International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Head and Neck Cancer

"Pharyngocise": Randomized Controlled Trial of Preventative Exercises to Maintain Muscle Structure and Swallowing Function During Head-and-Neck Chemoradiotherapy

Giselle Carnaby-Mann, M.P.H., Ph.D.,* Michael A. Crary, Ph.D.,† Ilona Schmalfuss, M.D.,‡ and Robert Amdur, M.D.§

*Departments of *Behavioral Science and Community Health, †Speech Language and Hearing Sciences, and §Radiation Oncology, University of Florida, Gainesville, FL; ‡Department of Radiology, North Florida/South Georgia Veterans Health System, Gainesville, FL*

Received Feb 18, 2011, and in revised form Jun 3, 2011. Accepted for publication Jun 3, 2011

Summary

Phayngo-esophageal dysfunction is common after chemo-radiation for HNC. A program of preventative exercise for swallowing was tested in a randomized phase II study. Subjects receiving the swallowing program demonstrated significant benefit over the comparator arms (usual care and placebo) in maintenance of swallow muscle composition and preservation of swallowing function, salivation and chemosensation. Thus simple swallowing exercises administered daily throughout chemo-radiation treatment may offer a cost effective way to prevent swallowing related morbidity

Purpose: Dysphagia after chemoradiotherapy is common. The present randomized clinical trial studied the effectiveness of preventative behavioral intervention for dysphagia compared with the "usual care."

Methods and Materials: A total of 58 head-and-neck cancer patients treated with chemoradiotherapy were randomly assigned to usual care, sham swallowing intervention, or active swallowing exercises (pharyngocise). The intervention arms were treated daily during chemoradiotherapy. The primary outcome measure was muscle size and composition (determined by T_2-weighted magnetic resonance imaging). The secondary outcomes included functional swallowing ability, dietary intake, chemosensory function, salivation, nutritional status, and the occurrence of dysphagia-related complications.

Results: The swallowing musculature (genioglossus, hyoglossuss, and mylohyoid) demonstrated less structural deterioration in the active treatment arm. The functional swallowing, mouth opening, chemosensory acuity, and salivation rate deteriorated less in the pharyngocise group.

Conclusion: Patients completing a program of swallowing exercises during cancer treatment demonstrated superior muscle maintenance and functional swallowing ability.

Keywords: Swallowing dysfunction, Chemoradiotherapy, Swallowing therapy, Randomized controlled trial

Reprint requests to: Giselle Carnaby-Mann, M.P.H., Ph.D., Tel: (352) 273-6164; Fax: (352) 392-7018; E-mail: gmann@phhp.ufl.edu

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 210–219, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.06.1954

Introduction

The swallowing deficits from oropharyngeal cancer and the therapies used to control the disease are devastating to functional feeding outcome (1, 2). Specifically, the swallowing outcomes of patients treated with external beam radiotherapy are poorer than those of patients treated by surgical intervention alone (3–5). One reason for the effect of external beam radiotherapy on swallowing is the development of deep tissue fibrosis (6, 7). The formation of radiation-induced fibrotic tissue and the acute radiation effects (*i.e.,* edema, mucositis, xerostomia) can act collectively to promote muscular disuse or atrophy, contributing to the decline in swallowing function (8, 9).

Skeletal muscle demonstrates remarkable plasticity in response to functional demand (8). Muscles atrophy rapidly after immobilization or disuse (9–11). In contrast, aggressive treatment with weight-loaded exercises results in the recovery of strength and work capacity in previously weakened muscles (12, 13). Head-and-neck cancer (HNC) patients undergoing chemoradiotherapy (CRT) frequently demonstrate muscle changes as a result of fibrosis, muscle edema, and fatty infiltration. Moreover, they have a reduced swallowing frequency owing to the discomfort resulting from the acute radiation effects (14). In essence, they demonstrate constraint-induced muscular weakness from swallowing avoidance. We postulated that swallowing exercises would facilitate maintenance of oropharyngeal muscle function. The present study evaluated the benefit of a battery of exercises on the maintenance of muscle composition and function for swallowing in HNC patients undergoing CRT. Specifically, the maintenance of oropharyngeal muscle size and composition as identified by T_2-weighted magnetic resonance imaging (MRI), level of functional swallowing ability, maintenance of nutritional and chemosensory indexes, and the occurrence of dysphagia-related complications.

Methods and Materials

The present study was undertaken at a university hospital cancer center. The local institutional review board approved the study protocol. All participants signed an approved consent form.

Patients

Patients presenting to the Cancer Center from 2001 to 2004 were screened for inclusion. The patients were included if they presented with *(1)* HNC of the oropharyngeal regions, confirmed by the clinical history and examination findings, with positive cross-sectional imaging studies and histopathologic biopsy, excluding other pathologic factors; *(2)* external beam radiotherapy was planned; *(3)* and they had no history of nonoral feeding for cancer-related illness and were able to undergo MRI procedures.

Study design

The present study followed a randomized, controlled trial design. The treatment allocation used a computer-generated blocked random numbers list. The randomization schedule was held in the trial office, remote from the study environment. After review by the study radiation oncologist, the eligible patients were informed about the trial and, after consenting, randomly assigned to one of three treatment options.

Interventions

The three treatment groups included usual care, standardized sham treatment, and high-intensity behavioral treatment (pharyngocise).

The usual care (control) group included patient management by the attending radiation oncologist "as usual." Treatment, if offered, consisted of supervision for feeding and precautions for safe swallowing (*e.g.,* positioning, slowed rate of feeding) by the hospital speech pathology service. The patients in this group received focused attention sessions during the course of CRT from a research assistant, consisting of weekly telephone calls to monitor the swallowing outcome.

Standardized sham therapy included a buccal extension maneuver ("valchuff") and appropriate dietary modification, under the direction of the study speech pathologist, twice daily for the duration of the CRT. The patients assigned to this group completed the exercise for 10 repetitions over 4 cycles, each of 10 minutes' duration. The treatment sessions were 45 minutes in duration.

Standardized high-intensity swallowing therapy ("pharyngocise") included a battery of exercises (*e.g.,* falsetto, tongue press, hard swallow, and jaw resistance/strengthening using the Therabite Jaw Motion Rehabilitation System [15]) and dietary modification, under the direction of the study speech pathologist, twice daily for the duration of the CRT (up to a maximum of 6 weeks). The patients assigned to this condition completed the four swallowing exercises in 10 repetitions over 4 cycles, each of 10 minutes' duration. The treatment sessions were 45 minutes in duration.

Masking/blinding

Only the treating speech pathologist and patients were aware of the intervention assignment. The study staff worked independently of the hospital service and did not share trial information. The speech pathologists in the hospital service continued to receive sporadic referrals from the radiation oncology staff. The attending radiation oncologists were unaware of the randomization assignment of their patients.

Outcome events

Before CRT, all subjects received a standard clinical and instrumental swallowing assessment, nutritional examination, quality-of-life questionnaires, and T_2-weighted MRI. All baseline measures were repeated at CRT completion and at 6 months after CRT.

The outcome was assessed by 2 independent speech pathologists (M.C., G.C.), who were unaware of the treatment allocation. The swallowing progress and occurrence of possible complications were sought from multiple overlapping sources. Information about the specific swallow treatment was not requested, and the direct treatment records were not reviewed to maintain the blinding. Additionally, patients in both the sham and the pharyngocise arms completed a daily home record of the exercise conducted between treatment sessions. The outcomes after discharge was recorded by the patient or caregiver in a diary and reviewed at monthly telephone interviews.

The primary outcome measure was the change in muscle size and composition identified by T_2-weighted MRI from before to after treatment and at 6 months after randomization.

T_2-weighted MRI

Magnetic resonance imaging was conducted to quantify the baseline muscle parameters in the oral cavity and pharynx. The muscle size, composition, and T_2 signal intensity was documented. The patients were scanned using a Siemens 1.5 T Vision MRI scanner and a phase array neck coil. Multiplaner localizer and subsequent T_1-weighted sagittal images were acquired through the face and upper neck for localization. Subsequently, a T_2 relaxation mapping sequence (Carr-Purcell-Meiboom-Gill sequence) was performed in the axial plane. This T_2 mapping sequence was performed with a repetition time of 2,000 ms and 16 different excitation times (23, 45, 68, 90, 113, 135, 158, 180, 203, 225, 248, 270, 293, 315, 338, and 360 ms) to allow objective calculation of the T_2 value of the different anatomic structures of interest. The T_2 relaxation images were performed in two separate sets of five images of 5-mm slice thickness and an interslice gap of 2.5 mm using a 180-mm field of view through the oral cavity and glottic region. The T_2 relaxation images in the coronal plane through the oral cavity were done using the same imaging parameters. The axial T_1-weighted images aligned parallel to the true vocal folds were done from the hard palate to the upper trachea with a repetition time of 700 ms, excitation time of 15 ms, and flip angle of 90° using the same field of view and slice thickness as used for the T_2 relaxation images.

Axial T_2 relaxation images through the oral cavity were used to measure the length, width, and T_2 relaxation time of the genioglossus muscle and the thickness and T_2 relaxation time of the mylohyoid, hyoglossus, and middle pharyngeal constrictor muscles. In addition, the thickness and T_2 relaxation time of the mylohyoid muscles were measured on the coronal T_2 relaxation images. Images through the glottic level were used to measure the thickness and T_2 relaxation times of the inferior pharyngeal constrictor and cricopharyngeus muscle, as well as of the cervical esophagus. For the measurement of the T_2 relaxation time, the regions of interest were placed into the widest portions of the visible muscle at the level of best differentiation of the muscle to the adjacent tissue planes. For patients with significant muscle wastage, the size of the regions of interest was adjusted to the size of the wasted muscles to avoid a skew of the readings by capturing the relaxation time of the adjacent tissue planes. The distance measurements were performed by a board-certified radiologist (I.S.), with qualification in neuroradiology, who was unaware of the clinical and disease status of the patients. The measurements were recorded for each side separately.

The secondary outcomes included the following:

Changes in the Functional Oral Intake Scale score (FOIS) (16). An abnormal diet was defined as nonoral feeding or oral intake requiring a restricted consistency or special preparation (*i.e.,* FOIS level of $\leq$5). Functional swallowing was defined as a return to the pre-CRT diet without swallowing-related complications.

Swallowing function measured using the Mann Assessment of Swallowing Ability (MASA) (17), confirmed by the videoendoscopic and videofluoroscopic evaluation findings. A significant change was defined as $\pm$10 points on the MASA. The videofluoroscopic assessment included a standard protocol of thin liquid, nectar-thick liquid, and pudding (Varibar, EZ-Em, Westbury, NY) in 5- and10-mL amounts. If appropriate (*i.e.,* did not place the patient at risk of airway compromise), the patients were offered a cup to drink self-selected volumes of liquids and a cracker coated with barium pudding to masticate and swallow. The videofluoroscopic assessment was conducted by a radiologist, who was unaware of the results of the clinical assessment. Scoring followed a published median-weighted scoring system (18, 19).

Change in mouth opening during the study period.

Change in nutritional status, reflected by patient weight during the study period.

Favorable outcome (*i.e.,* composite variable of weight loss $<$10%, maintenance of oral feeding, and change in MASA of $\leq$5 points).

Occurrence of dysphagia-related complications (*e.g.,* pneumonia, dehydration).

Change from baseline to 6 week assessment in unstimulated whole saliva production measured using standard saliometric techniques (20).

Change in smell and taste perception evaluated using the University of Pennsylvania Smell Identification Test (21) (Sensonics, Haddon Heights, NJ) and Accusens T Taste function kit (22) (Westport Pharmaceuticals, Westport, CT).

Statistical analysis

Sample size calculations were determined from previous reports that 30% of HNC patients with dysphagia returned to a pretreatment diet by 6 months. Because previous studies had not used concomitant swallowing therapy, we hypothesized that the patients assigned usual care would have greater muscle decline and that concomitant swallowing therapy would improve that rate by 20% in absolute terms to 50% at 6 months. Therefore, we estimated that 60 patients would provide 80% power at the 5% (two-tailed) significance level to identify this treatment effect.

Repeated measures analysis of variance were used to evaluate the primary MRI outcome. Post hoc testing used Dunnett's and Bonferroni's corrections. The risk ratios and 95% confidence intervals were derived for the functional outcomes. Chi-square tests were used for the discrete counts of patients with adverse events. The three treatment groups were directly compared as the numbers permitted. Subsequently, the primary comparison of interest was between the pharyngocise and usual care groups. A trend analysis was conducted using the chi-square test for linear trend in proportion for all three groups. Exploratory logistic regression analysis was conducted for a favorable outcome at the CRT endpoint.

Results

A total of 703 HNC patients were reviewed between November 2001 and April 2004. Of these 703 patients, 92 (13%) were eligible for inclusion (Fig. 1). Of the 92 eligible patients, 58 (70%) provided written informed consent and were randomized to the usual care (n = 20), sham (n = 18), and pharyngocise (n = 20) groups. The reasons for nonenrollment are provided in Fig. 1. The ineligible patients did not differ significantly from the enrolled subjects in tumor type ($p \leq .95$), location ($p \leq .81$), or size ($p \leq .57$). All randomized patients were included in the intent-to-treat analysis.

The three study arms were characterized by a similar proportion of baseline factors (Table 1). The mean interval to recruitment was 35.1 $\pm$ 28.6 days after diagnosis, and the mean interval to

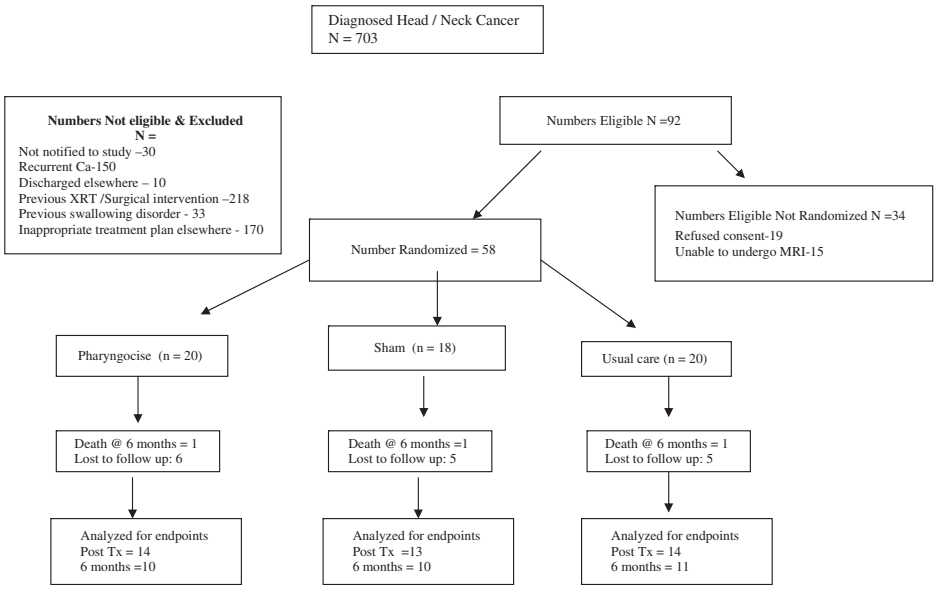


Fig. 1. Trial profile.

randomization in the study was 2.8 ± 8.2 days after the radiation oncology assessment. Of the 58 patients, 36 underwent radiotherapy and 22 underwent concurrent chemotherapy. The mean duration of CRT was not different among the three groups. No significant difference was found among the groups in age, gender, tumor size, tumor site, tumor location side, radiation dose administered, or provision of concurrent chemotherapy (Table 1). During the treatment course, 3 patients died of complications associated with their primary diagnosis or treatment.

Swallowing intervention

The number and duration of swallowing therapy sessions for the patients assigned to the treatment arms (pharyngocise and sham) were significantly greater than those for the usual care group [$F(2,81) = 4.8$, $p < .0001$]. No differences emerged between the treatment arms in the intervention length ($p \leq .58$), total work/exercise performed (cycles) ($p \leq .42$), or duration of sessions (minutes) ($p \leq .016$). The number of sessions received differed significantly between the groups (pharyngocise, 19.9; sham, 25.8; $t = -2.194$; $p \leq .03$).

Home practice

On average, 68% of the subjects complied with the home practice activities. Significantly more subjects in the sham group (28.3) than in the pharyngocise group (20.4; $t = -3.096$; $p < .007$) complied with home practice.

Follow-up

The follow-up data to 6 months were complete for 31 (56%) of the 55 survivors. The data from the 3 patients who died and the 24 patients lost to follow-up (16 at 6 weeks and 8 at 6 months) were censored for the time spent in the study and included in the analysis (Fig. 1).

Primary outcome

Maintenance of muscle composition

All groups demonstrated deterioration in muscle composition during CRT (Fig. 2). Our primary focus was to prevent the deterioration in muscle and swallowing characteristics. The MRI data calculated for the primary side of radiation exposure are presented in Table 2. The data for three muscle groups (*i.e.,* middle pharyngeal constrictor, inferior pharyngeal constrictor, and cervical esophageal wall) demonstrated movement and image artifact in the follow-up examinations and are not presented. From the remaining muscles groups, the muscle size and T_2 relaxation time were significantly different among the study arms (Table 2). Specifically, three muscles related to swallowing function demonstrated greater preservation in the pharyngocise group. The genioglossus showed more deterioration in the usual care group (length, $p \leq .03$; T_2 value, $p \leq .01$). Similar findings were obtained for the mylohyoid (thickness, $p \leq .02$; T_2 value, $p \leq .017$) and the hyoglossus (length, $p \leq .01$; T2 value, $p \leq .037$; Table 2). The T_2 relaxation time demonstrated a significant reduction in all three muscle groups for the pharyngocise group compared with the other study groups.

Secondary outcomes

Functional swallowing ability

Thirty-one percent of the patients demonstrated a significant reduction in the MASA score (defined as ≥10 points) during the CRT period. The functional swallowing ability deteriorated less (chi-square = 3.28, $p \leq .03$) in the pharyngocise group than in the usual care (Table 4) or sham (p for trend < .06; Table 5) groups. The absolute risk difference for achieving functional swallowing after treatment in the pharyngocise group was 36% compared with the usual care group.

Oral feeding

All patients consumed a normal oral diet at baseline. Only 9 patients (23%) were able to maintain a normal oral diet throughout

Table 1 Demographic characteristics

Characteristic	Usual care group	Sham group	Pharyngocise group
Age (y)	54 ± 11.3	60 ± 12.2	59 ± 10.4
Gender			
Male	15	11	18
Female	5	7	2
Interval after diagnosis (d)	33.4 ± 34.3	38.9 ± 32	33 ± 25.3
Interval to randomization (d)	2.5 ± 3.15	2.7 ± 2.5	2.8 ± 4
Tumor size (T grade)			
Median	2	2	2
Range	0–4	1–4	1–4
Tumor site (mode)			
Base of tongue	3	3	5
Tonsil	9	4	3
Tumor side			
Left	6	7	9
Right	5	5	6
Bilateral	9	6	5
Radiotherapy			
Conventional	9	6	9
IMRT	11	12	11
Plus chemotherapy *(n)*	10	6	6
Mean dose (cycles)	3.5 ± 5	2.72 ± 4.2	3.1 ± 3.9
Cisplatin *(n)*	8	2	4
Carboplatin *(n)*	3	4	2
Taxol *(n)*	4	4	3
Combined agents *(n)*	4	4	3
Radiotherapy dose (Gy)	67.5 ± 2.5	69.2 ± 1.4	72.5 ± 1.18
Neck dissection *(n)*	8	6	8
Left	3	1	4
Right	5	5	4
Baseline BMI (kg/m^2)	28.6 ± 1.3	26.9 ± 1.3	26.8 ± 1.0

Abbreviations: IMRT = intensity-modulated radiotherapy; BMI = body mass index.
Data presented as mean ± standard deviation, unless otherwise noted.

the CRT period. The patients in the pharyngocise group maintained oral feeding more often than those in the usual care group (42% vs. 14%, respectively). During CRT, 12 patients (31%) began nonoral (gastrostomy tube) feeding, including 10% with prophylactic tube placement. Fewer subjects received gastrostomy tube feeding in the pharyngocise group (20%) than in the usual care group (30%). At 6 months, 6 patients (21%) were not oral feeding, with most ($n = 4$) in the usual care arm.

Functional oral intake scale

All groups demonstrated diet alteration (reduction in the FOIS score) during CRT. Although the pharyngocise group demonstrated a greater median FOIS score after treatment. However, this change was not significantly different statistically among the groups after treatment (Table 3).

Video endoscopic and videofluoroscopic

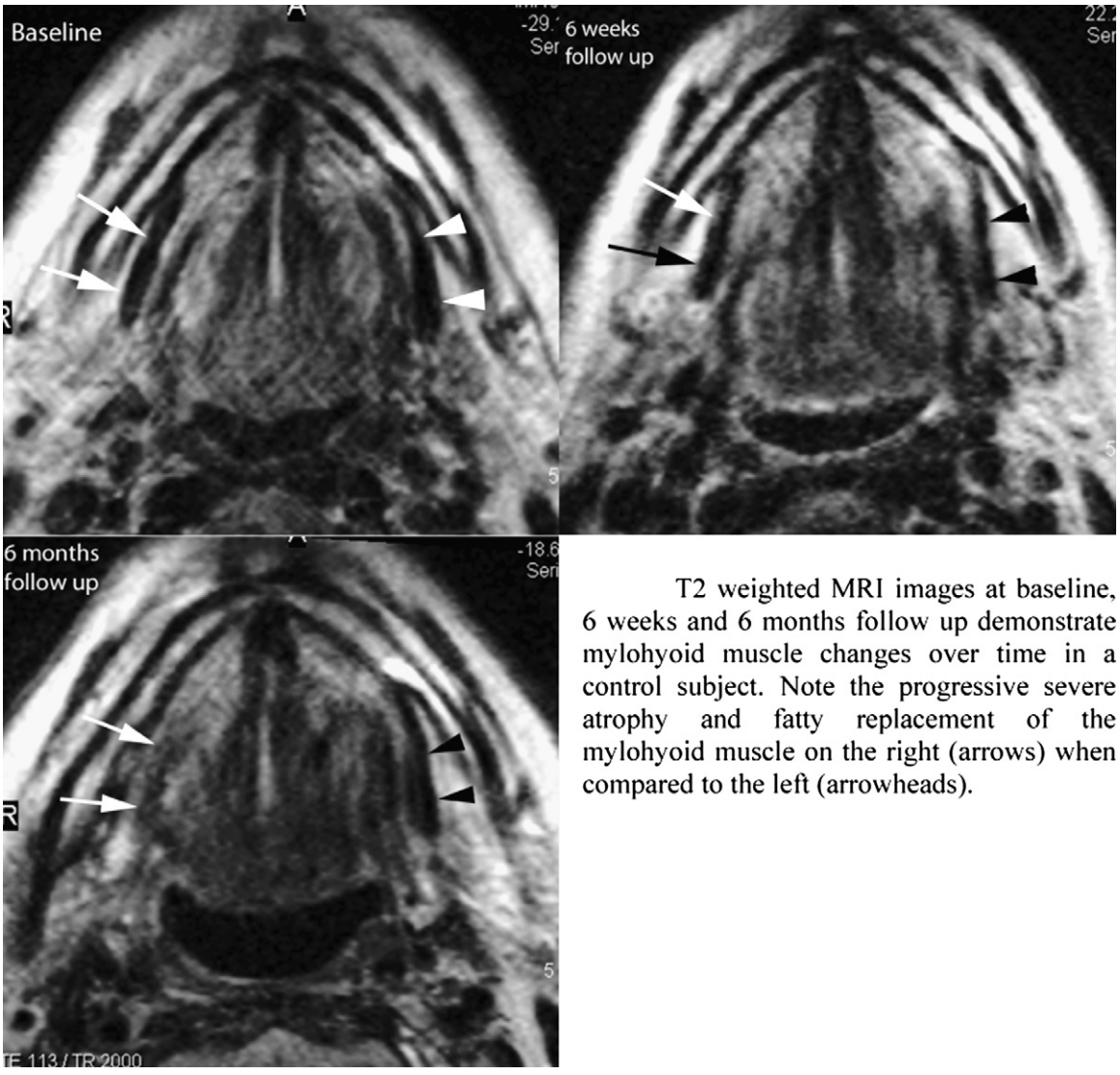
The video endoscopic review demonstrated significant changes in pharyngeal structure across all groups during the study period (Fig. 3). Similarly, videofluoroscopic evaluation (Table 3) demonstrated an alteration in swallowing ability within all arms. The common changes included reduced tongue base retraction, hyolaryngeal elevation, and pharyngeal clearance. The weighted scores were not significantly different among the groups. The prevalence of aspiration was low (14%, $n = 8$), with no statistically significant differences among the groups.

Mouth opening

During the CRT period, the mouth opening reduced by a mean of 3.8 ± 5.08 mm. A greater declination in opening was noted in patients receiving radiotherapy (4.8 mm) than in those receiving CRT (2.7 mm). However, this difference was not statistically significant. The pharyngocise group demonstrated significantly less decline in mouth opening (1.6 mm) than did the sham and usual care groups [5.1 mm and 4.3 mm, respectively; $F(2,43) = 3.28$, $p \leq .47$]. The post hoc analysis identified a significantly superior outcome for the pharyngocise group (6.38, $p \leq .046$) compared with the usual care (Table 3).

Nutrition

The mean weight loss per patient during the study period was 6.69 kg (mean ± standard deviation, 14.75 ± 4.9 lb). A total of 23 patients (40%) lost >10% of their baseline body weight by the 6-week point. A greater number of subjects receiving CRT (61%) lost >10% of their body weight than those receiving RT alone (38%). The average weight loss was not significantly different among the groups after treatment.



T2 weighted MRI images at baseline, 6 weeks and 6 months follow up demonstrate mylohyoid muscle changes over time in a control subject. Note the progressive severe atrophy and fatty replacement of the mylohyoid muscle on the right (arrows) when compared to the left (arrowheads).

Fig. 2. Example of T_2-weighted muscle change in control arm subject.

Favorable outcome after CRT

The *a priori* composite for a favorable outcome (weight loss <10%, maintenance of oral feeding and minimal change in MASA score [≤5 points]) was reached by 57% ($n = 33$) of the sample at the post-treatment evaluation point. A greater proportion of patients in the intervention arms (86% in the pharyngocise and 82% in the sham groups) reached this endpoint than in the control arm (47%). Participation in the pharyngocise arm was associated with a more favorable outcome ($p \leq .009$). Exploratory logistic regression analysis ($n = 58$; 5 fitted variables) revealed that participation in the pharyngocise arm produced a superior benefit (odds ratio, 6; 95% confidence interval, 1−37.2). The final model indicated significant predictive power for the variables pharyngocise ($p = .05$) and sham ($p = .06$). The odds that a patient receiving pharyngocise treatment for swallowing would have a favorable outcome after CRT were six times greater than the corresponding odds for a patient who did not receive preventative exercise during CRT. In addition, the post hoc Homer-Lemeshow test from this model yielded a p value of .987, suggesting a model with adequate predictive value.

Salivation

Reduced salivary flow was identified in >80% of the patients by the end of CRT. The mean reduction in salivary flow was 0.182 ± 0.21 mL/min. Repeated measures analysis of variance demonstrated a significant difference in salivation decline [$F(1,36) = 30$, $p \leq .0001$] with the post hoc comparison [$F(1,36) = .238$, $p \leq .020$], demonstrating significant preservation of the salivary flow in the pharyngocise group. The absolute risk reduction for salivation decline in the pharyngocise group was 35% compared with the usual care group (Table 4).

Taste

Taste reduction was noted in 32 patients (82%) during the CRT period. The taste decline demonstrated a significant difference among the groups [chi-square (trend) = 5.8, $p \leq .053$]; with fewer patients in the pharyngocise group demonstrating a decline in taste acuity (Table 5). The absolute risk reduction for the taste decline in the pharyngocise group compared with the usual care group was 19% (Table 4).

Table 2 Muscle composition at 6 weeks

Muscle	Study arm			*p*
	Usual care	Sham	Pharyngocise	
Genioglossus*				
Length				<.03
Before	37.08 ± 6.4	34 ± 4.7	34.9 ± 4.8	
After	33.6 ± 5.7	32.5 ± 3.9	34.4 ± 2.7	
Change	3.67	1.5	0.5	
Thickness				NS
Before	7.31 ± 1.9	7.41 ± 0.7	7.54 ± 1.8	
After	6.89 ± 0.7	6.97 ± 0.6	7.11 ± 1.8	
Change	0.42	0.43	0.44	
T_2				<.01
Before	108.1 ± 5.2	107 ± 6.6	111.2 ± 3.8	
After	108.05 ± 2.1	104.9 ± 4.1	101.6 ± 5	
Change	0.05	2.1	9.6	
Hyoglossus*				
Length				<.018
Before	21.04 ± 4.1	17.9 ± 4.1	17.4 ± 3.9	
After	17.2 ± 3.6	16.9 ± 3.4	17.9 ± 3.07	
Change	3.84	1	−0.05	
Thickness				NS
Before	4.11 ± 0.88	3.1 ± 0.73	2.9 ± 0.95	
After	3.06 ± 0.86	3.2 ± 0.9	2.5 ± 0.6	
Change	1.05	−0.1	0.4	
T_2				<.037
Before	104.2 ± 4.1	106.8 ± 6.2	114.7 ± 8.8	
After	104.9 ± 3.7	105.1 ± 2.6	105.1 ± 2.6	
Change	−0.07	1.7	9.6	
Mylohyoid*				
Thickness				<.021
Before	4.4 ± 1.1	2.86 ± 0.7	3.86 ± 0.96	
After	2.8 ± 0.78	3.01 ± 1.0	3.8 ± 1.2	
Change	1.6	−0.15	0.06	
T_2				<.017
Before	104.1 ± 4.6	103.7 ± 4.4	111.8 ± 11.3	
After	106.3 ± 6.5	104.1 ± 5.6	103.8 ± 3.4	
Change	−2.2	−0.4	8	

Data presented as mean ± standard deviation, unless otherwise noted.
data displayed is from primary field of irradiation.
* Repeated measures analysis of variance within measures − time group.

Smell

Overall, 12 (32%) patients demonstrated a decline in olfactory acuity by the end of CRT. A significant difference between the pharyngocise and usual care groups was identified in olfactory decline (chi-square = 4.1, $p \leq .03$), with a superior outcome identified in the pharyngocise group. The absolute risk reduction for olfactory decline in the pharyngocise group was 39% compared with the usual care group (Table 4).

Dysphagia-related complications

No significant associations were noted between the treatment group and dysphagia-related complications. Pneumonia was uncommon, occurring in 3.4% ($n = 2$) of the patients. Dehydration was identified in 17.2% ($n = 10$) of the group and was significantly associated with concurrent chemotherapy (chi-square = 5.97, $p \leq .015$). Mucositis occurred in 35 patients (65%) during CRT and oral yeast infections in 8 patients (14%). No association was identified between the occurrence of mucositis and oral yeast infection and the treatment group.

Discussion

The results from the present study have demonstrated that swallowing exercises administered during CRT results in the maintenance of head-and-neck musculature and improved swallowing indexes. Furthermore, mobilizing swallowing muscles at any level could affect the feeding and chemosensory outcomes in this population.

The present study identified maintenance of muscle characteristics from swallow exercise during CRT. Previous research has reported muscle thickening and T_2 elongation associated

Table 3 Swallowing outcomes

Variable	Study arm			*p*
	Usual care	Sham	Pharyngocise	
MASA				
Baseline	195.5 ± 4	194.7 ± 3.5	195.1 ± 5.9	NS
6-wk Outcome	171.5 ± 14.2	173.6 ± 11.8	177.14 ± 12.5	≤.006
Change	24.16 ± 13.4	20.8 ± 12.9	17.7 ± 10.1	
FOIS				
Baseline				NS
Median	7	7	7	
Range	5–7	5–7	5–7	
6-wk Outcome				
Median	4	4	5	
Range	1–6	1–7	2–7	
VFE score				
Baseline	0.186 ± 0.09	0.272 ± 0.15	0.214 ± 0.02	NS
At 6 wk	0.214 ± 0.09	0.343 ± 0.16	0.200 ± 0.16	
Mouth opening				
Baseline	36.6 ± 8.05	39.2 ± 6.4	41.6 ± 8.4	NS
At 6 wk	32.3 ± 5.9	34.07 ± 7.3	40.05 ± 8.3	<.047*
Change	4.3	5.1	1.6	

Data presented as mean ± standard deviation, unless otherwise noted.
* Dunnett's post hoc comparison.

with edema in head-and-neck muscles receiving doses of >50 Gy (23). Accordingly, the reduction in T_2 relaxation time and maintenance of muscle size associated with the pharyngocise protocol might reflect a deterrent to inflammatory changes noted with CRT. Although T_2 declination could be influenced by multiple factors, the reduction in muscle edema or fatty infiltration is likely to be a contributing factor. The combination of T_2 declination with maintenance in the muscle structure and preservation of swallowing function in the pharyngocise group supports this conclusion. The MRI results for the sham group were between those of the pharyngocise and usual care groups, suggesting that patients might receive a benefit from lower intensity exercise regimens.

The subjects in all three groups were treated by the same team of radiation oncologists, received comparable CRT regimens, and did not differ in tumor site or disease extent. Specific swallowing muscle dosimetry was not available for all subjects to confirm the balanced exposure to the muscles of interest. Notwithstanding, we believe the application and exposure to medical intervention did not differ by group.

The present study is the first truly randomized trial to evaluate a systematic program of swallowing exercises completed during CRT. Two previously published studies suggested that pretreatment swallowing therapy improved the post-treatment quality of life and limited swallowing variables (epiglottic inversion and tongue base position) in HNC patients (24, 25). These studies, conducted by the same center, provided swallowing intervention for 2 weeks before CRT not concomitantly. Furthermore, the design of those studies (unmatched case control and cross sectional) was not as rigorous as the design of the present trial and the total number of patients was smaller ($n = 9$ and $n = 37$, respectively). Similar to our study, Van Der Molen *et al.* (26) described the application of swallowing exercises concurrent with CRT in 49 patients treated for HNC. That study did not

Table 4 Comparison of pharyngocise vs. usual care at 6 weeks

Outcome (at 6 wk)	Intervention		Analyses		
	Usual care	Pharyngocise	RR	95% CI	ARR (%)
Normal diet	2/14	5/12*	2.91	0.68–12.4	27
Nonoral feeding	6/14	3/12*	0.58	0.18–1.84	18
Functional swallowing	2/14	6/12*	3.5	0.86–14.2	36†
Weight loss (>10%)	6/13*	4/14	0.62	0.22–1.7	18
Salivation decline	12/13*	8/14	0.62	0.38–1.02	35†
Taste decline	10/12*	9/14	0.77	0.48–1.23	19
Smell decline	6/11*	2/13*	0.28	0.07–1.13	39†
Any complication	7/14	5/12*	0.71	0.31–1.6	17

Abbreviations: RR = relative risk; CI = confidence interval; ARR = absolute risk reduction (risk difference).
* Chi-square significance.
† Missing data points.

Table 5 Comparison of pharyngocise vs. sham vs. usual care at 6 weeks

Outcome (at 6 wk)	Intervention			Trend analyses, p for trend
	Usual care (n = 14)	Sham (n = 13)	Pharyngocise (n = 14)	
Normal diet	2	2	5	.185
Nonoral feeding	6	3	3	.295
Functional swallowing	2	2	6	.067*
Weight loss (>10%)	6	6	4	.604
Salivation loss	12	12	8	.061*
Taste decline	10	13	9	.053*
Smell decline	6	4	2	.123
Any complication	7	4	5	.597

* Trend toward significance from chi-square trend analysis.

include a control group but compared two forms of swallowing therapy. Both swallowing therapies involved patient-controlled and clinician-directed exercises. The results indicated significant decreases in oral intake, mouth opening, and weight at 10 weeks after CRT. However, the patients in both treatment groups demonstrated reduced feeding tube dependency. Thus, although their results did not address the efficacy of active exercise on the outcome, they did address the potential benefit from any exercise and the acceptability and feasibility of swallowing therapy for this population. In this respect, although limited, the results from previous studies support our results.

Our sample included both RT and CRT patients, providing greater generalization to the HNC treatment population. The exercise protocol used was significantly different between the groups and used validated muscle and swallowing outcome measures. Although the number of patients and outcome events at the 6-month follow-up period were small (because of morbidity and measurement artifact), we were able to demonstrate the consistency of results across several outcome events (all favoring the pharyngocise group), strongly suggesting a positive treatment effect.

Although our study results suggest benefit (physiologically and functionally) from swallowing exercises, the dose–response curve

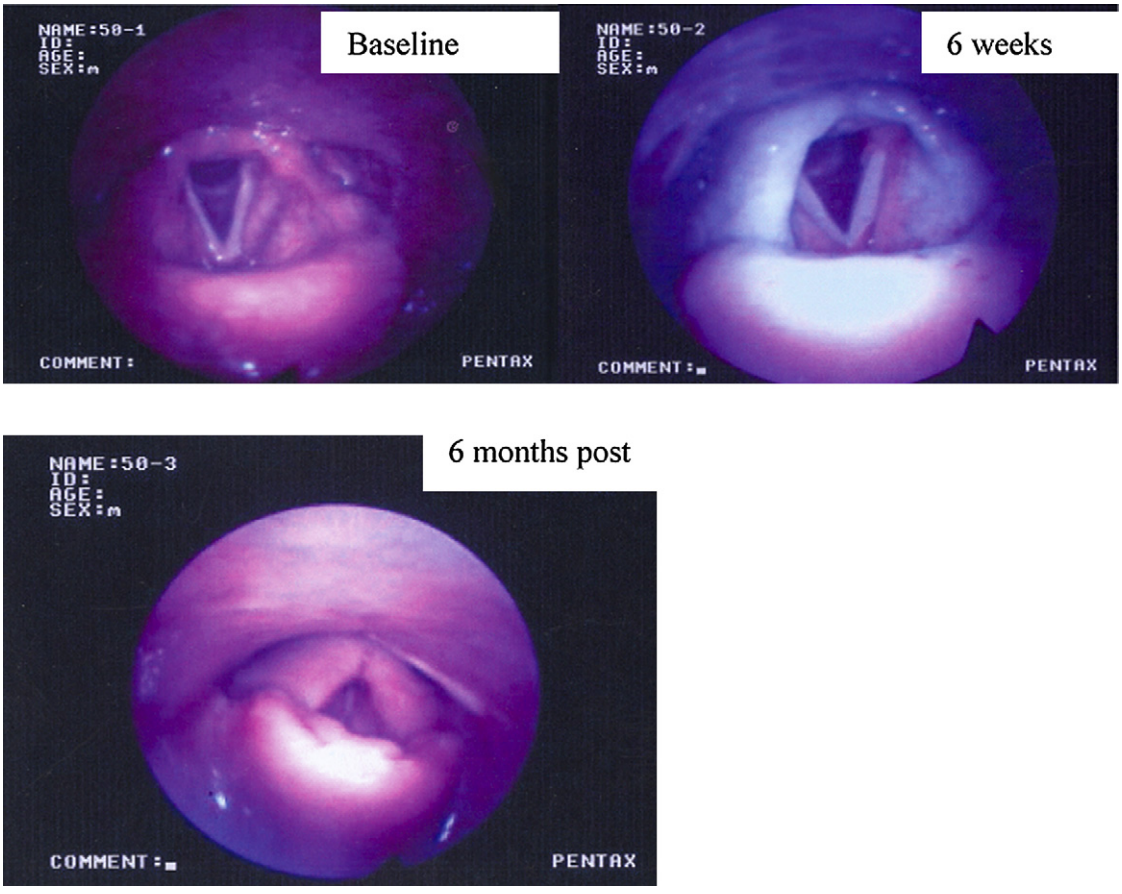


Fig. 3. Endoscopic image showing change in anatomy of oropharynx in control arm subject.

for this form of behavioral treatment remains unclear. Benefit was derived not only from the intensive intervention arm but also from sham intervention. These arms did not differ in length or duration of intervention or total work performed. Whether the benefits obtained by the sham group can be ascribed to a placebo effect of behavioral attention or to the affect of attenuated movement is unclear. A larger study is underway to review the dose—response effect of low- and high-intensity pharyngocise intervention.

The data from our study were most complete up to the 6-week post-treatment point. We experienced a withdrawal rate at 6 months that precluded the meaningful analysis of many outcomes to that point. This is not an unusual finding in the HNC population, for whom the high morbidity levels and associations with negative lifestyle factors elevate the lost-to-follow-up rates. A comparison between the enrolled patients with and without complete data in the present study did not reveal significant differences in age, cancer stage, or swallowing comorbidity, suggesting that our results are representative.

Conclusion

The results of the present study demonstrated a benefit from a program of simple swallowing exercises administered during CRT. This approach is novel in timing of delivery and preventative design. Given the health costs of dysphagia from HNC and positive outcomes reported from the present study, it is imperative that additional research be undertaken to refine the swallowing treatments and their delivery for this population. Preventative swallowing programs can offer a cost-effective alternative to prevent medically related complications and optimize functional outcome for HNC patients.

References

1. Colangelo LA, Logemann JA, Pauloski BR, *et al*. T stage and functional outcome in oral and oropharyngeal cancer patients. *Head Neck* 1996;18:259—268.
2. Chasen MR, Bhargava R. A descriptive review of the factors contributing to nutritional compromise in patients with head and neck cancer. *Support Care Cancer* 2009;17:1345—1351.
3. Pauloski B, Logemann JA, Rademaker AW, *et al*. Speech and swallowing function after oral and oropharyngeal resections: One year follow-up. *Head Neck* 1994;16:313—322.
4. Lazarus C. Effects of radiation therapy and voluntary maneuvers on swallow functioning in head and neck cancer patients. *Clin Commun Disord* 1993;3:11—20.
5. Lazarus C, Logemann JA, Pauloski BR, *et al*. Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy. *Laryngoscope* 1996;106:1157—1166.
6. Riekki R, Jukkola A, Sassi M, *et al*. Modulation of skin collagen metabolism by irradiation: Collagen synthesis is increased in irradiated human skin. *Br J Dermatol* 2000;142:874—880.
7. Kendall K, McKenzie M, Leonard R, Jones C. Structural mobility in deglutition after single modality treatment of head and neck carcinomas with radiotherapy. *Head Neck* 1998;20:720—725.
8. Tyml K, Mathieu-Costello O. Structural and functional changes in the microvasculature of disused skeletal muscle. *Front Biosci* 2001;6: D45—D52.
9. Berg HE. *Effects of unloading on skeletal muscle mass and function in man*. Stockholm: Physiology and Pharmacology, Karolinska Institutet; 1996.
10. Berg HE, Tesch PA. Changes in muscle function in response to 10 days of lower limb unloading in humans. *Acta Physiol Scand* 1996;157:63—70.
11. Piquet F, Stevens L, Butler-Browne G, Mounier Y. Differential effects of a six-day immobilization on newborn rat soleus muscles at two developmental stages. *J Muscle Res Cell Motil* 1998;19:743—755.
12. Warfield SK, Mulkern RV, Winalski CS, *et al*. An image processing strategy for the quantification and visualization of exercise-induced muscle MRI signal enhancement. *J Magn Reson Imaging* 2000;11:525—531.
13. Foley JM, Jayaraman RC, Prior BM, *et al*. MR measurements of muscle damage and adaptation after eccentric exercise. *J Appl Physiol* 1999;87:2311—2318.
14. Zuydam AC, Rogers SN, Brown JS, *et al*. Swallowing rehabilitation after oro-pharyngeal resection for squamous cell carcinoma. *Br J Oral Maxillofac Surg* 2000;38:513—518.
15. Buchbinder D, Currivan RB, Kaplan AJ, Urken ML. Mobilization regimens for the prevention of jaw hypomobility in the radiated patient: A comparison of three techniques. *J Oral Maxillofac Surg* 1993;51:863—867.
16. Crary MA, Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Arch Phys Med Rehabil* 2005;86:1516—1520.
17. Mann G. *The Mann assessment of swallowing ability*. Clifton Park, NJ: Singular, Thompson, Delmar Learning; 2002.
18. Mann G, Hankey G, Cameron D. Swallowing disorders following acute stroke: Prevalence and diagnostic accuracy. *Cerebrovasc Dis* 2000;10:380—386.
19. Carnaby-Mann G, Crary M. McNeill Dysphagia Therapy Program: A case-control study. *Arch Phys Med Rehabil* 2010;91:743—749.
20. Ben-Aryeh H, Miron D, Szargel R, Gutman D. Whole-saliva secretion rates in old and young healthy subjects. *J Dental Res* 1984;63:1147—1148.
21. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiol Behav* 1984;32:489—502.
22. Henkin R. Human taste and smell disorders. In: Adelman G, editor. Encyclopedia of neuroscience. 2nd ed. Boston: Birkhauser; 1999. p. 2010—2013.
23. Popovtzer A, Cao Y, Feng F, Eisbruch A. Anatomical changes in the pharyngeal constrictors after chemoirradiation of the head and neck cancer and their dose—effect relationships: MRI-based study. *Radiother Oncol* 2009;93:510—515.
24. Carroll WR, Locher JL, Canon CL, *et al*. Pretreatment swallowing exercises improve swallow function after chemoradiation. *Laryngoscope* 2008;118:39—43.
25. Kulbersh BD, Rosenthal EL, McGrew BM, *et al*. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. *Laryngoscope* 2006;116:883—886.
26. van der Molen L, van Rossum MA, Burkhead LM, *et al*. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: Feasibility, compliance, and short-term effects. *Dysphagia* 2011,26(2):155-70.