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Effect of Induction Chemotherapy on Swallow Physiology and Saliva Production in Patients with Head and Neck Cancer: A Pilot Study

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Abstract

Background—No objective data are available to assess the potential damage induction chemotherapy alone contributes to swallowing physiology and salivary production in patients with locally and regionally confined head and neck cancer.

Methods—Thirteen patients with head and neck cancer were evaluated pre- and post-induction chemotherapy. Assessment included 1) percent nutrition taken orally and food consistencies in diet; 2) videofluorographic swallow evaluation; 3) whole mouth saliva collection; 4) quality-of-life questionnaire; 5) pain and oral mucositis scores.

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Results—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. Pharyngeal residue decreased significantly following chemotherapy.

Conclusions—Induction chemotherapy alone did not significantly negatively alter swallowing physiology and salivary secretion although the trend was toward worsening in function.

Keywords

chemotherapy; swallow physiology; saliva; videofluorography; head & neck cancer; quality of life

Introduction

Over the past 30 years, there has been increasing interest in the effects of treatment for head and neck cancer on oropharyngeal swallow. Initial attention was placed on surgical procedures and their impact on swallow function.^{1–6} Attention then turned to radiation therapy and its effects on oropharyngeal swallow. Currently, chemotherapy in combination with radiotherapy either sequentially or concurrently is being studied.^{7–16} Swallowing dysfunction and altered saliva production are common sequelae of radiation with or without chemotherapy in the management of head and neck cancers. The quantitative and qualitative alteration in swallowing physiology and saliva production caused by radiation alone^{17–25} or radiation with chemotherapy^{26–31} are well documented. The damage to swallowing structures caused by radiation with chemotherapy is much greater than that seen with radiation alone.³² Clinically, chemotherapy alone does not appear to alter swallow biomechanics. However, no objective data are available to assess the magnitude of damage chemotherapy alone may contribute in combined modality therapy. In order to understand the complex effects of treatment for head and neck cancer on oropharyngeal swallow and those factors that create the greatest changes, all aspects of treatment must be examined. This present study serves as a pilot examination of the effects of chemotherapy alone in a small number of patients to determine whether a larger study of induction chemotherapy effects on oropharyngeal swallow is warranted.

The primary aim of this pilot study was to document the effect of induction chemotherapy alone on swallowing physiology for the treatment of head and neck cancers. In addition to providing mucosal protection and hydration to the oral cavity, the oropharyngeal axis, and the esophagus, saliva also plays an important role in the oral preparatory phase of swallowing mechanics.³³ Therefore, we evaluated swallowing measures and saliva production in patients pre- and post-induction chemotherapy to assess the effect of chemotherapy on these separate endpoints. We also evaluated pain and mucositis that might affect swallowing in these patients.

Materials and Methods

Subjects

In this prospective study, 13 patients with local and regional stage IV head and neck cancer whose treatment plan included induction chemotherapy were consecutively enrolled in the study. The subjects, 12 men and 1 woman, were between the ages of 31 and 68 (mean age 53 years). The induction chemotherapy protocol consisted of docetaxel (75 mgm/M² on day 1); cisplatin (75 mgm/M² on day 1); and 5 fluorouracil (750 mgm/M²/day on days 1–5). After completion of 2 to 3 cycles of induction chemotherapy administered 3 weeks apart, all patients underwent concomitant chemoradiotherapy. The average time between completion of induction chemotherapy and concomitant chemoradiotherapy was 15 days.

Study Protocol

The study protocol was approved by the Institutional Review Board of Northwestern University. Each patient received an assessment pre- and post-induction chemotherapy which included: 1) documentation of percent nutrition taken orally and the food consistencies in the patient's diet; 2) videofluorographic (VFG) swallow evaluation; 3) whole mouth saliva collection; 4) quality-of-life questionnaire; 5) pain and oral mucositis scores.

Dietary Consistencies and Oral Intake—Pre- and post-induction chemotherapy, patients were asked which of the various food consistencies they included in their oral diets (thin liquids, thick liquids, paste/pureed foods, soft-masticated foods, crunchy foods). An oral diet was considered normal if the patient could consume all of these consistencies. Patients were also asked to estimate the percentage of their nutrition they consumed orally.

Videofluorographic (VFG) Swallow Evaluation—During both the pre- and post-induction VFG studies, patients were asked to take 3 swallows each of 3 mL and 10 mL of thin liquid, 3 swallows of 3 mL of pudding barium, and 3 swallows of ¼ piece of a shortbread cookie. During the study, the fluoroscopy tube was focused on the lips anteriorly, the cervical vertebrae posteriorly, the soft palate superiorly, and the bifurcation of the airway inferiorly. Fluoroscopic data were recorded on video at 30 frames per second.

Whole-Mouth Saliva Collection—Whole-mouth saliva was collected using the Saxon Test.³⁴ During this test, stimulated whole-mouth saliva production was evaluated by weighing a 4" × 4" sterile gauze pad before and after the patient chewed the gauze for 2 minutes.

Patient-Reported Quality of Life (QOL), Patient-Reported Pain, and Mucositis Scoring—Patients were asked to complete the Performance Status Scale for Head and Neck Cancer (PSS-H&N)³⁵ Diet Subscale and Eating in Public Subscale at both evaluation points. Each scale is scored from 0 to 100, with 100 representing the best function. For analysis, the scale results were dichotomized as 100 vs. <100. Patients reported pain at each evaluation point on a 10-point scale, with 0 representing no pain and 10 representing extreme pain.³⁶ Mucositis was measured using a validated scale for assessing ulceration and

erythema at various sites in the mouth.³⁷ For analysis, this scale was dichotomized as no mucositis vs. some mucositis. The mucositis scale on the CTC Criteria Version 3.0 was not scored during the provision of induction chemotherapy.

Data Reduction from Videofluorographic Swallow Study

The following measures and observations were made from the VFG studies:

1. oral transit time (OTT): time in seconds it takes the bolus to move through the oral cavity;
2. pharyngeal transit time (PTT): time in seconds for the bolus to move through the pharynx;
3. pharyngeal delay time (PDT): time in seconds required to trigger the pharyngeal swallow;
4. pharyngeal response time (PRT): time in seconds required for the pharyngeal swallow to activate;
5. duration of laryngeal vestibule closure (LAC): time in seconds that the laryngeal entrance between the arytenoid and the base of the epiglottis is closed during swallow;
6. duration of cricopharyngeal opening (CPO): time in seconds that the cricopharyngeal region is open during swallow;
7. approximate percent oral residue (ORES): estimated percent of bolus residue in the oral cavity after the swallow
8. approximate percent pharyngeal residue (PRES): estimated percent of bolus residue in the pharynx after the swallow
9. oropharyngeal swallowing efficiency (OPSE): percent of the bolus swallowed divided by the 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.³⁸

Statistical Analysis

Change in dichotomous measures of eating ability were assessed for statistical significance using McNemar's test.³⁹ The Wilcoxon signed rank test³⁹ was used to assess change in saliva weight, pain and mucositis score. Mixed linear model analysis using maximum likelihood tests was used to compare change in the temporal measures, as measured by videofluoroscopy, pooling data across all bolus types. The effect of each demographic and disease variable on OPSE was evaluated by including them one at a time into the mixed effects model as a covariate.

Results

Patient demographics and tumor characteristics are detailed in Table 1. Mean cumulative dose of induction chemotherapy consisted of docetaxel (289 mgm), cisplatin (307 mgm),

and 5 fluorouracil (15,730 mgm). Eleven patients received 2 cycles of induction chemotherapy while 2 patients had 3 cycles of induction chemotherapy. Data collection was completed before any additional tumor treatment was initiated, including radiation therapy and any concurrent chemotherapy.

The effect of the variables of age, race, primary tumor site (oropharynx vs. other sites combined), T classification, smoking history (smokes currently vs. not smoking currently), and alcohol history (drinks currently vs. not drinking) on OPSE were examined. Sex, N classification, M classification, and disease stage were not evaluated because the sample sizes were too small. Age ($p=0.88$), primary tumor site ($p=0.94$), T classification ($p=0.27$), smoking history ($p=0.98$), alcohol history ($p=0.98$) and race ($p=0.07$) did not significantly affect OPSE, although there was a trend for race to have a marginal effect with African Americans exhibiting higher (better) OPSE scores than Caucasians (means: 84 vs. 67, respectively).

Dietary Consistencies and Oral Intake

Pre- and post-induction chemotherapy, all 13 patients included thin liquids, thick liquids, paste/pureed foods, and soft masticated foods in their diet (Table 2). No statistically significant difference was observed in patients' ability to eat crunchy food (92% pre vs 77% post, $p=0.32$) or eat a normal diet (92% pre vs 69% post, $p=0.18$) by evaluation point, although the trend indicated a reduction in the percent of each measure post-induction chemotherapy. All patients were able to take 100% of their nutrition orally at both time points.

Videofluorographic (VFG) Swallow Evaluation

Before and after induction chemotherapy, all patients studied were able to swallow all bolus types. Temporal swallowing measures pre- and post-induction chemotherapy are shown in Table 3. There were no significant differences between pre- and post-induction chemotherapy swallowing measures except for mean approximate pharyngeal residue, which was significantly lower post-induction chemotherapy ($p=0.007$). At the pre-induction chemotherapy study, one patient aspirated trace amounts during the swallow on thin liquid because of a slight delay in airway closure. He continued to aspirate trace amounts of pharyngeal residue after the swallow on thin liquid at the post-induction chemotherapy study, because of a continued slight delay in airway closure. No other subjects aspirated on either the pre- or post-induction chemotherapy studies.

Whole-Mouth Saliva Collection

Mean weight in grams (SEM) of the chewed gauze was 5.71 (0.45) pre-induction chemotherapy vs. 5.83 (0.76) post-induction chemotherapy. There was no significant difference ($p=0.73$) between the chewed gauze weight pre- and post-induction chemotherapy. None of the subjects used prescription or over-the-counter salivary replacement medications at either of the evaluation points.

Patient-Reported Quality of Life (QOL)

No significant differences were observed on the Performance Status Scale for Head and Neck Cancer Diet and Eating in Public subscales between pre- and post-induction chemotherapy evaluations (Table 4). Post-induction chemotherapy, there was a decrease in both the Diet Subscale (92% of the subjects scored 100 pre-induction chemotherapy and 69% of the subjects scored 100 post-induction chemotherapy, $p=0.18$) and the Eating in Public Scale (100% scored 100 pre-induction chemotherapy and 77% scored 100 post-induction chemotherapy, $p=0.083$).

Patient-Reported Pain

The mean pain score (SEM) pre- and post-induction chemotherapy was 1.69 (0.51) vs. 2.11 (0.85). There was no significant difference ($p=0.88$) between the pre- and post-induction chemotherapy evaluations although the clear trend was toward an increase in pain post-induction chemotherapy.

Mucositis Scores

Pre-induction chemotherapy, 2/13 (15%) of patients demonstrated mild erythema only while post-induction chemotherapy, 6/13 (46%) demonstrated some level of mucositis ranging from mild erythema to moderate ulceration. This percent increase in incidence of mucositis was not significant ($p=0.10$). The mean mucositis score (SEM) pre- and post-induction chemotherapy was 0.085 (0.077) vs. 0.521 (0.281). There was no significant difference ($p=0.17$) between pre- and post-induction chemotherapy.

Discussion

Because there are no published data on temporal swallowing measures following chemotherapy alone in head and neck cancer, it is important to document the effects of chemotherapy in the absence of radiation therapy, as done in this study. There is a general belief that chemotherapy does not alter swallowing physiology and that acute dysphagia following chemotherapy is the result of oropharyngeal mucositis. In this study, chemotherapy alone had no significant short term impact on patients' ability to swallow foods of different consistencies, maintain oral nutrition, or enjoy a normal diet and eating in public, although the results showed a consistent though non-significant trend toward negative effects. Objective temporal measures of swallowing were similar pre- and post-induction chemotherapy. Only one measure showed a significant change following induction chemotherapy; pharyngeal residue decreased (an improvement), most likely as a result of a reduction in tumor size. This observation is similar to that reported by Salama and colleagues⁴⁰ where advanced T classification was associated with improved swallowing after treatment as a result of tumor reduction. Because all temporal measures were performed less than 3 weeks following induction chemotherapy, we cannot comment on the long-term effect of chemotherapy on swallowing physiology. Also, all the subjects went on to have intensity-modulated radiotherapy (IMRT) and most had concurrent chemotherapy, so no long term follow-up was available to evaluate the effects of induction chemotherapy only.

Various patient-specific and tumor-specific factors can influence swallowing physiology. Patients with head and neck cancers tend to be elderly and smokers. With advanced age, swallow physiology becomes compromised.^{41,42} Smoking history also adversely affects swallowing following radiation treatment for head and neck cancer.⁴³ However, the effect of smoking on pharyngeal biomechanics is not known. In our study, advanced age and smoking history had no impact on swallow efficiency before or after chemotherapy. Also, advanced T classification and location of the primary tumor in the larynx and hypopharynx can increase the risk of dysphagia and aspiration.^{44,45} We found no such correlation in our study. We cannot comment on the effect of Human Papilloma Virus (HPV) status and swallow biomechanics because biopsy specimens from these patients were not tested for HPV status.

Mucositis-induced oropharyngeal dysphagia varies significantly among different chemotherapy regimens, with up to 70% of patients with grade 3 oral mucositis requiring a feeding tube to maintain nutrition.⁴⁶ It is estimated that >20% of patients with solid tumors who have grade 3 oral mucositis require parenteral nutrition.⁴⁷ In our study, mucositis status and swallow measures were assessed on average 15 days following completion of induction chemotherapy. The degree of mucositis after induction chemotherapy was moderate at most, and was not a significant increase from baseline. This low level of mucositis could be caused by the chemotherapy agents and the dose of chemotherapy used, or by the amount of time that elapsed between the end of chemotherapy and the mucositis assessment.

Oropharyngeal dysphagia can be a common sequela of salivary gland dysfunction in head and neck cancer treatment.⁴⁸ Chemotherapy alone has been shown to produce damage to immortalized salivary acinar and ductal cells in vitro,⁴⁹ produce histological changes and decreased density of secretory granules, and cause nuclear degeneration, interstitial fibrosis, and necrosis of acinar and ductal cells in rats.⁵⁰ Degeneration of minor salivary glands in humans has also been reported.⁵¹ Conflicting data have emerged from clinical studies. In an exploratory study of patients with breast cancer, Harrison and colleagues⁵² showed a reduction in stimulated salivary production and secretory IgA following cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy. Clinical studies also support the additive effect of cisplatin in enhancing radiation-induced salivary gland dysfunction by the mechanism of DNA cross-linkage and possibly by blockage of aquaporine expression in the acinar cells.³¹ In contrast, Kosuda et al.⁵³ observed no effect of chemotherapy when salivary function was assessed using quantitative salivary gland scintigraphy. Our study also supports chemotherapy alone as having no short-term effect on whole-mouth saliva production. These differing observations could be the result of a small number of patients, the multiple drug combinations used, and variable time intervals between the end of chemotherapy and evaluation of salivary function.

When comparing VFG swallow data between the two time points, 13 patients had 80% power to detect a mean difference of 0.85 standard deviations. Effect sizes observed for the VFG swallow measures demonstrated effect sizes ranging from 0.03 (pharyngeal response) to 0.55 (pharyngeal residue), with most effect sizes between 0.03 and 0.33. Effect sizes this small would require a sample size of 150 patients to demonstrate adequate power. It is

unlikely that the results observed are false-negative, due to the consistently low effect sizes observed across most VFG swallow measures.

Although chemotherapy alone is rarely used in the curative treatment of head and neck cancers, the contribution of chemotherapy to radiation in altering swallowing physiology is not known. This is the first study to systematically evaluate the temporal measures of swallowing pre- and post-induction chemotherapy; no significant short term adverse impact was observed though trends toward some negative swallow effects were seen. Despite the small sample size, this study presents useful pilot data for planning of a larger study.

Conclusion

Chemotherapy alone, in the short term, did not significantly negatively impact swallowing biomechanics and quantitative saliva production. The results of this study cannot be generalized because of the small sample size. Further studies with larger numbers of patients are needed to tease out the confounding effects of age, tumor location and stage, pre-existing dysphagia, dental status, xerostomia, smoking history, and other comorbidities, and to follow up the trends on the swallow measures seen in this study. The long-term effect of chemotherapy on swallowing physiology and saliva production needs further investigation.

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Table 1

Patient demographics, tumor site and T/N classification.

Sex	
Male	12
Female	1
Race	
White	11
Black	2
Age (yr)	
Mean (range)	53 (31–68)
Smoking History	
Never smoked	4
Used to smoke but quit	6
Still smokes	3
Alcohol Intake	
Never drank	0
Used to drink but quit	3
Still drinks	10
Primary Tumor Site	
Oropharynx	8
Hypopharynx	2
Unknown	3
Tumor T and N Classification	
T ₀ N ₂ A	1
T ₀ N ₂ B	2
T ₁ N ₂ B	1
T ₂ N ₂ B	4
T ₂ N ₂ C	2
T ₃ N ₂ B	2
T ₃ N ₂ C	1

Table 2

Percent of patients including various food consistencies included in diet, eating a normal diet, and taking all nutrition orally. Values reported are the number (percent) of patients who responded “yes” by evaluation point. No statistical test was performed when both percentages were 100%.

Consistency	Pre-Induction No. (%) of Subjects eating consistency	Post-Induction No. (%) of Subjects eating consistency	<i>p</i> -value
Thin liquids	13 (100)	13 (100)	No test
Thick liquids	13 (100)	13 (100)	No test
Paste/pureed foods	13 (100)	13 (100)	No test
Soft-masticated foods	13 (100)	13 (100)	No test
Crunchy foods	12 (92.3)	10 (76.9)	0.32
Normal diet (all consistencies)	12 (92.3)	9 (69.2)	0.18
100% Oral nutrition	13 (100)	13 (100)	No test

Table 3

Mean and standard error (SEM) for swallow temporal measures and observations from videofluoroscopy by evaluation point (n=13).

Swallowing Measure	Pre-induction chemotherapy Mean (SEM)	Post-induction chemotherapy Mean (SEM)	Difference Mean (SEM)	p-value
Oral transit time (s)	0.370 (0.035)	0.331 (0.036)	−0.039 (0.038)	0.34
Pharyngeal transit time (s)	0.933 (0.080)	0.956 (.081)	0.023 (.056)	0.67
Pharyngeal delay time (s)	0.162 (0.077)	0.175 (0.078)	0.012 (0.055)	0.82
Pharyngeal response time (s)	0.772 (0.022)	0.782 (0.022)	0.010 (0.024)	0.68
Laryngeal Vestibule closure duration (s)	0.501 (0.041)	0.468 (0.041)	−0.033 (0.020)	0.12
Cricopharyngeal opening duration (s)	0.501 (0.021)	0.516 (0.021)	0.015 (0.013)	0.27
Oral residue (%)	3.5 (1.0)	3.5 (1.0)	−0.01 (0.53)	0.98
Pharyngeal residue (%)	4.2 (1.2)	2.4 (1.2)	−1.8 (0.5)	0.007*
Oropharyngeal swallow efficiency (%/s)	80.1 (3.7)	82.7 (3.7)	2.6 (3.2)	0.43

Table 4

Performance Status Scale for Head and Neck Cancer Diet Subscale and Eating in Public Subscale. Values reported are the number (percent) of patients with a score of 100 by evaluation point.

Subscale	Pre-Induction No. (%) of Subjects with a score of 100	Post-induction No. (%) of Subjects with a score of 100	<i>p</i> -value
Diet Scale	12 (92.3)	9 (69.2)	0.18
Eating in Public	13 (100)	10 (76.9)	0.083