p = 0.01$). On multivariate analysis, BT was the predominant factor associated with reduced symptoms, because its use significantly reduced the doses to the superior and middle PCs. Additional details of the results at Rotterdam have been previously published (6).

## DISCUSSION

In the Michigan and Rotterdam studies, statistically significant correlations were found between the dysphagia endpoints, including aspiration, and the dose–volume parameters for the superior and middle PCs. These relationships can be explained by several important details of the swallowing mechanism. Elevation of the larynx and pharynx during swallowing is essential for airway protection and bolus propulsion. This elevation is facilitated by contraction of the longitudinal muscles, which blend with the circular fibers of the superior PC, including the stylopharyngeus, salpingopharyngeus, and palatopharyngeus. 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 cricopharyngeal level (3,10). These mechanisms of swallowing and protection from aspiration, as well as our results, suggest that the benefits from efforts to spare the swallowing structures are likely to be maximized if they include the superior PCs, rather than being confined to the esophagus and its upper inlet (*i.e.*, the caudal part of the inferior PCs).

The dose–effect relationships we have reported can now serve to define the optimization goals for IMRT. They should motivate efforts to reduce these doses as much as possible using either IMRT or BT, or both. 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 or BT.

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