A Prospective Investigation of Swallowing, Nutrition, and Patient-rated Functional Impact Following Altered Fractionation Radiotherapy with Concomitant Boost for Oropharyngeal Cancer

Author

Cartmill, Bena, Cornwell, Petrea, Ward, Elizabeth, Davidson, Wendy, Porceddu, Sandro

Published

2012

Journal Title

Dysphagia

Version

Accepted Manuscript (AM)

DOI

10.1007/s00455-011-9333-5

FUNCTIONAL OUTCOMES AFTER ALTERED FRACTIONATION RADIOTHERAPY

A prospective investigation of swallowing, nutrition, and patient-rated functional impact following altered fractionation radiotherapy with concomitant boost for oropharyngeal cancer[*]

Bena Cartmill B. Sp.Path (Hons)

Speech Pathology Department, Princess Alexandra Hospital

Ipswich Rd, Woolloongabba Q 4102

Phone: +61 403 160 913

Dr Petrea Cornwell B. Sp.Path.(Hons), PhD

Metro North Health Service District, Queensland Health

Professor Elizabeth Ward B.Sp.Thy.(Hons) Grad Cert Ed., PhD

Centre for Functioning and Health Research, Queensland Health

Level 3, Buranda Shopping Centre

Ipswich Rd, Woolloongabba Q 4102

Wendy Davidson

Dietetics Department, Princess Alexandra Hospital

Ipswich Rd, Woolloongabba Q 4102

Associate Professor Sandro Porceddu BSc MBBS (Hons)

Radiation Oncology Department, Princess Alexandra Hospital

Ipswich Rd, Woolloongabba Q 4102

[*] Funding for this research was obtained as PhD scholarships through the Cancer Council Queensland and Cancer Collaborative Group (Princess Alexandra Hospital)

Abstract

Altered fractionation radiotherapy for head and neck cancer has been associated with improved locoregional control, overall survival, and heightened toxicity compared with conventional treatment. Swallowing, nutrition and patient-perceived function for altered fractionation radiotherapy with concomitant boost (AFRT-CB) for T1-T3 oropharyngeal SCC has not been previously reported. Fourteen consecutive patients treated with AFRT-CB for oropharyngeal SCC were recruited from November 2006 to August 2009 in a tertiary hospital in Brisbane, Australia. Swallowing, nutrition and patient-perceived functional impact assessments were conducted pre-treatment, at 4-6 weeks post-treatment and at 6 months post-treatment. Deterioration from pre-treatment to 4-6 weeks post-treatment in swallowing, nutrition and functional impact was evident, likely due to the heightened toxicity associated with AFRT-CB. There was significant improvement at 6 months post-treatment in functional swallowing, nutritional status, patient-perceived swallowing and overall function, consistent with recovery from acute toxicity. However, weight and patient-perception of their physical function and side effects remained significantly worse than pre-treatment scores. The ongoing deficits related to weight and patient-perceived outcomes at 6 months revealed this treatment has a long-term impact on function possibly related to the chronic effects of AFRT-CB.

Key words: deglutition; deglutition disorders; nutrition; patient rated function; altered fractionation radiotherapy; oropharynx; squamous cell carcinoma

INTRODUCTION

The use of altered fractionation radiotherapy (AFRT) for treatment of oropharyngeal cancer has demonstrated superiority in locoregional control and long-term survival when compared with conventionally fractionated radiotherapy[1-3]. AFRT with concomitant boost (AFRT-CB) delivers radiotherapy in an accelerated format without total dose reduction, resulting in heightened toxicity which may persist longer and result in a higher incidence of severe functional injury, including possible deleterious effects on swallowing and nutrition[4-9]. Anecdotal clinical evidence suggests that there is a more severe functional impact following AFRT-CB compared to conventional treatment; however as yet, there has been no detailed or systematic research investigating swallowing and nutrition outcomes following this treatment regimen. Consequently, the challenge ahead is to gain a better understanding of the nature of the dysphagia associated with new treatment modalities and the impact of this treatment modality on nutritional outcomes[10].

The majority of research studies to date that have investigated the functional outcomes of AFRT on swallowing and nutrition have been confounded by the concurrent use of chemotherapy[11-17]. With the known exacerbation of toxicity associated with combined chemotherapy and radiotherapy[18, 19] it is not adequate to assume the functional results following combined AFRT plus chemotherapy treatment would be equivalent to receiving AFRT alone. Indeed, multimodality treatment has been shown to cause greater weight loss than single modality treatment regimens[20] and more severe dysphagia presentation and aspiration risk[11].

Yu et al.[8] have reported the only known study that examined swallowing outcomes and the impact on nutrition for a heterogenous head and neck cancer patient group treated with

intensive radiation protocols (i.e. accelerated with concomitant boost and accelerated hyperfractionation). They found that 18% of patients had developed swallowing dysfunction by 1-2 months post-treatment that was severe enough to require enteral feeding, with resolution of function for the majority (93%) of patients at 1 year post-treatment follow-up. However, their study was conducted as a retrospective chart review and used a simple rating scale to document swallowing status pre-treatment and at variable follow-up intervals (range = 3.7 to 66 months). Consequently, although the study provides preliminary evidence that negative swallowing outcomes appear to resolve in the long term for the majority of this population, the constraints in the study design did not allow for detailed description of the nature of swallowing dysfunction in the acute phase. The lack of systematic follow-up at set time intervals also limits the understanding of patterns of resolution, or possibly exacerbation, of swallowing and nutritional status over time. In addition, the heterogenous population studied with varying tumour sites further limits the interpretation of the results.

Existing studies suggest swallowing and nutrition may be negatively impacted in head and neck cancer patients both before[21, 22] and after existing modes of radiotherapy treatment[11, 23-25], although currently there is limited information regarding the status of patients within the head and neck cancer population who are receiving AFRT-CB alone. Although several studies have found improved survival with concurrent chemoradiotherapy protocols and a subsequent trend to treat in this manner, many patients are not deemed appropriate for this combined treatment and are still treated with radiotherapy alone [8, 26]. This study aims to describe the nature, severity, and course of dysphagia, nutritional status and patient-perceived functional impact in individuals who undergo AFRT-CB for T1-T3 oropharyngeal SCC from pre-treatment to 6 months post-treatment. Thus, it remains clinically relevant to establish the

evidence base regarding the nature of the swallowing and nutritional outcomes that can be anticipated by patients undergoing altered fractionated regimens.

MATERIALS AND METHODS

Participants

Participants were identified from consecutive presentations to the Princess Alexandra Hospital (PAH) Multidisciplinary Head and Neck Clinic, a large tertiary referral centre in Brisbane, Australia between November 2006 and August 2009. Only those patients with T1, T2, or T3 SCC of the oropharynx (tonsil, base of tongue [BOT], pharyngeal wall, or supraglottis) who were recommended for treatment with curative intent AFRT-CB were suitable for inclusion. Participants were ineligible if they had previously diagnosed head and neck cancer and/or treatment affecting the tonsil, BOT, pharyngeal wall, or supraglottis, and/or a pre-existing neurological or neurodegenerative condition that may have impacted on swallowing function. Patients with glottic SCC were excluded because the tumour location had the potential to impact on swallowing function and airway protection prior to treatment.

During the study period, AFRT-CB was the recommended treatment for 17 patients, all of whom were eligible for recruitment. Of the eligible participants, two patients declined to participate, leaving a cohort of 15 participants who consented to involvement in the study. Of these, complete data sets were available for only 14 individuals as one participant (T1N2c left BOT, male, 70 years of age) died during treatment from causes unrelated to his cancer diagnosis. The remaining participants form the subject of this analysis.

The cohort was predominantly male (12 male, 2 female) with a mean age of 66.4 years (*SD* = 8.92; range = 53-82). Demographic and clinical characteristics are reported in Table 1. The

primary site of the tumour for the majority of participants was tonsil (n = 9, 64.3%), followed by supraglottis (n = 3, 21.4%). Fifty percent of participants had T2 tumours (28.6% T1; 21.4% T3) and the majority of patients (64.3%) had no nodal disease (N0) (14.3% N1; 21.4% N2). Disease staging revealed that the majority of participants had stage III disease (35.7%), while in decreasing frequency of occurrence, 28.6% had stage II disease, 21.4% stage IV, and 14.3% stage I disease. Half of the participants were ex-smokers and 85.7% reported being current alcohol drinkers. All patients received their treatment at the Metro South Radiation Oncology Service in Brisbane, Australia. Ethics approval was obtained from the Princess Alexandra Hospital and The University of Queensland Human Research and Ethics Committees.

[insert table 1 near here]

Procedure

All participants underwent AFRT-CB in which a total dose of 66Gy was delivered in 35 fractions within a schedule that employs a daily dose of 2Gy for five weeks, with a second daily dose of 1.6Gy (the concomitant boost) in the final 2 weeks of treatment, with at least 6 hours interfraction interval. At pre-treatment, 4-6 weeks post-treatment, and at 6 months post-treatment, participants underwent a range of assessments encompassing three areas: (1) swallow function, (2) nutritional status, and (3) global measures of the functional impact of head and neck cancer.

Swallow Function

Swallow function was evaluated at each assessment time point by a speech pathologist with more than 5 years experience with the head and neck oncology caseload using both a clinical swallowing examination and a videofluoroscopic assessment of swallowing.

The clinical examination of dysphagia included a compilation of medical history and discussions with the patient regarding side effects which were impacting on oral intake, followed by an oromotor assessment and subsequent trials of food and fluids as per standard protocols[27]. Food (full, soft, minced, pureed) and fluid (thin, mildly thick, moderately thick, extremely thick) consistencies were consistent with Australian standards[28]. From this assessment, the level of diet and fluids that could be managed safely without aspiration risk or excessive fatigue/pain was established. In addition, a level of functional swallowing status was assigned using the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS)[29], a 10-part validated outcome measure scale designed to measure everyday performance of swallowing function based on clinical indicators. The scale ranges from the most inferior swallowing status at level 1 (described as "patient aspirates secretions"), to level 10, the highest functional status for swallowing outcome (described as "swallowing function at better than premorbid/preadmission level")[29]. These levels map onto four functional stages: (A) Nil by mouth (levels 1-3), (B) Commencing oral intake (level 4), (C) Establishing oral intake (level 5-7), and (D) Maintaining oral intake (levels 8-10).

Instrumental swallow examination was conducted via a videofluoroscopic swallow assessment (VFS), guided by a radiologist and speech pathologist. Participants were assessed in the lateral plane. The intent at each assessment session was to evaluate swallowing physiology on four fluid and three solid consistencies. A barium solution mixed at a ratio of 100 grams of barium (E-Z-HD Barium Sulfate for Suspension 98% w/w Cat. No. 764) to 65ml water was added to the three thickened liquids (pre-packaged Flavour Creations products in extremely thick, moderately thick, and mildly thick, www.flavourcreations.com.au) and coated onto the three solid (diced fruit, marshmallow, and

biscuit) consistencies. A barium solution mixed with water to a ratio of 50:50 was used to approximate thin fluids. A standard protocol was followed during the VFS procedures, and was discontinued only when participants aspirated greater than 90% of a bolus (approximated), were unable to clear a solid consistency without subsequent fluids (due to severe xerostomia), experienced severe pain or discomfort, or refused to continue the assessment. The protocol involved completing three mouthfuls of each consistency in the following sequence: extremely thick fluids, moderately thick fluids, mildly thick fluids, thin fluids, diced fruit, marshmallow and biscuit. It has been previously described that three trials per consistency are necessary to achieve 80% reliability[30].

Videofluoroscopic assessments were recorded onto video home system (VHS) cassettes and later converted onto digital video disc (DVD) using the MSI Digital@nywhere digital TV tuner Peripheral Component Interconnect (PCI) card and accompanying software (main interface version number 1.1.0.2). Video files were encoded as a Moving Picture Expert Group version 2 (MPEG2) video stream for analysis. Analysis of all VFS assessments was conducted by a single speech pathologist experienced in the procedure and evaluation of VFS assessments but not otherwise involved in the research study. The speech pathologist responsible for rating was provided with a compilation CD that contained all of the de-identified VFS files presented in random order.

The evaluation tools used for the VFS assessments included: (1) New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES)[31], and (2) the Penetration-Aspiration Scale (PAS)[32]. The NZIMES is a comprehensive scale that can be used to assist in the physiological interpretation of VFS. Only four components of subscale one “Swallowing Physiology” which divides the analysis of swallowing function into five parameters (Oral,

Oral Pharyngeal Transit, Pharyngeal, Crico-esophageal and Laryngeal), was utilised in the current investigation. The fifth component, Laryngeal parameters, which measures penetration and aspiration events and airway response, was discarded in preference for the validated Penetration-Aspiration Scale discussed below. The four parameters used in this study have between two and five sections that further specify the anatomical and physiological components involved in the swallowing process. For example, Oral parameters is divided into labial closure, lingual control, palatal closure, and mastication. Each component is rated according to a five point descriptive scale where 0 equates to no significant impairment and 4 indicates a profound impairment.

The scores from each physiological parameter of the NZIMES were interpreted individually and drawn from observations on all fluid and solid consistencies. There is no consensus on data reduction in VFS with some studies rating the first swallow[33], rating the average performance across two or three swallows[34-36], or giving no comment on the data analysis[37, 38]. In the current study, the worst performance observed across the food and fluid trials was used for analysis. Inter- and intrarater reliability was completed for this tool as reliability data have not been reported. Twenty percent of the VFS samples (n = 13) were randomly selected and compiled on to a CD for rating by a second experienced speech pathologist. In addition, intrarater reliability was calculated for the principle rater by requiring 20% of the samples (n = 8) to be re-rated no less than 3 months after the initial rating session. Percent agreement within one rating point for inter- and intrarater reliability was 99.4% and 99.2%, respectively.

The PAS[32] was used to provide quantification of penetration and aspiration events observed during VFS. The PAS is an eight-point interval scale with documented high inter- and intrarater reliability that scores aspiration events according to the depth of material entering

the airway and whether this material is expelled from the airway[32]. A rating of one (1) indicates material does not enter the airway, while a rating of eight (8) equates to material entering the airway and passing below the vocal folds, and no effort is made to eject.

Nutritional Status

Data collection on nutritional status at each time point was completed by an experienced dietitian who was a member of the Multidisciplinary Head and Neck Clinic. Measures used to evaluate nutritional status included (1) measurement of the participant's weight, and (2) completion of the Patient-Generated Subjective Global Assessment (PG-SGA)[39]. A participant's weight was recorded to the nearest 0.1 kg using digital scales (G-Tech International GL-6000), with all participants being assessed at the same location. A single height measurement was reported by patients as listed on their driver's licence. Using this information, a body mass index (BMI) score was calculated using the standard formula: weight/height^2 (kg/m^2)[40, 41].

Nutritional outcomes were determined with the PG-SGA[39]. This assessment tool has been validated in the head and neck cancer population and is used extensively in clinical practice and clinical trials of nutrition intervention regimens[42, 43]. The PG-SGA comprises a patient completed section and a physical examination completed by a dietitian. The patient section is divided into four sections: weight, food intake, symptoms, and activities and function. Patients who experienced difficulty completing this independently were assisted by the dietitian in a structured interview format. The dietitian then completed three further sections: disease and its relation to nutritional requirements, metabolic demand, and a physical examination assessing fat stores, muscle status, and fluid status. The patient was rated globally as "well nourished" (PG-SGA A), "moderately malnourished" or "suspected of being

malnourished" (PG-SGA B), or "severely malnourished" (PG-SGA C). A numerical PG-SGA score was also calculated (range = 0 - 35) where a higher score is reflective of greater nutritional compromise, and scores greater than 9 are considered indicative of a critical need for nutritional intervention or symptom management[39, 43].

Global Measures of the Functional Impact of Head and Neck Cancer

Following the swallowing and nutrition assessments, participants were also asked to complete a dysphagia-specific and a general functional impact questionnaire at the three time points. Participants were provided with the questionnaires to complete independently. If participants had difficulty with self-administration, the scale was completed in a structured interview format.

Functional impact specifically related to dysphagia was assessed with the M.D. Anderson Dysphagia Inventory (MDADI)[44]. The MDADI is a validated and reliable questionnaire designed specifically to assess the functional impact of dysphagia in patients with head and neck cancer[44]. The MDADI consists of 20 items grouped under global, emotional, functional, and physical subscales. Patients rate each statement as "strongly disagree", "disagree", "no opinion", "agree", or "strongly agree". These ratings are converted to numerical scores for analysis where strongly agree = 1 and strongly disagree = 5. The MDADI is scored by summing the rating from statements under each subscale, calculating the mean and multiplying that by 20 to give a total score between 0 (extremely low functioning) and 100 (extremely high functioning). A global score is also obtained separately by asking the participant to rate the statement: "my swallowing ability limits my day to day activities" using the five-point scale described above. A number between 0 and 100 was calculated as above by multiplying the rating by 20.

General functional impact was measured using the Functional Assessment of Cancer Therapy Additional Concerns for Head and Neck version 4 (FACT-H&N)[45]. Comparison with the Performance Status Scale revealed that the FACT-H&N had moderately high internal validity and can differentiate patients according to overall performance status and treatment status using mean scores[46]. The FACT-H&N is a multidimensional self-reported tool with four core domains (27 individual items) examining physical, social/family, emotional and functional well being. Twelve additional items assess patient perceptions of treatment related side effects specifically for head and neck cancer [45, 47]. Patients were instructed to read the introductory statement prior to completing the scale. Once the patient had understood the directions for the questionnaire, they were instructed to complete all items by indicating how true each statement had been for them over the past 7 days using a five-point Likert scale, where 0 equated to 'not at all' and 4 was 'very much'. The FACT-H&N provides a score for each of the domains by summing the results of each item. A global score is calculated by adding each of the domain-specific results together with the additional concerns for head and neck cancer summed separately and added to the global score. Higher scores reflect superior quality of life[45].

Data Analysis

Descriptive measures including means and standard deviations were recorded for all outcome measures. Non-parametric Friedman tests, with post-hoc Wilcoxon signed rank tests, were used to compare changes in the ordinal data collected for swallowing, PG-SGA numerical score, and functional impact across the three time points. Change between time points for the global measure of the PG-SGA (rated as A, B, or C) was measured using chi-square tests. One-way repeated measures ANOVA was used to record change over time points with ratio

data (weight) with repeated measures t-tests used for post-hoc comparisons. For all statistical comparisons, $p<0.05$ was taken to indicate statistical significance.

RESULTS

Swallow Function

Analysis of diet level at each of the assessment stages revealed 78.6% of participants were tolerating a full diet and thin fluids pretreatment, and the remaining individuals had already made modifications to their diets, with 14.3% requiring a soft diet, and 6.7% a minced diet. Participants reported making these modifications due to pain related to their tumour, following biopsies, or difficulty chewing following pretreatment dental extractions. During and in the weeks following treatment, three patients received nasogastric tube (NGT) insertion. One patient received NGT insertion at week 3 of treatment (for 3 weeks), one at week 5 (for 3 weeks) and one was inserted one week post-completion of treatment (for 4 weeks). By 4-6 weeks post-treatment, only 28.6% of participants were managing a full diet. For the remainder, 14.2% were tolerating thin fluids only (one patient receiving supplemental nasogastric feeding), 41.3% managing pureed consistencies, 14.3% minced, and 28.6% on a soft diet. Only one patient required mildly thick fluids, the remainder tolerated thin fluids. At the 6 month post-treatment time point, all patients were safely managing thin fluids; however only 43% had returned to a full diet, with the remainder (57%) only capable of managing a soft diet. Consistent with this pattern, statistical analysis for the RBHOMS scores revealed a significant change ($X^2 = 19.45$, $p < 0.001$) across the pretreatment ($M = 8.43$, $SD = 0.94$), 4-6 weeks post-treatment ($M = 6.64$, $SD = 0.84$) and 6 months post-treatment ($M = 7.79$, $SD = 0.43$) time points. Post hoc analysis revealed a significant reduction in the level of swallow function at 4-6 weeks post treatment ($z = -3.22$, $p < 0.001$) compared to pretreatment. Between 4-6 weeks and 6 months post-treatment a significant improvement in functional level

(z = -3.03, p = 0.002) was observed; however levels at 6 months post treatment were still significantly lower than pre-treatment levels (z = -2.07, p = 0.04).

Videofluoroscopy (NZIMES and PAS)

As a cohort, statistical analysis revealed no significant change over time on any of the parameters evaluated by the NZIMES assessment (Table 2). This lack of statistical result was largely contributed to by high variability within the group and the fact that physiological deficits were identified both before and after treatment. To assist exploration of the main patterns of impairment in this population at each time point, the NZIMES scores were compressed into a binary scale where the parameters were reduced into “no impairment” (score of 0) versus “impairment” (score of > 0) (Table 3). Only those features that were observed in more than one third of the group (>33%) were considered noteworthy. This analysis revealed that at least one third of participants had some impairment in the Oral, Oral Pharyngeal Transit, Pharyngeal, and Cricoesophageal parameters at the pretreatment time point. Specific physiological impairment was observed in mastication, position of the bolus at the onset of the swallow, relative timing of the onset of the swallow, pharyngeal contraction/bolus propulsion, and laryngeal excursion (Table 3). By 4-6 weeks post-treatment, these physiological impairments were observed to persist and additional impairments in palatal closure, bolus propulsion through the UES, and clearance of pyriform sinus residual were observed. At 6 months post-treatment, there was no change in the areas of impairment.

[insert table 2 & 3 near here]

Analysis of penetration/aspiration ratings at each time point (Friedman test) revealed no significant change (X^2 = 2.08, p = 0.35 for fluids, and X^2 = 2.46, p = 0.29 for solids) across the pretreatment (M = 1.69, SD = 0.63), 4-6 week post-treatment (M = 2.31, SD = 1.55), and 6

months post-treatment (*M* = 2.08, *SD* = 1.85) time points. To assist in interpretation of group patterns over time, PAS ratings were classified into three broad categories of "no penetration or aspiration", representing ratings 1 and 2; "penetration" representing ratings 3, 4, and 5; and "aspiration" representing ratings 6, 7, and 8. This analysis revealed that the majority of patients had no penetration or aspiration on fluids (92%) or solids (69%) at the pretreatment time point. At 4-6 weeks, there was a 20% increase in penetration and aspiration events on fluids. At 6 months, penetration and aspiration events improved for fluids (although not to pretreatment levels) but continued to worsen for solids (Table 4). There was greater penetration/aspiration of fluids at 4-6 weeks and for solids at 6 months post-treatment compared with any other time point.

[insert table 4 near here]

Nutrition

Statistical analyses revealed significant change in weight and PG-SGA numerical scores over time (Table 5). Post-hoc repeated t-tests revealed significant weight loss at 4-6 weeks post-treatment (t = 6.22, $p < 0.01$), with mean weight loss greater than 10% total body mass compared with pretreatment scores. This significant weight loss from pretreatment continued at 6 months post-treatment (pre versus 6mths: $t = 4.93$, $p < 0.01$), with a mean total weight loss of 14.2%. There was no significant change in weight between 4-6 weeks and 6 months ($t = 1.23$, $p = 0.24$) post-treatment. BMI results followed the same pattern, deteriorating from a pretreatment mean of 26.9 kg/m2 (SD = 4.25) to 23.7 kg/m2 (SD = 3.28) at 4-6 weeks and 23.0kg/m2 (SD = 3.54) at 6 months post-treatment. Similarly, the numerical score of the PG-SGA revealed a significant increase ($Z = -3.19$, $p < 0.01$) in nutritional compromise at 4-6 weeks post-treatment compared to pretreatment. In contrast to weight and BMI, between 4-6 weeks and 6 months there was a significant improvement ($Z = -2.52$, $p = 0.01$) in the PG-SGA

score, with the PG-SGA score at 6 months not significantly different from pretreatment levels (Z = -0.77, p = 0.44) (Table 5). The global rating of the PG-SGA (A, B, or C) revealed significant deterioration from pretreatment to 4-6 week post-treatment scores (X^2 = 11.63, p = 0.001, Fisher's exact = 0.002), then significant improvement from 4-6 weeks to 6 months post-treatment (X^2 = 9.14, p = 0.002, Fisher's exact = 0.007). By 6 months the PG-SGA global rating revealed no significant difference between pretreatment and 6 months post-treatment scores (X^2 = 0.24, p = 0.622, Fisher's exact = 1.0).

[insert table 5 near here]

Participant-rated Functional Impact Questionnaires

Analysis of the MDADI results revealed a significant difference across the three time points for the global and functional domains of swallowing (Table 6). Post hoc analysis revealed a significant deterioration in the 4-6 week post-treatment scores in both global and functional domains compared to those of pretreatment. Following treatment there was significant improvement from 4-6 weeks to 6 months post-treatment in the global domain. The functional domain revealed a similar pattern, although this was not statistically significant (Table 6). For both domains there was no statistically significant difference between pretreatment and 6 months post-treatment scores. Regarding the emotional and physical domains, no significant difference was found between time points; however, a similar trend of deterioration at 4-6 weeks with improvement (not to pretreatment levels) at 6 months was observed.

[insert table 6 near here]

Statistically significant change across time was also observed in the overall scores as well as the physical, functional, and head and neck specific domains of the FACT-H&N (Table 6). Only the social/family and emotional components did not differ significantly across time

points. Post-hoc analyses revealed significant decline in the overall, physical, functional, head and neck specific scores at 4-6 weeks post-treatment compared with pretreatment scores. Two parameters (physical and head and neck specific) remained significantly lower than pre-treatment scores at the 6 months post-treatment. There was significant improvement for the overall score and the physical and functional domains between 4-6 weeks and 6 months post-treatment (Table 6). The head and neck specific domain did not change between the 4-6 week and the 6 month assessment, remaining significantly below baseline assessment.

DISCUSSION

Short-term and chronic side effects of organ preservation treatments for head and neck cancer with radiotherapy, with or without systemic therapy, have been documented to include dysphagia, nutritional compromise, and functional change. While radiotherapy treatment intensification has resulted in improved locoregional control, there have been reports of increased severity and duration of treatment-related toxicity[4-9] which may impact on functional outcomes such as swallowing and nutrition. This study investigated the impact of one altered fractionation radiotherapy protocol (curative intent AFRT-CB) and found significant changes from pretreatment to 6 months post-treatment for swallowing, nutrition, and patient-perceived function. The current study revealed a trend for functionally preserved swallowing (some mild-moderate physiological impairment) prior to treatment that deteriorated at 4-6 weeks post-treatment, with the majority of patients requiring dietary modifications with concurrent significant negative change in weight. Six months post-treatment swallowing function was variable, with stabilisation in some areas and further deterioration in others, with weight stabilisation and improvement in overall nutritional status. There was also a significant detrimental impact on patient-perceived function related to

general everyday participation and swallowing function that did not improve to pretreatment levels at 6 months post-treatment.

Pretreatment

In the current study, the results of the clinical and instrumental swallowing assessments revealed patterns of performance that were consistent with those previously reported for the head and neck population in the literature. The majority of patients exhibited a clinically functional swallow and were managing a normal diet prior to commencing treatment, with only a small proportion of the group requiring softer food consistencies due to pain or difficulty chewing. This is consistent with previous reports in heterogenous head and neck cancer populations where 75% of patients tolerated normal diets[21, 22, 48, 49]. Pretreatment physiological impairment observed on instrumental assessment was predominantly mild to moderate in severity in the study population. Oral phase deficits (mastication and timing/onset of the swallow) may be largely attributable to dental extractions and biopsies, reducing chewing efficiency and affecting oropharyngeal sensation leading to delayed onset of the pharyngeal swallow, as found by Pauloski, et al.[21]. The observed pharyngeal residue, pharyngeal transit times, and shorter UES opening durations in some individuals have also been observed previously in the literature[21]. Aspiration rates in our study population, noted predominantly on solid bolus trials, were also comparable to the rate of pretreatment aspiration (30%) found in oropharyngeal cancer patients by Stenson, et al.[22].

Four to Six Weeks Post-Treatment

Treatment side effects have been reported as symptoms that lead to an inability to adequately maintain oral intake, necessitating nonoral supplementation or feeding[50]. Consistent with the findings of Yu et al.[8], 21% received alternative feeding with NGT at this time point. The

current study shows that the majority of the patients treated with AFRT-CB experience swallowing complications at 4-6 weeks post treatment, with the significant deterioration in functional outcome a reflection of limitations in oral intake and reliance on texture-modified diets. AFRT-CB studies have documented the most severe reactions as occurring 5-7 weeks after commencing radiotherapy[51], with the endpoint of acute reactions in altered fractionation regimens documented to be around the 4-6 week post-treatment point [1, 52-55].

Physiologically, at 4-6 weeks post-treatment, functional swallow impairment was reflected in physiological deterioration across all parameters of the NZIMES: Oral (mastication and palatal closure), Pharyngeal (pharyngeal contraction/bolus propulsion and laryngeal excursion), and Crico-esophageal (bolus propulsion through the UES and clearance of pyriform sinus residue). The degree of penetration and aspiration events on fluids was also found to be greater than that at pretreatment. Therefore, oral phase impairment at this stage post treatment may have resulted from residual acute toxicity, namely, xerostomia and mucositis and subsequent oral ulceration, inflammation and pain impacting on patients' ability to chew and effectively achieve tongue to palate closure[56, 57]. Ongoing oedema, pain, secretion, and sensation changes may have further affected efficient passage of the bolus and airway protection[12, 58, 59]. Observed deterioration across a large number of physiological parameters appears to reflect the impact of the large treatment field required for curative intent radiotherapy in oropharyngeal carcinoma with similar oropharyngeal structures targeted for most head and neck cancer patients to ensure adequate coverage of macroscopic disease [58-60].

Conversely, although still affecting more than one third of patients at the 4-6 week post-treatment time point, there appeared to be physiological improvement in the Oropharyngeal

Transit parameter (both position of the bolus at the onset of the swallow and relative timing of the onset of the swallow components on the NZIMES). This improvement may reflect patient adjustment to managing oral intake without teeth. Equally though, a more prompt oropharyngeal transit may reflect pain, hypersensitivity and phagophobia[61] which may have influenced the speed and timing of the swallow for some individuals at the 4-6 week post-treatment time point. In the absence of pain ratings documented at the time of the VFS, we are unable the further elucidate the basis of this change in the Oral Pharyngeal Transit parameter.

The significant mean weight loss, reduced BMI, and overall deteriorating nutritional status between pretreatment and 4-6 weeks post-treatment found in this study are similar to those prospective examinations that measure nutritional status in the heterogenous head and neck cancer population[20, 43, 62] and mirror the deterioration in swallowing function. The limitations to swallowing caused by acute toxicity may have led to reduced oral intake which influenced weight and overall nutrition status. In the current cohort, the PG-SGA scores paralleled weight loss, which is similar to that of previous studies[43], however peak difficulties in meeting nutritional requirements usually occurred prior to the 4-6 week post-treatment time point.

Patient-rated swallowing and overall everyday function also deteriorated significantly at 4-6 weeks post-treatment when compared with pretreatment scores. Acute toxicity related to treatment would appear to contribute to worse physical outcomes (i.e. reduced energy, increased pain, greater impact of side effects) and function (i.e. cooking, socialising, enjoying life/work) for the majority of patients. Similarly, symptoms specific to head and neck cancer, like taste and smell changes, dry mouth, sticky saliva, and coughing were significantly worse than pretreatment scores and have been described previously[63]. At this early stage, Örhn et

al.[63] found 56% of patients reported that their oral symptoms had been a hindrance to everyday life, reflecting the global swallowing score found in the current AFRT-CB group.

Six Months Post-Treatment

At 6 months post-treatment, prolonged acute reactions to radiotherapy have usually settled and general improvement is expected[1], as was observed with functional swallowing outcomes and tolerance of diet textures. At this time point the impact of chronic side effects on function is unclear; however, the current study observed both unchanging deficits and further deterioration in swallowing physiology, nutrition and patient-rated functional impact. Ongoing deficits may reflect a decline in early effects, where further deterioration in components may be a reflection of the onset of late effects, found to be significantly greater (for pharynx and salivary gland) in concomitant boost regimens when compared to standard fractionation[1].

Persistent deficits in swallowing physiology occurred in four physiological parameters from 4-6 weeks to 6 months post-treatment, indicating that if there was no improvement in the period immediately following treatment, participants experienced impairment in that parameter for at least 6 months post-treatment, similar to findings in the chemoradiation literature[15, 36, 37]. Impairments of palatal closure, position of the bolus at the onset of the swallow, and laryngeal excursion have been found in the early post-treatment phase in chemoradiation patients with little functional improvement by 12 months post-treatment[30, 58, 60], and findings from the current study may suggest AFRT-CB causes similar long-term functional impairment. It has been proposed that the ongoing impairments in these components may be due to unhealed acute reactions giving rise to consequential late reactions, rather than true chronic impairments[64, 65].

Deterioration in swallowing physiology up to 6 months post-treatment for mastication, pharyngeal contraction/bolus propulsion, bolus propulsion through the UES, and clearance of pyriform fossa residue also parallels patterns of physiological decline observed in the chemoradiation literature[58, 66]. Such changes have been attributed to chronic fibrotic changes affecting function of salivary glands, and range of movement of musculature and cartilage/bone[12, 30, 67-72]. Trismus and xerostomia are common post radiotherapy side effects for patients with head and neck cancer, and can deleteriously affect the ability to chew solid foods, manipulate solid boluses and prepare cohesive boluses ready for swallowing[70, 71]. Chronic fibrotic changes can also impact on the movement of structures in the pharynx, namely epiglottic deflection, pharyngeal contraction and UES opening, resulting in pharyngeal residue and subsequent aspiration [12, 30, 67, 69, 72], as seen in the current study.

At 6 months post-treatment, mean weight remained relatively unchanged from 4-6 weeks, although overall nutrition (as scored by the PG-SGA) significantly improved reflecting the fact that, in general, nutrient intake was sufficient for weight stabilisation. Isenring et al.[43] report that although weight loss is a component of the overall nutritional status determined by the PG-SGA, it accounts for less than 10% of the score, thus accounting for this apparent discrepancy. Similar discrepancies have been reported by a number authors who found an increase in post-treatment intake did not correspond with increased weight[20, 73] and was significantly associated with elevated resting energy expenditure[74]. Despite not returning to pretreatment weight, the absence of further weight loss by 6 months post-treatment is considered a positive outcome[20] and has been previously reported in the head and neck literature[43, 62, 75, 76].

In the current cohort at 6 months, there was significant improvement in both global swallowing and overall everyday function compared to 4-6 weeks post, moving toward pretreatment scores. Specifically, significant improvement was found for physical and functional components of performing everyday activities, as reported by Epstein and colleagues[77] who found almost 60% of a heterogenous head and neck cancer population treated with surgery and/or radiotherapy reported no limitations at work or performing household jobs at 6-12 months post-treatment. As in the current study, negative outcomes at 6 months have been reported for the physical and head and neck specific concerns, largely reflecting the ongoing trouble with swallowing, social eating, dry mouth, sticky saliva, and mouth opening in the irradiated population[78, 79]. In addition, weight loss of 10% or more in 6 months, as found in the current study, has been associated with increased morbidity such as impaired wound healing, reduced immune function, and increased mortality, and has also been shown to impact on quality of life and functional outcomes[80-83].

While this is the first study to systematically examine swallowing, nutrition and patient-rated function longitudinally in patients undergoing AFRT-CB, the limitations of the current study are acknowledged. Firstly the small cohort numbers limit the statistical interpretation and generalisation of our results. The current research attempted to accrue a homogenous oropharyngeal patient population who were recommended for treatment with AFRT-CB. In doing so, the numbers of eligible participants were limited and disease staging variability increased among participants. Second, the follow-up period in this study was only until 6 months post treatment. Several authors have found that as the time post-treatment lengthens patients' quality of life improves. This may be a result of the resolution of tumour related symptoms or treatment side effects or improved patient adjustment to the ongoing deficits caused by head and neck cancer and its treatment, a pattern which emerged in the current

study[44, 84-86]. Such preliminary evidence may suggest that further improvements in functioning may be observed.

CONCLUSION

Patients with T1-T3 oropharyngeal cancer who are treated with curative intent using AFRT-CB boost experienced significant functional swallowing and nutrition changes related to treatment. Patients with this type of cancer who undergo AFRT-CB also report significant negative functional impact that lasts up to 6 months post-treatment. Management of these patients requires multidisciplinary intervention from pretreatment to assess swallowing, nutrition and treatment related side effects. Education should be provided to these patients regarding the possible course of their treatment and recovery, so they are better prepared for the impact these deficits may have on their day to day functioning. Early discussion regarding the impact of acute side effects on swallowing and nutritional may help to limit the weight loss that many patients experience by increasing acceptance of symptom control and nutrition support measures.

Future research needs to examine the functional outcomes of the relatively novel altered fractionation regimens for a longer time frame to determine the long-term functional outcomes of this population. In addition, this group should be compared with the more conclusively examined chemoradiation protocols to determine how swallowing and nutrition outcomes compare across treatment types. Future studies need to elucidate the duration and grading of acute toxicity until its resolution and its association with swallowing and nutrition impairment following non-surgical treatment for head and neck cancer.

References

1. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, Garden, AS, Ridge, JA, Cooper, JS, Ang, KK: A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys 48*:7-16, 2000.
2. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, Gardani, G, Van Den Bogaert, W, Danczak, S, Bolla, M, Van Glabbeke, M, De Pauw, M: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol 25*:231-241, 1992.
3. Saunders MI, Dische S, Barrett A, Parmar MKB, Harvey A, Gibson D: Randomised multicentre trials of CHART vs conventional radiotherapy in head and neck and non-small-cell lung cancer: an interim report. *Br J Cancer 73*:1455-1462, 1996.
4. Ang KK, Peters LJ, Weber RS, Maor, MH, Morrison, WH, Wendt, CD, Brown, BW: Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. *Int J Radiat Oncol Biol Phys 19*:1339-1345, 1990.
5. Johnson CR, Schmidt-Ullrich RK, Wazer DE: Concomitant boost technique using accelerated superfractionated radiation therapy for advanced squamous cell carcinoma of the head and neck. *Cancer 69*:2749-2754, 1992.
6. Knee R, Fields RS, Peters LJ: Concomitant boost radiotherapy for advanced squamous cell carcinoma of the head and neck. *Radiother Oncol 4*:1-7, 1985.
7. Mak AC, Morrison WH, Garden AS, Ang KK, Goepfert H, Peters LJ: Base-of-tongue carcinoma: treatment results using concomitant boost radiotherapy. *Int J Radiat Oncol Biol Phys 33*:289-296, 1995.
8. Yu K, Chua M, Vlantis A, Kam MKM, Lee WY, Tsang RKY, Yuen HY, Hui EP, Chan ATC:

Swallowing function after altered fractionation radiotherapy for head and neck carcinoma. *J HK Coll Radio 8*:207-213, 2005.

9. Zouhair A, Azria D, Pasche P, Stupp R, Chevalier J, Betz M, Mirimanoff RO, Ozsahin M: Accelerated postoperative radiotherapy with weekly concomitant boost in patients with locally advanced head and neck cancer. *Radiother Oncol 70*:183-188, 2004.

10. Grobbelaar EJ, Owen S, Torrance AD, Wilson JA: Nutritional challenges in head and neck cancer. *Clin Otolaryngol 29*:307-313, 2004.

11. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, Magnuson JS, Spencer SA, Bonner JA: Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys 73*: 410-415, 2009.

12. Kotz T, Abraham S, Beitler JJ, Wadler S, Smith RV: Pharyngeal transport dysfunction consequent to an organ-sparing protocol. *Arch Otolaryngol Head Neck Surg 125*:410-413, 1999.

13. Kumar S, Pandey M, Lal P, Rastogi N, Maria Das KJ, Dimri K: Concomitant boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: a phase II trial. *Radiother Oncol 75*:186-192, 2005.

14. Smith R, Goldman S, Beitler J, Wadler S: Decreased short-and long-term swallowing problems with altered radiotherapy dosing used in an organ-sparing protocol for advanced pharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg 130*:831-836, 2004.

15. Smith R, Kotz T, Beitler J, Wadler S. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. *Arch Otolaryngol Head Neck Surg 126*:384-389, 2000.

16. Vokes E, Kies M, Haraf D, Stenson K, List M, Humerickhouse R, Dolan ME, Pelzer H, Sulzen L, Witt ME: Concomitant chemoradiotherapy as primary therapy for locoregionally

advanced head and neck cancer. *J Clin Oncol 18*:1652-1661, 2000.

17. Medina JA, Rueda A, de Pasos AS, Contreras J, Cobo M, Moreno P, Benavides M, Villanueva A, Alba E: A phase II study of concomitant boost radiation plus concurrent weekly cisplatin for locally advanced unresectable head and neck carcinomas. *Radiother Oncol 79*:34-38, 2006.
18. Bentzen SM, Trotti A: Evaluation of early and late toxicities in chemoradiation trials. *J Clin Oncol 25*:4096-4103, 2007.
19. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A, Ang KK: Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol 26*:3582-3589, 2008.
20. van den Berg M, Rasmussen-Conrad E, Gwasara G, Krabbe P, Naber A, Merkx M: A prospective study on weight loss and energy intake in patients with head and neck cancer, during diagnosis, treatment and revalidation. *Clin Nutr 25*:765-772, 2006.
21. Pauloski BR, Rademaker AW, Logemann JA, Stein D, Beery Q, Newman L, Hanchett C, Tusant S, MacCracken E: Pretreatment swallowing function in patients with head and neck cancer. *Head Neck 22*:474-482, 2000.
22. Stenson KM, MacCracken E, List M, Haraf DJ, Brockstein B, Weichselbaum R, Vokes EE: Swallowing function in patients with head and neck cancer prior to treatment. *Arch Otolaryngol Head Neck Surg 126*:371-377, 2000.
23. Frowen JJ, Perry AR: Swallowing outcomes after radiotherapy for head and neck cancer: A systematic review. *Head Neck 28*:932-944, 2006.
24. Kendall KA, Leonard RJ, McKenzie SW, Jones CU: Timing of swallowing events after single-modality treatment of head and neck carcinomas with radiotherapy. *Ann Otol Rhinol Laryngol 109*: 767-775, 2000.
25. Lazarus C, Logemann JA, Pauloski BR, Rademaker AW, Helenowski IB, Vonesh EF,

MacCracken E, Mittal BB, Vokes EE, Haraf DJ: Effects of radiotherapy with or without chemotherapy on tongue strength and swallowing in patients with oral cancer. *Head Neck 29*:632-637, 2007.

26. Argiris A. Update of chemoradiotherapy for head and neck cancer. *Curr Opin Oncol 14*:323-329, 2002.
27. Logemann JA: Evaluation of swallowing disorders. In: Logemann JA (ed.): *Evaluation and treatment of swallowing disorders*, 2nd ed. Austin: Pro-Ed; 1998, pp 89-100.
28. Dietitians Association of Australia and Speech Pathology Association of Australia Limited: Texture-modified foods and thickened fluids as used for individuals with dysphagia: Australian standardised labels and definitions. *Nutr Diet 64*:S53-S63, 2007.
29. Ward EC, Conroy A-L: Validity, reliability, and responsivity of the Royal Brisbane Hospital Outcome Measure for Swallowing. *Asia Pac J Sp Lang Hear 4*:109-129, 1999.
30. Lazarus CL: Effects of radiation therapy and voluntary maneuvers on swallow functioning in head and neck cancer patients. *Clin Commun Disord 3*:11-20, 1993.
31. Huckabee M-L: New Zealand Index for Multidisciplinary Evaluation of Swallowing http://www.cmds,canterbury.ac.nz/documetns/nzimesa4.pdf. Accessed February 20, 2009.
32. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL: A penetration-aspiration scale. *Dysphagia 11*:93-98, 1996.
33. van der Molen L, van Rossum M, Ackerstaff A, Smeele LE, Rasch C, Hilgers FJM: Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. *BMC Ear Nose Throat Disord 9*, 2009.
34. Hughes P, Scott P, Kew J, Cheung DMC, Leung SF, Ahuja AT, van Hasselt CA: Dysphagia in treated nasopharyngeal cancer. *Head Neck 22*:393-397, 2000.
35. Kendall K, Leonard R: Bolus transit and airway protection coordination in older dysphagic patients. *Laryngoscope 111*:2017-2021, 2001.

36. Ku P, Yuen E, Cheung D, Chan BY, Ahuja A, Leung SF, Tong MC, van Hasselt A: Early swallowing problems in a cohort of patients with nasopharyngeal carcinoma: symptomatology and videofluoroscopic findings. *Laryngoscope 117*:142-146, 2007.

37. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Gaziano J, Stachowiak L, Newman L, MacCracken E, Santa D, Mittal B: Swallowing disorders in the first year after radiation and chemoradiation. *Head Neck 30:*148-158, 2008.

38. Nguyen N, Moltz C, Frank C, Vos P, Smith HJ, Karlsson U, Nguyen LM, Rose S, Dutta S, Sallah S: Evolution of chronic dysphagia following treatment for head and neck cancer. *Oral Oncol 42*: 374-380, 2006.

39. Ottery F: Patient-Generated Subjective Global Assessment. In: McCallum P, Polisena C (eds.): The Clinical Guide to Oncology Nutrition. Chicago: The American Dietetic Association, 2000:pp 11-23.

40. Bannerman E, Miller MD, Daniels LA, Cobiac L, Giles LC, Whitehead C, Andrews GR, Crotty M: Anthropometric indices predict physical function and mobility in older Australians: the Australian Longitudinal Study of Ageing. *Public Health Nutr 5*:655-662, 2002.

41. National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in adults. Commonwealth of Australia, 2003 http://www.health.gov.au/internet/main/Publishing.nsf/Content/7AF116AFD4E2EE3DCA256F190003B91D/$File/adults.pdf). Accessed 15 September 2010.

42. Bauer J, Capra S, Ferguson M: Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr 56*:779-785, 2002.

43. Isenring E, Bauer J, Capra S. The scored patient-generated subjective global assessment (PG-SGA) and its association with quality of life in ambulatory patients receiving radiotherapy. *Eur J Clin Nutr 57*:305-309, 2003.

44. Chen AY, Frankowshi R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, Goepfert H: The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson Dysphagia Inventory. *Arch Otolaryngol Head Neck Surg 127*:870-876, 2001.

45. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman, M, Yellen SB, Winicour P, Brannon J, Eckberg K, Lloyd S, Purl S, Blendowski C, Goodman M, Barnicle M, Stewart I, McHale M, Bonomi P: The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol 11*:570-579, 1993.

46. List MA, D'Antonio LL, Cella DF, Siston A, Mumby P, Haraf D, Vokes E: The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale: a study of utility and validity. *Cancer 77*:2294-2301, 1996.

47. D'Antonio LL, Zimmerman GJ, Cella DF, Long SA: Quality of life and functional status measures in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg 122*:482-487, 1996.

48. Colangelo LA, Logemann JA, Rademaker AW: Tumor size and pretreatment speech and swallowing in patients with resectable tumors. *Otolaryngol Head Neck Surg 122*:653-661, 2000.

49. Pauloski BR, Rademaker AW, Logemann JA, Lazarus CL, Newman L, Hamner A, MacCracken E, Gaziano J, Stachowiak L: Swallow function and perception of dysphagia in patients with head and neck cancer. *Head Neck 24*:555-565, 2002.

50. Cheng SS, Terrell JE, Bradford CR, Ronis DL, Fowler KE, Prince ME, Teknos TN, Wolf GT, Duffy SA: Variables associated with feeding tube placement in head and neck cancer. *Arch Otolaryngol Head Neck Surg 132*:655-661, 2006.

51. Kaanders JHAM, Van Daal WAJ, Hoogenraad WJ, Van der Kogel AJ: Accelerated fractionation radiotherapy for laryngeal cancer, acute, and late toxicity. *Int J Radiat Oncol Biol Phys 24*:497-503, 1992.

52. Ang KK, Peters LJ: Concomitant boost radiotherapy in the treatment of head and neck cancers. *Semin Radiat Oncol 2*:31-33, 1992.

53. Delaney GP, Fisher RJ, Smee RI, Hook C, Barton MB: Split-course accelerated therapy in head and neck cancer: an analysis of toxicity. *Int J Radiat Oncol Biol Phys 32*:763-768, 1995.

54. Fu KK, Clery M, Ang KK, Byhardt RW, Maor MH, Beitler JJ: Randomized phase I/II trial of two variants of accelerated fractionated radiotherapy regimens for advanced head and neck cancer: results of RTOG 88-09. *Int J Radiat Oncol Biol Phys 32*:589-597, 1995.

55. Olmi P, Cellai E, Chiavacci A, Faliai C: Accelerated fractionation in advanced head and neck cancer: results and analysis of late sequelae. *Radiother Oncol 17*:199-207, 1990.

56. Pauloski BR, Rademaker AW, Logemann JA, Colangelo LA: Speech and swallowing in irradiated and nonirradiated postsurgical oral cancer patients. *Otolaryngol Head Neck Surg 118*:616-624, 1998.

57. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, Komaroff E, Nalysnyk L, Zilberberg MD: Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol 66*:253-262, 2003.

58. Dworkin JP, Hill SL, Stachler RJ, Meleca RJ, Kewson D: Swallowing function outcomes following nonsurgical therapy for advanced-stage laryngeal carcinoma. *Dysphagia 21*:66-74, 2006.

59. Logemann JA, Rademaker AW, Pauloski BR, Lazarus CL, Mittal BB, Brockstein B, MacCracken E, Haraf DJ, Vokes EE, Newman LA, Liu D: Site of disease and treatment protocol as correlates of swallowing function in patients with head and neck cancer treated

with chemoradiation. *Head Neck 28*:64-73, 2006.

60. Chang YC, Chen SY, Lui LT, Wang TG, Wang TC, Hsiao TY, Li YW, Lien IN: Dysphagia in patients with nasopharyngeal cancer after radiation therapy: a videofluoroscopic swallowing study. *Dysphagia 18*:135-143, 2003.

61. Shapiro J: Evaluation and treatment of swallowing disorders. *Compr Ther 26*:203-209, 2000.

62. Beaver ME, Matheny KE, Roberts DB, Myers JN. Predictors of weight loss during radiotherapy. *Otolaryngol Head Neck Surg 125*:645-648, 2001.

63. Öhrn KE, Sjoden PO, Wahlin YB, Elf M: Oral health and quality of life among patients with head and neck cancer or haematological malignancies. *Support Care Cancer 9*:528-538, 2001.

64. Denham JW, Peters LJ, Johansen J, Poulsen M, Lamb DS, Hindley A, O'Brien PC, Spry NA, Penniment M, Krawitz H, Williamson S, Bear J, Tripcony L: Do acute mucosal reactions lead to consequential late reactions in patients with head and neck cancer? *Radiother Oncol 52*: 157-164, 1999.

65. Dörr W, Hendry JH: Consequential late effects in normal tissues. *Radiother Oncol 61*:223-231, 2001.

66. Bleier B, Levine M, Mick R, Rubesin SE, Sack SZ, McKinney K, Mirza N: Dysphagia after chemoradiation: analysis by modified barium swallow. *Ann Otol Rhinol Laryngol 116*:837-841, 2007.

67. Eisbruch A, Lyden T, Bradford CR, Dawson LA, Haxer MJ, Miller AE, Teknos, TN, Chepeha DB, Hogikyan ND, Terrell JE, Wolf GT: Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys 53*:23-28, 2002.

68. Eisele DW, Koch DG, Tarazi AE, Jones B: Aspiration from delayed radiation fibrosis of the neck. *Dysphagia 6*:120-122, 1991.

69. Ekberg O, Nylander G: Pharyngeal dysfunction after treatment for pharyngeal cancer with surgery and radiotherapy. *Gastrointest Radiol 8*:97-104, 1983.

70. Logemann JA, Smith CH, Pauloski BR, Rademaker AW, Lazarus CL, Colangelo LA, Mittal B, MacCracken E, Gaziano J, Stachowiak L, Newman LA: Effects of xerostomia on perception and performance of swallow function. *Head Neck 23*:317-321, 2001.

71. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Mittal B, Gaziano J, Stachowiak L, MacCracken E, Newman LA: Xerostomia: 12-Month changes in saliva production and its relationship to perception and performance of swallow function, oral intake, and diet after chemoradiation. *Head Neck 25*:432-437, 2003.

72. Wu C, Hsiao T, Ko J, Hsu M: Dysphagia after radiotherapy: Endoscopic examination of swallowing in patients with nasopharyngeal carcinoma. *Ann Otol Rhinol Laryngol 109*:320-325, 2000.

73. Ng K, Leung SF, Johnson PJ, Woo J: Nutritional consequences of radiotherapy in nasopharynx cancer patients. *Nutr Cancer 49*:156-161, 2004.

74. Bosaeus I, Daneryd P, Svanberg E, Lundholm K: Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. *Int J Cancer 93*:380-383, 2001.

75. Lee H, Havrila C, Bravo V, Shantz K, Diaz K, Larner J, Read P: Effect of oral nutritional supplementation on weight loss and percutaneous endoscopic gastrostomy tube rates in patients treated with radiotherapy for oropharyngeal carcinoma. *Support Care Cancer 16*:285-289, 2008.

76. Lees J: Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional oncology centre. *Eur J Cancer Care 8*:133-136, 1999.

77. Epstein JB, Emerton S, Kolbinson DA, Le ND, Phillips N, Stevenson-Moore P, Osoba D: Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck*

21:1-11, 1992.

78. Campbell BH, Spinelli K, Marbella AM, Myers KB, Kuhn JC, Layde PM: Aspiration, weight loss, and quality of life in head and neck cancer survivors. *Arch Otolaryngol Head Neck Surg 130*:1100-1103, 2004.

79. Tschudi D, Stoeckli S, Schmid S: Quality of life after different treatment modalities for carcinoma of the oropharynx. *Laryngoscope 113*:1949-1954, 2003.

80. Barbosa-Silva MC, Barros AJ: Bioelectric impedance and individual characteristics as prognostic factors for post-operative complications. *Clin Nutr 24*:830-838, 2005.

81. Seltzer MH, Slocum BA, Cataldi-Betcher EL, Fileti C, Gerson N: Instant nutritional assessment: absolute weight loss and surgical mortality. *JPEN 6*:218-221, 1982.

82. Van Bokhorst-De Van der Schueren M, Langendoen S, Vondeling H, Kuik D, Quak J, Van Leeuwen P: Perioperative enteral nutrition and quality of life of severely malnourished head and neck cancer patients: a randomized clinical trial. *Clin Nutr 19*:437-444, 2000.

83. van Bokhorst-de van der Schueren M, van Leeuwen P, Sauerwein H. Assessment of malnutrition parameters in head and neck cancer and their relation to postoperative complications. *Head Neck 19*:419-425, 1997.

84. de Graeff A, de Leeuw JRJ, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM: Long-term quality of life of patients with head and neck cancer. *Laryngoscope 110*:98-106, 2000.

85. Terrell J, Ronis D, Fowler K, Bradford CR, Chepeha DB, Prince ME, Teknos TN, Wolf GT, Duffy SA: Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg 130*:401-408, 2004.

86. Weymuller Jr E, Alsarraf R, Yueh B, Deleyiannis F, Coltrera M: Analysis of the performance characteristics of the University of Washington Quality of Life instrument and its modification (UW-QOL-R). *Arch Otolaryngol Head Neck Surg 127*:489-493, 2001.

Tables

Table 1. Demographic details

Participant Number	Age	Sex[a]	TNM[b] classification and location[c]	Stage	Smoking (current, ex, never)	Alcohol (current, ex, never)
01	82	M	T1N0 L pharyngeal wall	I	Ex	Current
02	63	M	T2N0 supraglottis	II	Current	Current
03	79	M	T3N0 BOT	III	Ex	Current
04	72	M	T2N0 L tonsil	II	Never	Current
05	69	F	T2N2b L tonsil	IV	Ex	N/A
06	73	M	T2N0 L tonsil	II	Ex	Ex
07	70	M	T1N0 L tonsil	I	Ex	Current
08	69	M	T2N1 R tonsil	III	Ex	Current
09	69	M	T3N0 R supraglottis	III	Current	Current
10	59	M	T2N0 R supraglottis	II	Ex	Current
11	59	M	T1N2a R tonsil	IV	Never	Current
12	58	F	T3N0 R tonsil	III	Current	Current
13	53	M	T2N1 R tonsil	III	Never	Current
14	54	M	T1N2a R tonsil	IV	Never	Current

[a] M = male, F = female

[b] T = T stage, N = N stage

[c] L = left, R = right

Table 2. New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES) results

NZIMES Parameter		Pre-treatment m (SD)	4-6 wks post-treatment m (SD)	6 mths post-treatment m (SD)	X^2 df = 2	Friedman *p*
Oral	Labial Closure	0	0	0	0	0
	Lingual Control	0.15 (0.38)	0.15 (0.38)	0.08 (0.28)	1.0	0.61
	Palatal Closure	0.38 (0.65)	0.46 (0.52)	0.54 (0.66)	0.2	0.91
	Mastication	0.85 (0.69)	1.15 (0.99)	1.46 (0.66)	2.47	0.29
Oral Pharyngeal Transit	Position of bolus at onset of swallow	0.69 (0.48)	0.54 (0.78)	0.62 (0.87)	0.62	0.73
	Relative timing of onset of swallow	0.46 (0.52)	0.31 (0.48)	0.38 (0.51)	0.75	0.69
Pharyngeal	Velopharyngeal Closure	0	0.23 (0.44)	0	6.0	0.05
	Pharyngeal Contraction/Bolus Propulsion	0.77 (0.83)	0.77 (0.6)	1.0 (0.58)	1.64	0.44
	Laryngeal Excursion	0.54 (0.66)	0.54 (0.66)	0.46 (0.52)	0.29	0.87
Crico-esophageal	Bolus Propulsion through UES	0.31 (0.63)	0.31 (0.48)	0.54 (0.66)	0.89	0.64
	Clearance of Pyriform Sinus Residual	0.38 (0.65)	0.38 (0.51)	0.54 (0.66)	0.22	0.9
	Upper Esophageal Parameters	0	0	0	0	0

Table 3. Compressed videofluoroscopy data: “no impairment” versus “impairment”

NZIMES Parameter		Pre-treatment % impairment	4-6 wks post-treatment % impairment	6 mths post-treatment % impairment
Oral	Labial Closure	0	0	0
	Lingual Control	15	14	7
	Palatal Closure	**31**	**50**[a]	**50**
	Mastication	**69**	**71**	**100**
Oral Pharyngeal	Position of bolus at onset of swallow	**69**	**43**	**43**
	Relative timing of onset of swallow	**46**	**36**	**43**
Pharyngeal	Velopharyngeal Closure	0	21	0
	Pharyngeal Contraction/Bolus Propulsion	**54**	**71**	**86**
	Laryngeal Excursion	**46**	**50**	**50**
Crico-esophageal	Bolus Propulsion through UES	23	**36**	**50**
	Clearance of Pyriform Sinus Residual	**31**	**43**	**50**
	Upper Esophageal Parameters	0	0	0

[a] Bold indicates 1/3 of group present with symptom

Table 4. Frequency count of penetration-aspiration events across time points

			Pre-treatment % (n)	4-6 weeks post-treatment % (n)	6 months post-treatment % (n)
Penetration-Aspiration Scale	Nil	Fluids	92 (12)	71 (10)	86 (12)
		Solids	69 (9)	69 (9)	57(8)
	Penetration	Fluids	8 (1)	21 (3)	7 (1)
		Solids	23 (3)	23 (3)	29 (4)
	Aspiration	Fluids	0	7 (1)	7 (1)
		Solids	8 (1)	8 (1)	14 (2)

Table 5. Patient-Generated Subjective Global Assessment (PG-SGA) score and weight from pre-treatment to 6 months post-treatment

	Pre-treatment m (SD)	4-6 wks post-treatment m (SD)	6 mths post-treatment m (SD)	Statistic	*p*
Weight (kg)	83.2 (22.72)	73.1 (17.88)	71.4 (17.61)	0.75	λ *<0.01*
PG-SGA (numerical)	3.7 (3.25)	10.3 (5.31)	4.8 (3.79)	0.66	*p <0.01*

Table 6. Participant-rated functional impact scores as defined by the MDADI[a] and FACT-H&N[b] from pre-treatment to 6 months post-treatment

	Quality of Life Measure	Pre-treatment m (SD)	4-6 wks post-treatment m (SD)	6 mths post-treatment m (SD)	Friedman	Post-hoc Wilcoxon					
						Pre versus 4-6 weeks		Pre versus 6mths		4-6 weeks versus 6mths	
					p	Z	*p*	Z	*p*	Z	*p*
MDADI	Global	76.9 (22.87)	50.8 (22.53)	67.7 (22.42)	*0.03*	-2.33	*0.02*	-1.03	0.30	-2.16	*0.03*
	Emotional	82.3 (13.69)	73.1 (18.58)	76.4 (18.28)	0.08						
	Functional	83.7 (13.71)	68.0 (20.0)	77.2 (14.46)	*0.03*	-2.59	*0.01*	-1.43	0.15	-1.74	0.08
	Physical	76.0 (20.14)	58.1 (21.46)	68.8 (12.48)	0.06						
FACT-H&N	Physical	23.8 (4.67)	18.7 (6.92)	21.23 (6.21)	*<0.01*	-2.67	*<0.01*	-2.21	*0.03*	-1.97	*0.049*
	Social/ Family	22.44 (5.99)	20.1 (6.77)	20.6 (7.59)	0.94						
	Emotional	19.0 (4.0)	18.7 (4.21)	20.6 (2.39)	0.22						
	Functional	20.0 (6.98)	13.8 (6.28)	17.9 (6.63)	*0.02*	-2.59	*0.01*	-1.31	0.19	-2.28	*0.02*
	Head/Neck Specific	37.1 (6.15)	27.2 (7.22)	29.8 (6.79)	*<0.01*	-2.97	*<0.01*	-2.75	*<0.01*	-1.23	0.22
	Overall	122.5 (21.29)	96.2 (17.86)	111.0 (20.73)	*0.03*	-2.82	*<0.01*	-1.92	0.06	-2.42	*0.02*

[a] MDADI = M. D. Anderson Dysphagia Inventory
[b] FACT-H&N = Functional Assessment of Cancer Therapy – Additional Concerns for Head and Neck Cancer