Comparison of Swallowing Function After IMRT and Conventional Radiotherapy For Head and Neck Cancer

Barbara Roa Pauloski, Ph.D.,

Communication Sciences and Disorders, Northwestern University, Evanston, IL

Alfred W. Rademaker, Ph.D.,

Preventive Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University
Feinberg School of Medicine, Chicago, IL

Jerilyn A. Logemann, Ph.D.,

Communication Sciences and Disorders, Northwestern University, Evanston, IL

Muveddet Discekici-Harris, MS¹, and

Communication Sciences and Disorders, Northwestern University, Evanston, IL

Bharat B Mittal, M.D.

Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University
Feinberg School of Medicine, Chicago, IL

Keywords

dysphagia; head & neck cancer; IMRT; conventional radiotherapy

Introduction

Over the past twenty years, there has been an increase in the use of radiotherapy with or without chemotherapy as a primary treatment modality for cancer of the head and neck [1-10]. Although the primary goal of treatment is cure, a perceived additional benefit of this modality is the preservation of the organs of the head and neck, with the underlying assumption being that preservation of structure will result in preservation of function [11,12]. The current literature on swallowing function in patients treated with radiotherapy with or without chemotherapy for cancer of the head and neck indicates that, despite preservation of the structures of the head and neck, swallow function is not maintained at normal levels after treatment [13-24]. Patients may experience significant functional abnormality during the first year post treatment completion. Swallow motility disorders reported at frequencies of greater than fifty percent for patients treated with chemoradiotherapy to various sites in the head and neck include reduced anterior-posterior oral tongue movement, reduced oral tongue strength, reduced tongue base retraction, increased oral residue, increased velopharyngeal closure duration, reduced epiglottic

Contact author: Barbara Roa Pauloski, Ph.D., Northwestern University, 2240 Campus Drive, Evanston, IL 60208-3540, Phone: (847) 917-6213, FAX: (847) 491-5692, bpauloski@sbcglobal.net.

¹Currently at: Searle Center for Advanced Learning and Teaching, Northwestern, University, Evanston, IL

inversion, slowed or reduced laryngeal elevation, impaired pharyngeal constrictor motility, increased pharyngeal residue, delayed pharyngeal swallow, and delayed laryngeal vestibule closure [13,15,16,17,19,25,26,27].

Attempts have been made to minimize the amount of damage to normal tissues and hopefully reduce the adverse effects of chemoradiation on swallowing function. The intensity of the radiation beam can be modulated in order to decrease doses to normal structures without compromising the dose to the tumor. Intensity modulated radiotherapy (IMRT) is an advanced form of 3-D conformal radiation therapy with the ability to precisely target and escalate radiation doses to the tumor while reducing radiation exposure to surrounding normal structures [28]. Initially studied in terms of its impact on salivary flow and xerostomia (the perception of “dry mouth”), IMRT has been successful in reducing damage to the parotid gland and preserving salivary flow [29-34].

The impact of IMRT on posttreatment swallowing function has also been investigated. Preliminary work with tissue sparing techniques indicate that patients demonstrate less severe ratings of dysphagia, significantly fewer days of tube feeding, increased oral intake, lower pharyngeal residue, and better oropharyngeal swallowing efficiency [35,36] with little long-term impairment of swallow function [37]. There is particular interest in applying IMRT techniques to reduce the dose to structures specifically related to swallowing function, especially the pharyngeal constrictors, supraglottic larynx and glottic larynx [38-46]. Investigators have found that mean dose to the pharyngeal constrictors, glottic and supraglottic larynx, and esophageal inlet are significantly correlated with aspiration and stricture formation [41], reduced laryngeal elevation, and reduced epiglottic inversion [39], and are predictive of long-term worsening of swallow function [43,45]. Restricting the dose to the larynx and esophageal inlet expedites removal of non-oral feeding [46].

Few studies are available comparing the functional outcomes of patients treated with either IMRT or conventional radiotherapy, either with or without chemotherapy because of the lack of randomized clinical trials that directly compare the treatment methods. A number of studies have compared quality of life outcomes in patients treated with IMRT or conventional radiotherapy [47]. On various quality of life scales, patients treated with IMRT demonstrated better scores in the areas of salivary dysfunction, oral comfort, and global quality of life [48,49], appearance, chewing, and mood [50], and physical functioning, swallowing, taste/smell, speech, and socialization [51] when compared with patients treated with traditional and 3-D conformal radiotherapy. A single randomized controlled clinical trial comparing xerostomia and quality of life after IMRT versus conventional radiotherapy for patients with nasopharyngeal carcinoma indicated that IMRT was significantly better at sparing parotid gland function and improving quality of life during the first year after cancer treatment [52]. Although these studies demonstrate the advantage that IMRT provides in the realm of quality of life, none of them compare objective measures of swallowing function between treatment types. The aim of this study was to compare post-treatment swallow function in 7 pairs of head and neck cancer patients matched on tumor characteristics treated with either IMRT or conventional radiotherapy (RT).

Methods and Materials

Subjects

The study protocol was approved by the Institutional Review Board of Northwestern University. Subjects included 14 patients treated for head and neck cancer with either conventional radiotherapy or IMRT. Table 1 presents each patient's tumor site, tumor classification, age, gender, and treatment parameters. Seven patients with either treatment type (IMRT versus conventional radiotherapy) were matched on tumor site and disease stage, and on gender for 6 of the 7 pairs. Although it would be preferable to achieve matching on age as well as tumor characteristics, it was not possible to find matches on all these factors in our database.

Patients in the conventional radiotherapy group received 7 to 9 weeks of concomitant chemoradiation. Chemotherapy consisted of hydroxyurea, 5-fluorouracil (5-FU), and paclitaxel. Six of the patients in the conventional radiotherapy group received 5 cycles of chemotherapy while the seventh with an unknown primary received 4 cycles. Conventional radiotherapy was administered BID at 20 centigray (cGy) per fraction to an average dose to the primary of 7035 cGy (range 6000 to 7400). All patients received radiotherapy bilaterally to the neck. One patient with an unknown primary received a modified radical left neck dissection 6 weeks prior to beginning chemoradiation. No other surgical procedures were performed in the conventional radiotherapy group.

Patients in the IMRT group received one of two radiotherapy protocols with a number of variations in chemotherapy. The first radiotherapy protocol consisted of IMRT in 200 cGy per fraction doses once per day (QD) to a planned target dose to the primary of 7000 cGy. Five of the patients in the IMRT group received the QD protocol. Four of them had 2 to 3 cycles of concomitant cisplatin-based chemotherapy. The fifth subject received 3 cycles of induction chemotherapy consisting of cisplatin, docetaxel, and 5-FU followed by 3 cycles of concomitant carboplatin.

The second radiotherapy protocol consisted of IMRT in 150 cGy per fraction doses twice daily (BID) to a planned target dose to the primary of 7500 cGy. Two of the patients in the IMRT group received the BID protocol. Both received five cycles of concomitant chemotherapy consisting of hydroxyurea, docetaxel, and 5-FU. One of these subjects also had 2 cycles of induction chemotherapy consisting of cisplatin, docetaxel, and 5-FU.

All patients in the IMRT group received radiotherapy bilaterally to the neck. One patient with an unknown primary received a right selective neck dissection 4 weeks prior to beginning his concomitant chemoradiation. Two subjects in the QD radiotherapy protocol had surgery after completing chemoradiation. One subject required mandibular debridement for osteoradionecrosis; the other subject had a selective right neck dissection which yielded all negative nodes 9 weeks after completing IMRT.

Study Protocol

All procedures were approved by the Institutional Review Board for studies involving human subjects at Northwestern University. Subjects were examined at three points in time:

1) baseline, prior to cancer treatment; 2) 3 months after cancer treatment completion; and 3) 6 months after cancer treatment completion. Post-treatment testing times were measured from the completion of all primary chemoradiotherapy.

At each evaluation point, subjects completed the following tasks:

Modified barium swallow procedure with videofluoroscopy (VFG)—The swallow study protocol included swallows of 3 ml and 10 ml thin liquid barium and 3 ml barium paste. Two trials of each bolus type were given. The VFG studies were conducted in the lateral plane according to the procedure outlined by Logemann, 1993 [53] and recorded at 30 frames per second.

Xerostomia Assessment (Weight of Stimulated Saliva)—Stimulated whole mouth saliva production (from all salivary glands) was quantified by taking the difference in the weight of a 4" by 4" sterile gauze pad before and after chewing for two minutes [54]. Weight was reported in grams (gm).

Percent nutrition taken orally—Patients were asked to estimate the percentage of their nutrition that they take orally (based upon the number of calories taken orally versus number of calories taken via tube feedings).

Data Reduction

The main outcome measures were: oral transit time, pharyngeal transit time, percent oral residue, percent pharyngeal residue, laryngeal vestibule closure duration, cricopharyngeal opening duration, and oropharyngeal swallow efficiency. Videorecordings of the swallow studies were viewed in slow motion and frame-by-frame to obtain timing information to compute the swallowing outcome measures as follows:

Oral Transit Time (OTT): the time in seconds (s) it takes the bolus to move through the oral cavity, measured from the first backward movement of the bolus until the head of the bolus passes the point where the ramus of the mandible crosses the tongue base.

Pharyngeal Transit Time (PTT): the time in seconds (s) required for the bolus to move through the pharynx, measured from the time the head of the bolus passes the ramus of the mandible until the tail of the bolus leaves the cricopharyngeal region.

Approximate percent oral residue (ORES): estimated percent (%) of bolus residue in the oral cavity after the swallow

Approximate percent pharyngeal residue (PRES): estimated percent (%) of bolus residue in the pharynx after the swallow

Duration of Laryngeal Vestibule Closure (LAC): the length of time in seconds (s) the laryngeal entrance between the arytenoid and base of epiglottis is closed during the swallow.

Duration of Cricopharyngeal Opening (CPO): the length of time in seconds (s) the cricopharyngeal region is open during the swallow.

Oropharyngeal Swallow Efficiency (OPSE): the percent of the bolus swallowed (without residue or aspirated material) divided by total transit time.

OPSE is a global measure that describes the interaction of speed of movement of the bolus and the safety and efficiency of the mechanism in clearing material from the oropharynx while preventing aspiration [55-57].

Two research technicians shared the analysis of 42 VFG recordings consisting of 297 swallows total for this study. Ten percent of these swallows were randomly selected for reanalysis by the same research technician who analyzed it originally and again by the second research technician as a measure of intra-and inter-judge reliability. Average inter- and intra-observer reliability for these judgments were .94 and .99, respectively.

Statistical Analysis

Data were analyzed using multi-factor repeated measures analysis of variance with radiation type (IMRT, conventional RT), evaluation point and matched pair as the factors, and baseline levels as covariates. Pairwise comparisons across evaluation point were performed using post-hoc t-tests. The dichotomous variable of 100% nutrition was compared between groups using Fisher's exact test. Analyses were performed separately for each of the three bolus types. Statistical significance was indicated when $p < 0.05$ and comparisons across evaluation points were Bonferroni adjusted for multiple comparisons ($p < 0.017$). Statistical analyses were run using the MIXED procedure in SAS [58].

Results

There were no significant interactions among radiation type (IMRT vs. conventional RT), evaluation point, and matched pair, so the main effect of radiation type and evaluation point were evaluated with data pooled across the other factor. Data for each of the 3 bolus types were analyzed separately.

Main Effect of Treatment Group

The main effect of treatment group (IMRT vs. conventional RT) was evaluated with data pooled across evaluation point for each bolus type. Significant differences on the main effect of treatment group were observed for all measures except cricopharyngeal opening duration on at least one bolus type.

Table 2 summarizes the main effect of treatment group (IMRT versus conventional radiotherapy) for the significant bolus types and variables. Group means, standard errors, and main effect p-values are reported for data pooled over evaluation point, adjusted for baseline levels. Patients treated with IMRT demonstrated significantly shorter oral transit time than did those treated with conventional radiotherapy on the 3 ml liquid bolus, and significantly shorter pharyngeal transit time on 10 ml liquid and 3 ml paste bolus types.

Oral and pharyngeal residue were significantly reduced on the 10 ml liquid bolus for patients treated with IMRT. They also demonstrated significantly shorter laryngeal vestibule

closure duration on the 10 ml liquid bolus. The patients treated with IMRT had significantly larger (i.e. more nearly normal) OPSE on all three bolus types.

Main Effect of Evaluation Point

Table 3 summarizes the main effect of evaluation point (pretreatment, 3 months post-treatment, 6 months post-treatment) for those measures with significant effects; data were pooled over treatment group, adjusted for baseline function, and analyzed separately for each bolus type for this analysis. Significant differences on main effect of evaluation point were observed for oral residue, pharyngeal residue, laryngeal vestibule closure duration and OPSE.

Patients pooled across treatment group demonstrated significantly more oral residue on the paste bolus at 6 months post-treatment when compared to baseline oral residue. They also demonstrated significantly more pharyngeal residue on the 10 ml liquid bolus at 6 months post-treatment when compared to pharyngeal residue at baseline and 3 months post-treatment. The increase in residues after cancer treatment was also reflected in significantly lower OPSE on the paste bolus at 3 and 6 months post-treatment when compared to baseline.

Patients also demonstrated significantly longer laryngeal vestibule closure duration on the 10 ml liquid bolus at 3 and 6 months post-treatment when compared to baseline.

Stimulated whole mouth saliva weight and percent nutrition take orally were analyzed for the main effect of treatment group separately at each evaluation point. Saliva weight was adjusted for baseline levels. There was no significant difference in the level of saliva between the two groups at any of the evaluation points, although there was a trend for the IMRT-treated group to have slightly greater saliva weight (mean = 4.37 gm, se = 0.50 vs. mean = 3.77 gm, se = 0.21; $p = 0.59$ at baseline; mean = 0.99 gm, se = 0.50 vs. mean = 0.96, se = 0.54; $p = 0.97$ at 3 month evaluation; mean = 1.92, se = 0.54 vs. mean = 0.86, se = 0.54; $p = 0.17$ at 6 month evaluation).

The number of patients in each treatment group who took 100% of their nutrition orally was also analyzed. Patients in both treatment groups were able to take all their nutrition by mouth at baseline. All the patients treated with IMRT maintained 100% nutrition by mouth at both the 3 month and 6 month post-treatment evaluations. For those treated with conventional radiotherapy, 86% (6 of 7) were able to take all nutrition by mouth at 3 months post-treatment, and 71% (5 of 7) were able to take all nutrition by mouth at 6 months post-treatment. There were no significant differences by treatment group in the number of patients taking all nutrition by mouth at any of the evaluation points.

Discussion

The treatment of advanced head and neck cancer has evolved significantly over the past several decades, with a change from surgical intervention to radiotherapy to chemoradiation with or without IMRT. Difficulty swallowing is often the greatest complaint which patients have after their cancer treatment and the problem may persist for years. The purpose of

IMRT has been to shape the radiation dose to protect structures critical to swallowing in an effort to reduce the negative impact of cancer treatment on swallowing function.

In our study of 7 pairs of patients matched on tumor characteristics and adjusted for baseline oropharyngeal function, we observed that patients treated with IMRT demonstrated shorter oral and pharyngeal transit times, less oral and pharyngeal residue, shorter laryngeal vestibule closure, and larger oropharyngeal swallow efficiency within the first 6 months after cancer treatment. Patients treated with IMRT also demonstrated maintenance of 100% nutrition taken orally, although these differences were not significant.

Studies on oropharyngeal function after IMRT most often focus on xerostomia since IMRT is most often thought to avoid radiating the salivary glands in an effort to improve the swallow. The relationships among reduced salivary flow, xerostomia or the perception of “dry mouth,” and swallow function are not clear. Patients with significantly reduced saliva production after radiotherapy have increased reports of perceived difficulty swallowing as well as dry mouth, needing water while eating, food sticking in the mouth or throat, and changes in taste [39,59]. However, patients with objective improvement in salivary flow over time may still complain of xerostomia [60]. Reduced saliva weight does not correlate with slowed or inefficient swallow. Instead, reduced saliva weight seems to change the patient's perception of swallowing ability as demonstrated by studies on the relationship between xerostomia and quality of life [47,48,51]. Based upon the perception of impaired swallowing in the context of reduced salivary flow, patients will adjust their diet choices [39,59]. Although the patients in this study treated with IMRT demonstrated a trend toward greater preservation of salivary function (larger amount of whole mouth saliva), the difference was not significant.

The observed differences in the swallow function of the patients in this study suggest that treatment with IMRT reduced damage to normal tissues, especially in the pharynx, and resulted in a speedier, more efficient swallow. Patients treated with IMRT also demonstrate a trend toward a lower incidence of reduced tongue base retraction, a disorder that is observed in nearly all patients treated with conventional radiotherapy [61]. Such a positive impact on actual swallowing function has been predicted by the research of those examining dose limitation to the pharyngeal constrictors, larynx, and esophageal inlet [39,42,43,45,46].

Despite the significantly more efficient swallow pattern demonstrated by these patients, those treated with IMRT still have difficulty swallowing after cancer treatment when compared to their pretreatment function. Patients pooled over treatment type and adjusted for baseline function demonstrated greater residues, longer laryngeal vestibule closure duration, and less efficient swallows which persisted at 6 months post-treatment completion. Patients are likely prolonging laryngeal vestibule closure in order to protect the airway in the presence of significantly increased pharyngeal residue. Although the level of swallow impairment after IMRT was not as great as after conventional radiotherapy, these patients still do not return to normal pretreatment levels of swallow function by 6 months after completing cancer treatment. This lack of return to pretreatment status after IMRT has been noted in other domains such as quality of life and salivary function by other researchers [37,62].

Oropharyngeal functional outcome at 3 and 6 months after completion of treatment for cancer of the head and neck may not reflect long term function several years after treatment. Severe impairments of swallowing function have been observed years after completion of treatment with conventional chemoradiation, including reduced tongue control resulting in premature spillage into the pharynx [22,63,64], reduced tongue base retraction [65,66], impaired pharyngeal contraction [67,63,68,64], increased vallecula and pyriform sinus residue [22,66, 63,68], impaired epiglottic function [63,64], reduced laryngeal elevation [65,67], and reduced laryngeal vestibule and true cord closure [65]. Dysphagia has been reported to persist decades after treatment [67] and in fact there is evidence of continued deterioration of swallowing function for years after chemoradiation as a result of progressive fibrosis in irradiated tissues of the head and neck [63,64]. It is not clear from this study that the functional advantage of the patients treated with IMRT at 3 and 6 months post-treatment can be maintained years or decades after completion of cancer treatment. Long term follow-up of patients treated with IMRT for cancer of the head and neck is needed in order to understand fully the impact of IMRT on swallowing and other oropharyngeal functions.

There are a number of weaknesses in this study that may have influenced the results. Among these weaknesses are imperfect matches between subjects and use of induction chemotherapy in two patients in the IMRT group. Although we attempted to match subjects as closely as possible on tumor characteristics for this study, it was impossible to match each pair on site and stage of disease as well as T/N/M classification. For example, the conventional radiotherapy patients in Pair 1 and Pair 4 had larger tumors, while those in Pair 5 and Pair 6 had greater neck disease than their match in the IMRT group. It can be argued that the trend toward more advanced T/N/M classification in the conventional radiotherapy group in four of the seven pairs could have skewed the results of the study to indicate greater swallowing dysfunction in that group.

Use of induction chemotherapy in two patients in the IMRT group may also have influenced the study results. Induction chemotherapy is used to reduce the size of the tumor prior to concomitant chemoradiotherapy with the aim of diminishing the amount of radiation needed for cure. In fact, the IMRT patient in Pair 4 did receive a lower total dose to the primary (7000 cGy vs. 7350 cGy) than his conventional radiotherapy mate. However, the IMRT patient in Pair 5 received a greater total dose to the primary (7500 cGy vs. 7050 cGy) than did his matched conventional radiotherapy counterpart. In a recent publication [69], Mittal et al. (in press), examined the effects of chemotherapy alone on oropharyngeal swallow in a small number of patients. Thirteen patients with head and neck cancer were evaluated pre- and post-induction chemotherapy. Their assessment included percent nutrition taken orally, food consistencies in diet, VFG swallow evaluation, whole mouth saliva collection, quality-of-life questionnaire, and pain and oral mucositis scores. All patients were able to consume most foods and took 100% of their nutrition orally both pre- and post-induction chemotherapy. While a number of swallow measures worsened, no statistically significant differences were observed in diet, quality of life measures, pain, or saliva weight, or in most temporal swallow measures. In this small group of patients, induction chemotherapy alone did not significantly positively or negatively alter swallowing physiology and salivary secretion although the trend was toward worsening oropharyngeal function after induction chemotherapy. The results of that study suggest then that use of induction chemotherapy in

the two IMRT patients in this study did not necessarily place them at a functional advantage over their match in the conventional radiotherapy group.

The goal of nearly normal swallowing function in light of cure after treatment for cancer of the head and neck has not yet been realized. More research is needed in order to determine an effective method of returning head and neck cancer patients treated with chemoradiation to full function. The retrospective nature of this study and the small number of patients involved are weaknesses that could be addressed in the future. In addition, potential avenues for future research include further refining the cancer treatment as well as examining post treatment intervention techniques, especially investigating swallow therapy in terms of type and timing in order to reduce oropharyngeal dysfunction in treated head and neck cancer patients.

Acknowledgments

NIH Grant R01DC007659 and the Robert H. Lurie Comprehensive Cancer Center – Director's Fund. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Robert H. Lurie Comprehensive Cancer Center – Director's Fund.

References

1. Robbins KT, Vicario D, Seagren S, et al. A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. *Am J Surg*. 1994; 168:419–422. [PubMed: 7977964]
2. Lefebvre JL, Chevalier D, Lubinski B, et al. EORTC Head and Neck Cancer Cooperative Group. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for research and treatment of Cancer Phase III trial. *J Natl Cancer Inst*. 1996; 88:890–899. [PubMed: 8656441]
3. Browman GP, Hodson DI, Mackenzie RJ, et al. Cancer Care Ontario Practice Guideline Initiative Head and Neck Cancer Disease Site Group. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. *Head Neck*. 2001; 23:579–589. [PubMed: 11400247]
4. Kies MS, Haraf DJ, Rosen F, et al. Concomitant infusional paclitaxel and fluorouracil, oral hydroxyurea and hyperfractionated radiation for locally advanced squamous cell head and neck cancer. *J Clin Oncol*. 2001; 19:1961–1969. [PubMed: 11283128]
5. Rosen FR, Haraf DJ, Kies MS, et al. Multicenter randomized Phase II study of paclitaxel (1-hour infusion), fluorouracil, hydroxyurea, and concomitant twice daily radiation with or without erythropoietin for advanced head and neck cancer. *Clin Cancer Res*. 2003; 9:1689–1697. [PubMed: 12738722]
6. Vokes EE, Stenson K, Rosen FR, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol*. 2003; 21:320–326. [PubMed: 12525525]
7. Weber RS, Berkey BA, Forastiere A, et al. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11. *Arch Otolaryngol Head Neck Surg*. 2003; 129:44–49. [PubMed: 12525193]
8. Kitamoto Y, Akimoto T, Ishikawa H, et al. Acute toxicity and preliminary clinical outcomes of concurrent radiation therapy and weekly docetaxel and daily cisplatin for head and neck cancer. *Jpn J Clin Oncol*. 2005; 35(11):639–44. [PubMed: 16275679]
9. Allal AS, Zwahlen D, Becker M, et al. Phase I trial of concomitant hyperfractionated radiotherapy with docetaxel and cisplatin for locally advanced head and neck cancer. *Cancer J*. 2006; 12(1):63–8. [PubMed: 16613664]

10. Allen AM, Elshaikh M, Worden FP, et al. Acceleration of hyperfractionated chemoradiation regimen for advanced head and neck cancer. *Head Neck*. 2007; 29(2):137–42. [PubMed: 17111432]
11. Moyer JS, Wolf GT, Bradford CR. Current thoughts on the role of chemotherapy and radiation in advanced head and neck cancer. *Current Opinion in Otolaryngology & Head & Neck Surgery*. 2004; 12:82–87. [PubMed: 15167042]
12. Schwarz JK, Giese W. Organ preservation in patients with squamous cancers of the head and neck. *Surg Oncol Clin N Am*. 2004; 13:187–199. [PubMed: 15062369]
13. Eisbruch A, Lyden T, Bradford CR, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2002; 53:23–28. [PubMed: 12007937]
14. Eisele DW, Koch DG, Tarazi AE, et al. Aspiration from delayed radiation fibrosis of the neck. *Dysphagia*. 1991; 6:120–122. [PubMed: 1935259]
15. Graner DE, Foote RL, Kasperbauer JL, et al. Swallow function in patients before and after intra-arterial chemoradiation. *Laryngoscope*. 2003; 113:573–579. [PubMed: 12616217]
16. Kotz T, Abraham S, Beitler JJ, et al. Pharyngeal transport dysfunction consequent to an organ-sparing protocol. *Arch Otolaryngol Head Neck Surg*. 1999; 125:410–413. [PubMed: 10208678]
17. Lazarus CL, Logemann JA, Pauloski BR, et al. Swallowing disorders in head and neck cancer patients with radiotherapy and adjuvant chemotherapy. *Laryngoscope*. 1996; 106:1157–1166. [PubMed: 8822723]
18. Smith RV, Kotz T, Beitler JJ, et al. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea. *Arch Otolaryngol Head Neck Surg*. 2000; 126:384–389. [PubMed: 10722013]
19. Kotz T, Costello R, Li Y, et al. Swallowing dysfunction after chemoradiation for advanced squamous cell carcinoma of the head and neck. *Head Neck*. 2004; 26:365–372. [PubMed: 15054740]
20. Nguyen NP, Vos P, Smith HJ, et al. Concurrent chemoradiation for locally advanced Oropharyngeal cancer. *American Journal of Otolaryngology–Head and Neck Medicine and Surgery*. 2007; 28:3–8.
21. Rieger JM, Zalmanowitz JG, Wolfaardt JF. Functional outcomes after organ preservation treatment in head and neck cancer: a critical review of the literature. *Int J Oral Maxillofac Surg*. 2006; 35:581–587. [PubMed: 16697144]
22. Dworkin JP, Hill SL, Stachler RJ, et al. Swallowing function outcomes following nonsurgical therapy for advanced-stage laryngeal carcinoma. *Dysphagia*. 2006; 21:66–74. [PubMed: 16544094]
23. Shiley SG, Hargunani CA, Skoner JM, et al. Swallowing function after Chemoradiation for advanced oropharyngeal cancer. *Otolaryngol Head Neck Surg*. 2006; 134:455–459. [PubMed: 16500444]
24. Nguyen NP, Moltz CC, Frank C, et al. Evolution of chronic dysphagia following treatment for head and neck cancer. *Oral Oncol*. 2006; 42:374–380. [PubMed: 16314138]
25. Logemann JA, Rademaker AW, Pauloski BR, et al. Site of disease and treatment protocol as correlates of swallowing function in patients with head and neck cancer treated with chemoradiation. *Head Neck*. 2006; 28:64–73. [PubMed: 16302193]
26. Logemann JA, Pauloski BR, Rademaker AW, et al. Swallowing disorders in the first year after radiation and chemoradiation. *Head Neck*. 2008; 30:148–158. [PubMed: 17786992]
27. Sullivan CA, Jaklitsch MT, Haddad R, et al. Endoscopic management of hypopharyngeal stenosis after organ sparing therapy for head and neck cancer. *Laryngoscope*. 2004; 114:1924–1931. [PubMed: 15510015]
28. Gregoire V, Jeraj R, Lee JA, O'Sullivan B. Radiotherapy for head and neck tumours in 2012 and beyond: conformal, tailored, and adaptive? *Lancet Oncol*. 2012; 13:e292–300. [PubMed: 22748268]
29. Eisbruch A, TenHaken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and Intensity-Modulated irradiation of Head and Neck Cancer. *Int J Radiat Oncol Biol Phys*. 1999; 45(3):577–587. [PubMed: 10524409]

30. Eisbruch A, Kim HM, Terrell JE, et al. Xerostomia and its predictors following parotid-sparing irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2001; 50:695–704. [PubMed: 11395238]
31. Dirix P, Nuyts S. Value of intensity-modulated radiotherapy in stage IV head-and-neck squamous cell carcinoma. *Int J Radiation Oncology Biol Phys.* 2010; 78:1373–1380.
32. Thariat J, Bolle S, Demizu Y, et al. New techniques in radiation therapy for head and neck cancer: IMRT, CyberKnife, protons, and carbon ions. Improved effectiveness and safety? Impact on survival? *Anti-Cancer Drugs.* 2011; 22:596–606. [PubMed: 21051993]
33. Wang ZH, Yan C, Zhang ZY, et al. Impact of salivary gland dosimetry on post-IMRT recovery of saliva output and xerostomia grade for head-and-neck cancer patients treated with or without contralateral submandibular gland sparing: A longitudinal study. *Int J Radiation Oncology Biol Phys.* 2011; 81:1479–1487.
34. Chen WC, Lai CH, Lee TF, et al. Scintigraphic assessment of salivary function after intensity-modulated radiotherapy for head and neck cancer: *Oral Oncology.* 2013; 49:42–48.
35. Mittal BB, Kepka A, Mahadevan A, et al. Tissue/dose compensation to reduce toxicity from combined radiation and chemotherapy for advanced head and neck cancers. *Int J Cancer.* 2001; 96(Suppl):61–70. [PubMed: 11992387]
36. Fua TF, Corry J, Milner AD, et al. Intensity-modulated radiotherapy for nasopharyngeal carcinoma: clinical correlation of dose to the pharyngo-esophageal axis and dysphagia. *Int J Radiat Oncol Biol Phys.* 2007; 67(4):976–81. [PubMed: 17234360]
37. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: Clinical and functional results. *Journal of Clinical Oncology.* 2010; 28:2732–2738. [PubMed: 20421546]
38. Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head and neck cancer: Which anatomic structures are affected and can they be spared by IMRT? *Int J Radiat Oncol Biol Phys.* 2004; 60:1425–1439. [PubMed: 15590174]
39. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: Early dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys.* 2007; 68:1289–1298. [PubMed: 17560051]
40. Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: A dose-effect relationship. *Radiation Oncol.* 2007; 85:64–73. [PubMed: 17714815]
41. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008; 72:1110–1118. [PubMed: 18468812]
42. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: Dose-effect relationships for the swallowing structures. *Int J Radiation Oncology Biol Phys.* 2009; 75:385–392.
43. Caudell JJ, Schaner PE, Desmond RA, et al. Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Int J Radiation Oncology Biol Phys.* 2010; 76:403–409.
44. Roe JW, Carding PN, Dwivedi RC, et al. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer—A systematic review. *Oral Oncology.* 2010; 46:727–733. [PubMed: 20850370]
45. Eisbruch A, Kim HM, Feng FY, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: Swallowing organs late complication probabilities and dosimetric correlates. *Int J Radiation Oncology Biol Phys.* 2011; 81:e93–e99.
46. Amin N, Reddy K, Westerly D, et al. Sparing the larynx and esophageal inlet expedites feeding tube removal in patients with stage III-IV oropharyngeal squamous cell carcinoma treated with intensity-modulated radiotherapy. *Laryngoscope.* 2012; 122:2736–2742. [PubMed: 22991101]
47. Tribuis S, Bergelt C. Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: Is there a worthwhile quality of life gain? *Cancer Treatment Reviews.* 2011; 37:511–519. [PubMed: 21324605]

48. Gaff P, Lapeyre M, Desandes E, et al. Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: Matched-pair comparison with conventional radiotherapy. *Int J Radiation Oncology Biol Phys*. 2007; 67:1309–1317.
49. Chen AM, Farwell DG, Luu Q, et al. Intensity-modulated radiotherapy is associated with improved global quality of life among long-term survivors of head-and-neck cancer. *Int J Radiation Oncology Biol Phys*. 2012; 84:170–175.
50. Mowry SE, Tang C, Sadeghi A, Wang MB. Standard chemoradiation versus intensity-modulated chemoradiation: A quality of life assessment in oropharyngeal cancer patients. *Eur Arch Otorhinolaryngol*. 2010; 267:1111–1116. [PubMed: 20039175]
51. Leung SW, Lee TF, Chien CY, Chao PJ, Tsai WL, Fang FM. Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. *BMC Cancer*. 2011; 11:128. Open Access. <http://www.biomedcentral.com/1471-2407/11/128>. [PubMed: 21486431]
52. Pow EHN, Kwong DLW, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: Initial report on a randomized controlled clinical trial. *Int J Radiation Oncology Biol Phys*. 2006; 66:981–991.
53. Logemann, J. A manual for videofluoroscopic evaluation of swallowing. 2. Austin, TX: Pro-Ed; 1993.
54. Kohler PF, Winter ME. A quantitative test for xerostomia: the Saxon test. *Arthritis Rheum*. 1985; 28:1128–32. [PubMed: 4052124]
55. Logemann, JA. Evaluation and treatment of swallowing disorders. 2nd. Austin, TX: Pro-Ed; 1998.
56. Logemann J, Kahrilas P, Kobara M, et al. The benefit of head rotation on pharyngo-esophageal dysphagia. *Arch Phys Med Rehabil*. 1989; 70:767–771. [PubMed: 2802957]
57. Rademaker AW, Pauloski BR, Logemann JA, Shanahan TK. Oropharyngeal swallow efficiency as a representative measure of swallowing function. *Journal of Speech and Hearing Research*. 1994; 37:314–325. [PubMed: 8028312]
58. SAS Institute Inc.. SAS OnlineDoc®9.4. Cary, NC: SAS Institute Inc.; 2013.
59. Logemann JA, Pauloski BR, Rademaker AW, et al. Xerostomia: 12-month changes in saliva production and its relationship to perception of swallow function, oral intake and diet after chemoradiation. *Head Neck*. 2003; 25:432–437. [PubMed: 12784234]
60. Franzen L, Funegard U, Ericson T, et al. Parotid gland function during and following radiotherapy of malignancies in the head and neck. A consecutive study of salivary flow and patient discomfort. *Eur J Cancer*. 1992; 28(2-3):457–62. [PubMed: 1591063]
61. Pauloski BR, Rademaker AW, Logemann JA, et al. Relationship between swallow motility disorders on VFG and oral intake in patients treated for head and neck cancer with radiotherapy ± chemotherapy. *Head Neck*. 2006; 28:1069–76. [PubMed: 16823874]
62. So WKW, Chan RJ, Chan DNS, et al. Quality-of-life among head and neck cancer survivors at one year after treatment—A systematic review. *European Journal of Cancer*. 2012; 48:2391–2408. [PubMed: 22579456]
63. Chang YC, Chen SY, Lui LT, et al. Dysphagia in patients with nasopharyngeal cancer after radiation therapy: A videofluoroscopic swallowing study. *Dysphagia*. 2003; 18:135–143. [PubMed: 12825907]
64. Bleier BS, Levine MS, Mick R, et al. Dysphagia after Chemoradiation: Analysis by Modified barium swallow. *Ann Otol Rhinol Laryngol*. 2007; 116:837–841. [PubMed: 18074669]
65. Lazarus CL. Effects of radiation therapy and voluntary maneuvers on swallow functioning in head and neck cancer patients. *Clin Commun Disord*. 1993; 3:11–20. [PubMed: 8111360]
66. Jensen K, Lambertsen K, Grau C. Late swallowing dysfunction and dysphagia after radiotherapy for pharynx cancer: Frequency, intensity and correlation with dose and volume parameters. *Radiother Oncol*. 2007; 85:74–82. [PubMed: 17673322]
67. Hughes PJ, Scott PJS, Kew J, et al. Dysphagia in treated nasopharyngeal cancer. *Head Neck*. 2000; 22:393–397. [PubMed: 10862024]

68. Wu C, Hsiao TY, Ko JY, et al. Dysphagia after radiotherapy: endoscopic examination of swallowing in patients with nasopharyngeal carcinoma. *Ann Otol Rhinol Laryngol.* 2000; 109:320–325. [PubMed: 10737318]
69. Mittal BB, Pauloski BR, Rademaker AW, et al. Effect of induction chemotherapy on swallow physiology and saliva production in patients with head and neck cancer: A pilot study. *Head Neck.* in press.

Table 1

Patient demographics, tumor characteristics and treatment parameters for 7 pairs of patients treated with either intensity-modulated radiotherapy (IMRT) or conventional radiotherapy (con-RT).

Pair	Primary Site	Treatment Group	Sex	Age	T/N/M classification	Disease Stage	Chemotherapy Regimen	dose per fraction (cGy)	QD/BID	dose to Primary (cGy)	Neck Dissection	Other Surgery
1	oral cavity	IMRT	f	57	T2N2bM0	IV	2 cycles concomitant cisplatin	200	QD	7000	no	no
		con-RT	m	44	T3N2bM0	IV	5 cycles concomitant paclitaxel, 5FU, HU	150	BID	7350*	no	no
2	nasopharynx	IMRT	f	51	T3N2cM0	IV	3 cycles concomitant cisplatin, 1 cycle adjuvant cisplatin, 5FU	200	QD	7000	no	no
		con-RT	f	50	T3N2cM0	IV	5 cycles concomitant paclitaxel, 5FU, HU	150	BID	7050	no	no
3	oropharynx	IMRT	m	67	T2N2bM0	IV	2 cycles concomitant cisplatin	200	QD	7000	no	mandibular debride-ment for osteoradio-necrosis
		con-RT	m	74	T2N2aM0	IV	5 cycles concomitant paclitaxel, 5FU, HU	200	QD	7400*	no	no
4	oropharynx	IMRT	m	31	T3N2bM0	IV	3 cycles induction cisplatin, docetaxel, 5FU; 3 cycles concomitant carboplatin	200	QD	7000	right selective all nodes negative	no
		con-RT	m	56	T4N2bM0	IV	5 cycles concomitant paclitaxel, 5FU, HU	150	BID	7350	no	no
5	hypopharynx	IMRT	m	57	T2N2bM0	IV	2 cycles induction cisplatin, docetaxel, 5FU; 5 cycles concomitant docetaxel, 5FU, HU	150	BID	7500*	no	no
		con-RT	m	52	T2N2cM0	IV	5 cycles concomitant paclitaxel, 5FU, HU	150	BID	7050	no	no
6	supraglottic larynx	IMRT	f	45	T4N2cM0	IV	5 cycles concomitant docetaxel, 5FU, HU	150	BID	7500*	no	no
		con-RT	f	56	T3N3M0	IV	5 cycles concomitant paclitaxel, 5FU, HU	150	BID	7050	no	no
7	unknown primary	IMRT	m	44	T0N2bM0	IV	3 cycles concomitant cisplatin, 5FU	200	QD	6000	right selective prior to CXRT	no

Pair	Primary Site	Treatment Group	Sex	Age	T/N/M classification	Disease Stage	Chemotherapy Regimen	dose per fraction (cGy)	QD/BID	dose to Primary (cGy)	Neck Dissection	Other Surgery
		con-RT	m	41	TON2bM0	IV	4 cycles concomitant paclitaxel, 5FU, HU	150	BID	6000	Left modified radical prior to CXRT	Pauloski et al. no

* Per institution protocol

Abbreviations: cGy = centigray; QD = daily; BID = twice a day; CXRT = chemoradiation; 5-FU = fluorouracil; HU = hydroxyurea

Table 2

Means, standard error (SE), and p-values for the significant main effect of group (IMRT vs. conventional radiotherapy) pooled over evaluation point for each of the bolus types. (n=number of swallows). All p-values are adjusted for baseline measures. (n = number of swallows)

measure	bolus type/size	IMRT	Conventional RT	p-value
Oral Transit Time (s)				
	3 ml liquid	.237 (.034) n = 38	.389 (.035) n = 47	0.0035
Pharyngeal Transit Time (s)				
	10 ml liquid	.703 (.024) n = 39	.822 (.037) n = 31	0.019
	paste	.823 (.079) n = 40	1.111 (.071) n = 52	0.013
Oral Residue (%)				
	10 ml liquid	3.02 (0.68) n = 40	6.12 (1.13) n = 31	0.026
Pharyngeal Residue (%)				
	10 ml liquid	3.56 (1.57) n = 40	13.18 (2.99) n = 31	0.005
Laryngeal Vestibule Closure Duration (s)				
	10 ml liquid	.495 (.063) n = 39	.947 (.107) n = 30	0.007
Oropharyngeal Swallow Efficiency (%/s)				
	3 ml liquid	95.5 (2.7) n = 38	82.2 (2.7) n = 47	0.0013
	10 ml liquid	102.8 (3.0) n = 39	79.7 (5.3) n = 31	0.0003
	paste	81.0 (4.3) n = 40	64.4 (4.0) n = 52	0.018

Table 3

Means, standard error (SE), and p-values for the significant main effect of evaluation point (pretreatment, 3 months post-treatment, 6 months post-treatment) adjusted for baseline function and pooled over group for each of the bolus types. (n=number of swallows)

measure	bolus type	pretreatment	3 months post	6 months post	p-value	Significant post-hoc tests
Oral Residue (%) Main Effect of Eval (pooled over group)						
	paste	2.28 (0.56) n = 33	3.26 (0.43) n = 30	4.27 (0.41) n = 30	0.016	2
Pharyngeal Residue (%) Main Effect of Eval (pooled over group)						
	10 ml liquid	3.18 (2.66) n = 30	3.78 (2.62) n = 25	18.17 (3.55) n = 16	0.0007	2, 3
Laryngeal Vestibule Closure Duration (s) Main Effect of Eval (pooled over group)						
	10 ml liquid	.501 (.050) n = 30	.820 (.050) n = 25	.842 (.071) n = 14	0.0001	1, 2
	paste	.393 (.037) n = 33	.534 (.029) n = 30	.470 (.027) n = 30	0.035	1
Oropharyngeal Swallow Efficiency (%/s) Main Effect of Eval (pooled over group)						
	paste	90.8 (5.9) n = 33	62.9 (4.6) n = 30	64.3 (4.4) n = 29	0.004	1, 2

Post-hoc Paired Comparisons

1. $p < 0.017$, pretreatment vs. 3 months post-treatment
2. $p < 0.017$, pretreatment vs. 6 months post-treatment
3. $p < 0.017$, 3 months post-treatment vs. 6 months post-treatment