Long-term functional outcomes and the patient perspective following altered fractionation with concomitant boost for oropharyngeal cancer

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ABSTRACT

Background: With no long-term data available in published research to date, this study presents details of the swallowing outcomes as well as barriers to, and facilitators of oral intake and weight maintenance at 2 years post altered fractionation radiotherapy with concomitant boost (AFRT-CB).

Methods: Twelve patients with T1-T3 oropharyngeal cancer who received AFRT-CB were assessed at baseline, 6 months, and 2 years post-treatment for levels of dysphagia and salivary toxicity, food and fluid tolerance, functional swallowing outcomes, patient-reported function, and weight. At 2 years, participants were also interviewed to explore barriers and facilitators of oral intake.

Results: Outcomes were significantly worse at 2 years when compared to baseline for late toxicity, functional swallowing, and patient-rated physical aspects of swallowing. Most patients (83%) tolerated a full diet pretreatment, falling to 42% (remainder tolerated soft diets) at 2 years. Multiple barriers to oral intake were identified which impacted on activity and participation levels. Participants lost 11kg from baseline to 2 years, which was not regained between 6 months and 2 years. Global, social, and emotional domains of patient-reported function returned to pretreatment levels.

Discussion: At 2 years post AFRT-CB, worsening salivary and dysphagia toxicity, declining functional swallowing, and multiple reported ongoing barriers to oral intake, had a negative impact on participants' activity and participation levels relating to eating. These ongoing deficits contributed to significant deterioration in physical swallowing functioning determined by the MDADI. In contrast, patients perceived their broader functioning had improved at 2 years, suggesting long-term adjustment to ongoing swallowing deficits.

Key words: deglutition; deglutition disorders; long-term outcomes; altered fractionation radiotherapy; oropharynx; squamous cell carcinoma

INTRODUCTION

Treatment intensification with altered fractionation radiotherapy (AFRT) for head and neck cancer (HNC) has demonstrated improved locoregional control and overall survival compared with conventionally fractionated radiotherapy (1). Despite this benefit, AFRT treatment has been associated with increased acute toxicity of greater severity and longer duration (2, 3). Both the presence of dysphagia and mucositis have been identified in the literature as persisting in the early phase post-treatment with AFRT (4-8). Acute toxicity, such as mucositis and pain, has been associated with deteriorating functional outcomes known to impact on swallowing and mastication (9), resulting in a large proportion of patients requiring modified diets and nutritional supplementation (10, 11).

There is, however, currently minimal information available about the extent to which dysphagia and associated toxicities persist long-term in the AFRT population. Based on radiobiological principles, late-radiation effects are dependent on the total dose and the dose per fraction, with larger fraction sizes increasing the risk of severe late effects (4, 12). Hence, as a consequence of the reduced dose per fraction used in accelerated radiotherapy regimens, late toxicity rates for necrosis, xerostomia, laryngeal edema, skin, and subcutaneous toxicity have been found to be significantly less for accelerated regimens compared with conventional counterparts post-treatment (7, 8). It is possible then that dysphagia and associated toxicities may also be less severe in the long term. However to what extent late effects exist and continue to impact on swallowing, nutrition, and patient-rated function at 2 years following AFRT, is currently unknown.

Generally, research examining radiotherapy treatment protocols has indicated that patient-reported function post-treatment is on an upward trajectory with the lowest point immediately post-treatment and improving to pretreatment levels within one year (13-18). Whether or not this same pattern is evident following AFRT requires further investigation, as few studies to date have employed longitudinal study designs which extend to 2 years or more post-treatment. The preliminary data that is currently available would suggest that significant improvements in dysphagia and functional swallowing status can be anticipated in the long term (10, 11). Eighteen percent of a heterogenous HNC population who received AFRT required alternative feeding due to dysphagia 1-2 months post-treatment (11). However, by 12 months post-treatment this had improved with only 7% having ongoing significant dysphagia

(11). In a more recent study of the impact of AFRT with a concomitant boost (AFRT-CB) in a homogeneous group of patients with oropharyngeal cancers, the current research team found significant deterioration in functional swallowing, nutrition, and patient-rated functional impact from pretreatment to 6 weeks post-treatment, with some recovery (but still below pretreatment levels) by 6 months post-treatment (10). This pattern of improvement toward 6 months post-treatment also concurs with previous research examining quality of life (QoL) following a hyperfractionated and accelerated radiotherapy protocol (dose/fraction size <1.5-1.6Gy), which found improved outcomes at 6 and 12 months post-treatment compared to baseline (18). Such data would tend to suggest ongoing improvements in swallowing function, swallowing-related toxicity, and patient perspectives of function may be evident in the longer term.

Following conventional, hypofractionated, and combined modality radiotherapy treatments for HNC, studies have shown that long-term treatment related side effects impact on swallowing and nutrition affect QoL and cause distress up to a decade post-treatment (19-22). Consequently, as part of understanding the full impact of AFRT on the individual, it is important that the extent of any persistent late effects following AFRT treatment and the potential impact of these on patient function is better understood. To this end, the aims of the current study were to: 1) examine the functional swallowing, nutritional status, and general and swallowing-related patient-rated function at 2 years post-treatment with AFRT-CB for locally advanced oropharyngeal cancer; and 2) to further explore the patient perspective of their ongoing side effects and barriers to oral intake at 2 years post-AFRT.

MATERIALS AND METHODS

Participants

Participants were drawn from the Multidisciplinary Head and Neck Clinic at the Princess Alexandra Hospital, Brisbane, Australia, following diagnosis of a T1-T3 locally advanced squamous cell carcinoma (SCC) of the oropharynx (base of tongue, tonsil, pharyngeal wall, or supraglottis [within 1cm of the oropharynx]). Eligible participants were those who commenced treatment with curative intent AFRT-CB during a 33 month period ending in August 2009. The AFRT-CB regimen involved elective sites being treated to 50Gy in 2Gy/day over 5 weeks. Known sites of disease received a concomitant boost schedule to a total of 66Gy over 5 weeks with an afternoon boost dose (minimum of 6 hours apart) of 1.6Gy/day in weeks 4 and 5. Ineligible patients were those recommended for surgical or

multimodality treatment, or had a previous diagnosis of oropharyngeal SCC or any other medical condition which may have affected long-term swallowing function (i.e. neurological or neurodegenerative disease). Any patient who developed in-field recurrence or subsequent neurological or neurodegenerative disease following treatment completion until 2 years post-treatment was also excluded. All patients received their treatment at the Metro South Radiation Oncology Service in Brisbane, Australia. This research was approved by the Human Research and Ethics Committees at the Princess Alexandra Hospital, Australia and The University of Queensland, and all participants consented to involvement in the study.

The cohort was drawn from that previously reported by Cartmill and colleagues (10). Seventeen patients were recommended for treatment with AFRT-CB, and all were eligible for recruitment. Of those, 15 participants consented to involvement but only 12 were eligible to complete all aspects required for this study. One participant died during treatment of causes unrelated to cancer, and 2 participants died between 6 months and 2 years post-treatment; one due to local recurrence and post-operative complications and another unrelated to the cancer diagnosis. Analysis was conducted on the 12 participants who were eligible for follow-up at 2 years post-treatment. The mean age at presentation was 66 years (range = 53-82 years, *SD* = 20.3) and 83% of participants were male (Table 1). The majority presented with tonsillar primaries, node negative neck disease, and 50% had T2 disease. One third of participants presented with stage III disease, and one quarter each with stage II and stage IV disease. The majority (67%) were current or ex-smokers, and 92% were current drinkers (n = 11).

Procedure

The current study employed a mixed methodology design to explore both patterns of change across time and detailed information of current swallowing status at 2 years post-AFRT. This methodology involved collection of toxicity ratings, current dietary tolerance, weight, and patient-rated swallowing and general function at baseline, 6 months and again at 2 years post-treatment. To further examine the patient perspective of their swallowing and nutrition function at 2 years post-treatment, participants were contacted via phone to complete a semi-structured interview.

At baseline, 6 months and 2 years post-treatment, specific toxicity information regarding dysphagia and xerostomia was collected using the relevant adverse event (AE) subscales of the Common Toxicity Criteria of Adverse Events version 3 (CTCAE v.3). These scales form

part of the total CTCAE tool, a comprehensive, multimodality toxicity grading schedule that scores both acute and late AEs in oncology (23). In this tool, dysphagia is rated on a 5-point scale (grade 1- mild, grade 2 - moderate, grade 3 - severe, grade 4 - life threatening or disabling, and grade 5 - death related to AE) and xerostomia on only a 3-point scale (grade 1- mild, grade 2 - moderate, grade 3 – severe) as this AE is not considered to have a life-threatening impact or cause death. Toxicity ratings were completed by participants' treating radiation oncologist.

At each time point dietary tolerance was determined based on clinical assessment and patient report of food and fluids consumed regularly as part of their dietary routine. Patient descriptions of their regular food and fluid consistencies were subsequently re-coded consistent with the terminology of the Australian national standards (24) for foods (full, soft, minced, pureed, or liquid only) and fluids (thin, mildly thick, moderately thick, and extremely thick). This information, and other clinical indicators reported by the patient were used to score functional swallowing outcome with the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS) (25). The RBHOMS measures everyday performance of swallowing function using a 10-part outcome measure scale (25). This scale is clinically valid and responsive to changes in swallowing function over time with high levels of sensitivity, specificity, and high interrater reliability (25). The scale is divided into four stages of swallowing function: 1) nil by mouth; 2) commencing oral intake; 3) establishing oral intake; and 4) maintaining oral intake. Each stage is further divided into levels that are described with specific clinical features allowing clinicians to differentiate between 10 specific ratings of swallow function.

At baseline, and 6 months-post-treatment, weight was collected to the nearest 0.1kg using digital scales (G-Tech International GL-6000). Weight was recorded at the same location, using the same scales throughout this study, with the exception being at two years post-treatment, where weight (in kg) was obtained through verbal patient report.

Patients completed the Functional Assessment of Cancer Therapy Additional Concerns for Head and Neck Cancer (FACT-H&N) (26) and the M. D. Anderson Dysphagia Inventory (MDADI) (27) at baseline, 6 months, and 2 years post-treatment. These questionnaires were chosen for their validity and reliability with the HNC population (26, 27). General patient-perceived function was measured using the FACT-H&N. Four core domains of patient-rated

function are assessed (physical, social/family, emotional and functional well-being) using 27 individual items. Twelve additional items assess patient perceptions of treatment-related side effects specifically for HNC (26, 28). Patient-rated swallowing function was scored using the MDADI. The MDADI contains 20 items that are divided into global, emotional, functional, and physical subscales, and scored between 0 (extremely low functioning) to 100 (extremely high functioning).

At the 2 year post-treatment time point only, an additional exploration of swallowing function was undertaken using a semi-structured patient interview. Interviews were conducted via the phone and the interviewer completed real time notations of patient responses. A series of questions were used to stimulate discussion around three themes: 1) the presence/absence of any ongoing side effects related to treatment; 2) current swallowing, eating and drinking function and any strategies used to improve oral intake; and 3) current nutritional status (need for nutritional supplements) and any strategies used to improve nutrition. The interviews took approximately 30 minutes to complete. During the interview, opportunities were taken to clarify and expand on the content of responses with the patient to ensure the nature of their reported side effects, and current swallowing and nutrition status were accurately recorded.

Data analysis

All quantitative data were entered into a Microsoft Excel spreadsheet. Stata version 10 for Mac was used for all statistical analysis. Descriptive measures including means and standard deviations were recorded for all outcome measures. Two analyses were conducted to compare changes in the ordinal data collected for toxicity, swallowing, and patient-rated functional impact: 1) change in function from pretreatment to 2 years post-treatment; and 2) change in function from 6 months to 2 years post-treatment. Non-parametric Wilcoxon signed rank tests were used for both analyses. Change for diet and fluid consistencies tolerated over time was measured using chi-square tests. Paired t-tests were used to record change over time points for ratio data (e.g. weight). For all statistical comparisons, $p < 0.05$ was taken to indicate statistical significance.

Information obtained from the semi-structured interviews was collated by the interviewing clinician (BC) and the patient descriptions of side effects and barriers to oral intake were reported as frequency data. This data was then subjected to secondary analysis, with each reported side effect or barrier classified using the core set descriptors from the World Health

Organisation International Classification of Functioning, Disability and Health (ICF) core set for HNC (29, 30). The ICF core set for HNC was developed in consensus with 33 international experts and includes 112 different ICF categories deemed relevant to the specific disease condition of HNC (30). Thirty-four categories outline body functions, 33 body structures, 26 activities and participation, and 19 contextual environmental factors. Analysis of patient responses using this framework was used to gain a more holistic understanding of the nature of functional swallowing and nutritional outcomes experienced at 2 years post AFRT-CB. Patient responses were coded across all relevant categories, for example, a reported presence of "dry mouth" was classified under a body impairment of "salivation", which resulted in an activity limitation in "eating". It is important to note that exploration of contextual factors was not a focus of the current study, and were therefore not included in the analysis.

RESULTS

Analysis over time revealed a significant worsening in xerostomia (salivary toxicity) and swallowing (dysphagia toxicity) as per the CTCAE between pretreatment and 2 years post-treatment, and 6 months and 2 years post-treatment (Table 2). Statistical comparisons revealed that functional swallowing level (as scored by the RBHOMS) at 2 years post-treatment was significantly reduced in comparison to pretreatment and 6 months post-treatment (Table 2). Change in functional swallowing ability was not related to fluid intake as all participants reported tolerating thin fluids at all time points. However food intake, as described by diet tolerance across time points, ranged from a minced diet to a full/normal diet, with the proportion of participants tolerating a full diet changing over time. The majority of patients (83%) tolerated a full diet pretreatment, which had reduced to 50% at 6 months post-treatment, and to 42% at 2 years post-treatment. At 6 months post-treatment the remaining 50% of participants were managing a soft diet, while at 2 years post-treatment 58% reported restricting their diet to softer consistencies (i.e. avoiding hard, chewy and dry solids). This showed a trend toward significant decline over time ($\chi^2 = 8.43$, $p = 0.08$). Significant weight loss was observed from pretreatment to 2 years post-treatment, with a mean 11kg loss during this time. Weight did not change significantly from 6 months to 2 years post-treatment (Table 2).

Analysis of patient-rated functional impact revealed that between pretreatment and 2 years post-treatment, participants noted there had been a significant negative impact on their life within the physical domain of the MDADI (Table 2). Between 6 months and 2 years post-treatment there was significant improvement for the head and neck specific domain of the FACT-H&N, however there were no other significant findings between pretreatment and 2 years post-treatment, and 6 months and 2 years post-treatment on either the MDADI or FACT-H&N (Table 2).

Outcomes of the semi-structured interviews revealed participants reported 15 barriers to oral intake with varying rates of frequency (Figure 1). These barriers were able to be classified into 9 categories of body function impairment using the comprehensive ICF core set for HNC. The most common patient-reported impairments in bodily functions were classified under salivation, energy and drive, taste function, and pharyngeal swallow (Table 3). These impairments in body function were also determined to have impact at the activity limitation and participation restriction levels. All patient-reported barriers resulted in activity limitations and participation restrictions in eating (100%). A smaller proportion of patient-reported barriers identified limitation and restrictions in looking after one's health (2/15) and carrying out daily routine (1/15) (Table 3).

Participants were also probed regarding strategies that facilitated the efficiency of their swallowing or their eating and drinking experience (Figure 2), and to prevent further weight loss at 2 years post-treatment (Figure 3). More than two thirds reported modifying their diet, adding fluid to food to assist with swallowing, and avoiding specific foods as strategies to manage their swallowing difficulties. Twenty-five percent reported not requiring any strategies for swallowing. Regarding strategies to avoid weight loss, over a third reported not requiring any strategies to maintain their weight (Figure 3). The remainder reported use of a variety of strategies including exercise to improve their appetite, a high protein high energy diet, or oral supplements as recommended by their dietitian during treatment (Figure 3).

DISCUSSION

The current study found a significant deterioration in salivary and swallowing toxicity at 2 years post-treatment when compared to pretreatment and 6 months post-treatment levels. As would be expected, this ongoing toxicity impacted on functional swallowing with the majority of the current cohort limiting their diet to soft foods. The current data supports that further

declines in swallowing function at 2 years following the AFRT-CB protocol can be anticipated, and thus long-term monitoring of swallowing function in this population is warranted.

While there may be an absence of data specifically relating to the AFRT-CB protocol outcomes at 2 years post-treatment, results from other definitive non-surgical treatment regimens have reported an ongoing functional impact on swallowing and nutrition long-term post-treatment (31-35). Studies have found that between 5 and 50% of participants are able to tolerate a full diet without restrictions at 1-2 years post-treatment with previously examined radiotherapy protocols for HNC (17, 36-38). The prevalence rate for impaired function observed in the current study is therefore at the high end (42%) of the expected long-term swallowing outcomes from other protocols. Although not specifically assessing dietary tolerance but perhaps an indicator of functional outcomes, concomitant boost protocols have been associated with a greater incidence of long-term dysphagia, as measured by incidence of aspiration pneumonia, feeding tube dependence, or stricture (39).

The long-term deficits in swallowing function observed following definitive non-surgical treatment for HNC have been attributed to late treatment effects including tissue atrophy, oedema, and fibrosis (32-34). Hence the reason for deterioration in toxicity and subsequent impact on functional swallowing and weight in the current cohort may be the result of similar late or chronic effects of the AFRT-CB protocol. However research has also demonstrated that late reactions following radiotherapy treatment are not only caused by the radiobiological dose to tissues, but can also be linked to the extent and duration of acute cellular mucosal depletion, as is found in accelerated and hyperfractionated regimens (4). Where such late mucosal reactions may occur in part as a consequence of a severe acute reaction (40), this has been referred to as “consequential” late toxicity. The underlying premise of AFRT is that through the use of smaller fraction sizes it is possible to reduce the impact of tumour cell repopulation, thus improving cell kill, but without increasing late toxicity. However it is well recognised that this form of treatment results in heightened acute toxicity (4) and hence, the potential for consequential late effects. Although it is impossible to make any definitive statements regarding the cause of the declining function observed in the current study, it is possible that the factors contributing to the observed decline in swallowing and salivary toxicity in the current cohort may be a combination of both “true” and/or “consequential” late effects of treatment (4, 5).

The nature of the long-term swallowing deficits reported in this study appears to be comparable to previous populations studied. Although the current study did not objectively assess function using videofluoroscopy, 75% of patients reported "food sticking in their throat", and 50% reported "coughing with food and/or fluid". These patient descriptions most likely relate to the presence of pharyngeal residue and penetration/aspiration which have been identified as key physiological deficits present in the long-term following treatment in heterogenous HNC populations studied (33, 34). The current data, however, does differ from most other radiotherapy research in relation to the pattern of declining function in the long-term, with the prevalence of swallowing difficulty in the current cohort observed to increase from 6 months to 2 years. This pattern of declining function over time also differs to the general pattern of improving swallowing outcomes reported by Yu et al. (2005) following AFRT. The differences found in results of the current study could be attributed to the retrospective nature of data collection, and the use of a crude rating scale to measure dysphagia in the Yu et al. (2005) study. However, equally it is acknowledged that there is currently minimal data specific to the AFRT-CB population available for comparison and further research is needed to confirm the current pattern of long-term declining function as observed in the current cohort.

Using the ICF framework, the functional swallowing and ongoing barriers to oral intake reported by participants at 2 years post-treatment were observed to primarily contribute to activity limitation and participation restriction relating to eating. Previous studies have linked impairments in body functions to activity limitations in eating, although without formally using the ICF framework. Ku et al. (2007) reported 90% of their heterogenous HNC cohort who received CRT reported a dry mouth (impairment in body function) at 12 months post-treatment, and this coincided with 100% alternating food and fluid boluses (eating limitation), and more than 80% avoiding specific foods in their diet (eating limitation) (41). Oral pain, mouth sores, taste changes, oral dryness, and loss of appetite have previously been reported as side effects which heighten awareness of functional swallowing difficulties (42, 43). Long-term xerostomia has been postulated as impacting on functional swallowing by decreasing bolus lubrication, and increasing bolus transit time (34), and has been reported by over 90% of the current cohort.

Fatigue and appetite were two patient-reported barriers to oral intake that were classified as impairments body functions for energy and drive (appetite and energy level subcategories). These impairments resulted in activity limitations and participation restrictions regarding looking after one's health and carrying out a daily routine, as well as eating. Previous literature has reported these impairments under social functioning, and work and day to day tasks (44). One of the restrictions to using the ICF framework is in the classification of enjoyment or pleasure regarding eating and drinking activity and participation, which could be classified under emotional functioning, or as a contextual factor. Despite participants being able to participate in eating and drinking activities, there is no current classification that outlines whether participation is enjoyable or not. For many HNC patients, not only is the act of eating made difficult as a result of treatment side effects, but the act of enjoyment or gaining pleasure from eating is also impaired, possibly resulting in poor nutrition, weight loss, and social isolation.

The current cohort described using a number of strategies to facilitate eating, which included dietary (modifying diet, avoiding specific foods), mealtime (alternating food/fluid boluses), and physiological (multiple swallows to clear residue, using salivary substitutes to alleviate the impact of a dry mouth during meals) facilitators. Each individual reported the use of multiple strategies to assist intake, and those which were most effective for each individual varied between patients. "Active planning' and the use of "trial and error" relating to strategies regarding food selection, consistency, preparation, caloric density, and the physical act of eating have similarly been described in heterogenous HNC populations (43-45). The information obtained from further, comprehensive study of patient strategies may help in the future to further optimise patient adjustment to the swallowing changes which continue in the long term post treatment.

Despite worsening functional swallowing, and perhaps as a result of these mealtime strategies, participants' weight remained stable between 6 months and 2 years post-treatment. Interestingly, fewer participants reported strategies to maintain their weight versus strategies to improve their swallowing, and this may have had an impact on participants' ability to regain lost weight between 6 months and 2 years post-treatment. In contrast, the lack of strategies to maintain weight may reflect the patient perspective that weight was no longer a concern to the study cohort. In the absence of data regarding each patient's personal goal

weight it is not possible to determine how many chose to remain at the lower post-treatment weight and how many were unable to intentionally regain the weight they had lost.

Reflecting the decline in swallowing function and its impact on activity and participation levels observed at 2 years, the patients self ratings for the physical component of the MDADI were found to reveal a significant deterioration between pretreatment and 2 years post-treatment. The results of this specific patient-rated physical domain of swallowing at 2 years post AFRT-CB is in contrast with the previously reported data for heterogenous HNC patients which have reported improving global function on the EORTC-QLQ-C30 scale by 12 months post-treatment (13-17). Furthermore, overall patient-rated functional outcomes (using the FACT-H&N) have also been found improve to pretreatment levels by 12 months post-treatment following a hyperfractionated , accelerated regimen (18). Examination of the physical components of the MDADI for the current cohort revealed a significant long-term concern regarding the ongoing limitations to the foods they could eat, and increased effort and time to complete meals.

Despite patients reporting some specific concerns, the remaining data from the broader functioning domains of the MDADI and FACT-H&N assessments revealed that patients perceptions of their levels of general function had returned to pretreatment levels by 2 years post-treatment. This pattern of long term adjustment has been found previously (13-18). In the current cohort, head and neck specific concerns such as cosmesis, voice and communication, and the presence of pain significantly improved from 6 months to 2 years post-treatment. The results from the current study reveal that for patients undergoing AFRT-CB, broadly speaking patient-rated function continues the upward trajectory of improvement post-treatment. In the absence of improvement in toxicity and functional swallowing, this finding may be an indication of patient adjustment to the ongoing deficits caused by HNC and its treatment (27, 46-48).

While the current study is the first to provide information on long term outcomes following a AFRT-CB protocol, the limitations of this study are acknowledged with small numbers having restricted the ability to make generalisations about long-term function from this population. While the aim of this study was to examine the functional outcomes and explore the patient perspective of their treatment and subsequent barriers to intake, the lack of videofluoroscopic assessment at this 2 year time point does not allow comment on long-term

swallowing physiology. Although not the focus of this study, the assimilation toward pretreatment patient-rated function (as scored by validated questionnaires) despite ongoing reports of body function impairment may also be related to the contextual personal and environmental factors, as well as premorbid body functions of optimism and other temperament and personality functions, outlined by the ICF. Factors such as support and relationships, personal attitudes, and access to ongoing services from health professionals may facilitate some individuals to consider their function in a more positive way. Although not within the scope of the current study, the functional impact these long-term barriers to oral intake have on spouses and family members is also unknown. Often close family are involved in food selection and preparation, and may report negative changes in cooking, mealtime routines, reduced social eating with their family, and greater stress related to caring for their family member who is a long-term HNC survivor. This notion of "third-party disability" (49) is an area which needs further investigation, as well as the impact of contextual factors on recovery and perception of impairment.

The current study has revealed the lasting impact of AFRT-CB on salivary and swallowing function at 2 years post-treatment, with the majority requiring ongoing dietary restriction, reporting a significant negative impact on the physical aspects of swallowing, which has contributed to activity limitation and participation restriction in eating. In general weight that was lost from baseline to 6 months, as a result of treatment side effects, had not been regained 2 years after treatment was completed. Several facilitatory strategies to manage their impairments were reported by participants. Overall, at 2 years post-treatment, participants rated that their global functioning had returned to pretreatment levels, possibly an indication of adjustment. The long-term swallowing and nutritional dysfunction highlights the need for ongoing speech pathology, dietetic, social work, and psychology involvement in assisting patients to return to their pretreatment oral intake, regain weight lost as a result of treatment, and in adapting and adjusting to potentially lifelong negative sequelae as a result of HNC treatment.

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TABLES

Table 1. *Demographic details of AFRT-CB cohort at presentation*

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[d]
06	70	M	T1N0 L tonsil	I	Ex	Current
07	69	M	T2N1 R tonsil	III	Ex	Current
08	59	M	T2N0 R supraglottis	II	Ex	Current
09	59	M	T1N2a R tonsil	IV	Never	Current
10	58	F	T3N0 R tonsil	III	Current	Current
11	53	M	T2N1 R tonsil	III	Never	Current
12	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. [d] Information regarding alcohol history not reported

Table 2. *Toxicity, functional swallowing, participant-rated functional impact, and weight at 2 years post-treatment with AFRT-CB compared with pretreatment and 6 months post-treatment*

Outcome Measure	Component	Pretreatment	6 mths post-treatment	2 years post-treatment	Post-hoc Wilcoxon signed rank/Paired t-test			
					Pre versus 2 years		6mths versus 2 years	
		M (SD)	M (SD)	M (SD)	Z/t	*P*	Z/t	*p*
CTCAE[a]	Xerostomia	0 (0)	1.08 (0.7)	1.67 (0.5)	*-3.18*	*<0.01*	*-2.33*	*0.02*
	Dysphagia	0 (0)	0.92 (0.7)	1.6 (0.7)	*-3.13*	*<0.01*	*-2.82*	*0.01*
RBHOMS[b]		8.67 (0.78)	7.83 (0.4)	7.33 (0.8)	*-3.1*	*<0.01*	*-3.0*	*<0.01*
MDADI[c]	Global	83.6 (17.5)	70 (21.7)	75 (33.2)	0.86	0.39	-1.0	0.32
	Emotional	87.9 (9.3)	77.8 (18.4)	78.5 (18.4)	1.56	1.12	-0.28	0.78
	Functional	86.2 (13.2)	78.3 (14.5)	81 (17.6)	1.43	0.15	-0.67	0.5
	Physical	81.4 (16.2)	70.2 (12.8)	70.8 (18.2)	*2.08*	*0.04*	-0.23	0.78
FACT-H&N[d]	Physical (0-28)	24.5 (4.6)	22.3 (6.1)	23.9	0.94	0.35	-1.5	0.12
	Social/ Family (0-28)	24.1 (4.9)	21.9 (7.7)	22.2 (6.1)	1.56	0.12	-0.43	0.66
	Emotional (0-24)	20.1 (3)	21.3 (2.6)	20.5 (3.5)	-0.31	0.76	0.48	0.63
	Functional (0-28)	22.1 (4.2)	20.7 (5.8)	22.3 (5.5)	0.05	0.96	*-1.93*	0.05
	Head/Neck Specific (0-48)	38.5 (5.6)	31 (6.7)	35.8 (6.7)	1.56	0.12	*-2.4*	*0.02*
	Overall (0-156)	129.7 (13.4)	120.4 (20.3)	123.8 (18)	1.89	0.06	-1.22	0.22
Weight (kg)		82.5kg (24.3)	70.2kg (20.2)	71.6kg (21.5)	*3.17*	*< 0.01*	-0.23	0.59

Note. Italicized values refer to significant results. [a]Common Toxicity Criteria of Adverse Events version 3.0. [b]Royal Brisbane Hospital Outcome Measure for Swallowing. [c]M. D. Anderson Dysphagia Inventory. [d]Functional Assessment of Cancer Therapy Additional Concerns for Head and Neck.

Table 3. *Frequency of patient reported barriers to oral intake in relation to body impairments, and activity limitations/participation restrictions as classified by the ICF, reported by participants at 2 years post-treatment with AFRT-CB*

Patient reported barrier	%	Impairment in body function	Activity Limitation / Participation Restriction
Dry mouth	92%	Salivation	Eating
Taste problems	75%	Taste function	Eating
Food gets stuck	75%	Pharyngeal swallowing	Eating
Appetite problems	58%	Energy and drive (appetite)	Looking after one's health, Eating
Cough with food/fluid	50%	Pharyngeal swallowing	Eating
Difficulty enjoying meals	50%	Emotional functions or contextual factor	Looking after one's self, Eating
Sticky saliva	42%	Salivation	Eating
Chewing difficulties	33%	Chewing	Eating
Ulcers	25%	Oral swallowing	Eating
Jaw stiffness	25%	Mobility of joint functions	Eating
Thrush	17%	Oral swallowing	Eating
Fatigue	17%	Energy and drive (energy level)	Carrying out daily routine
Painful swallowing	17%	Sensation of pain (pain in head and neck)	Eating
Sense of smell changed	8%	Smell function	Eating
Neck stiffness	8%	Mobility of joint functions	Eating

FIGURES

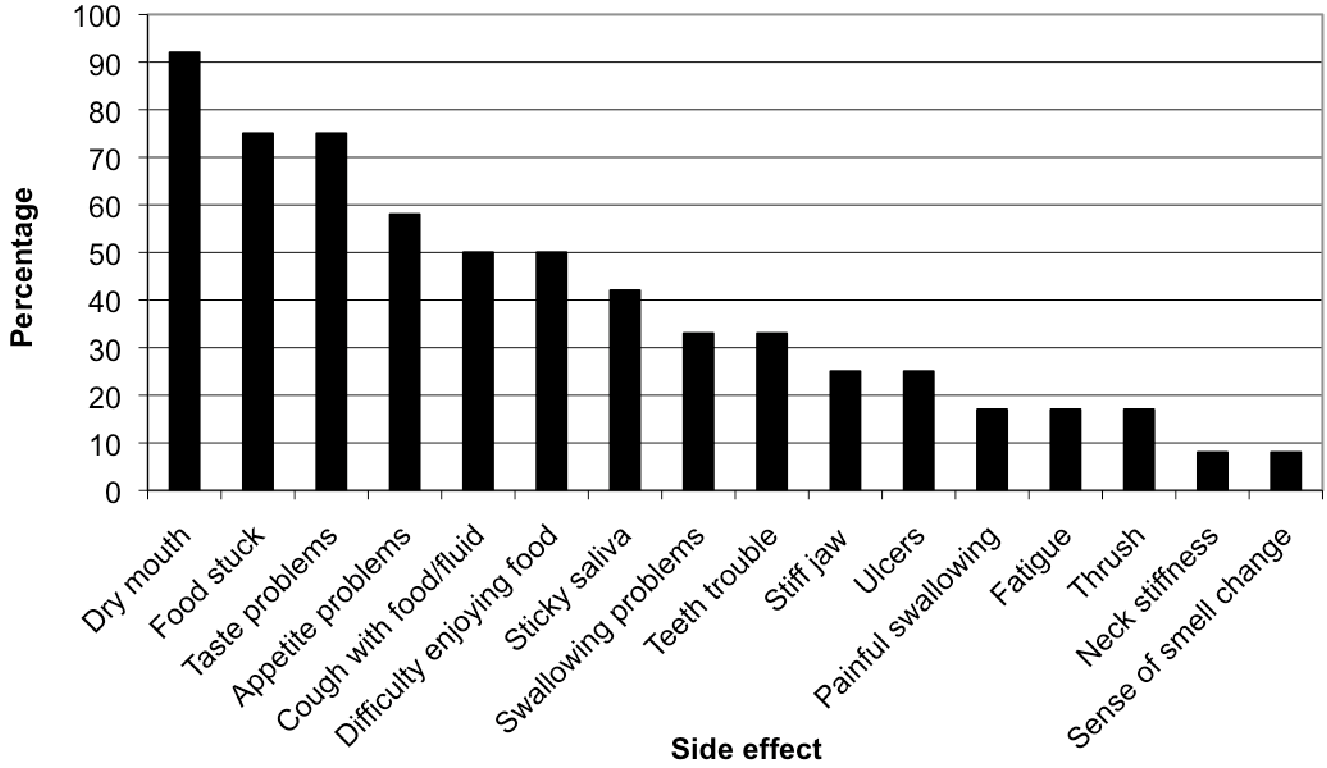

Figure 1. Frequency of patient reported barriers to oral intake at 2 years post AFRT-CB

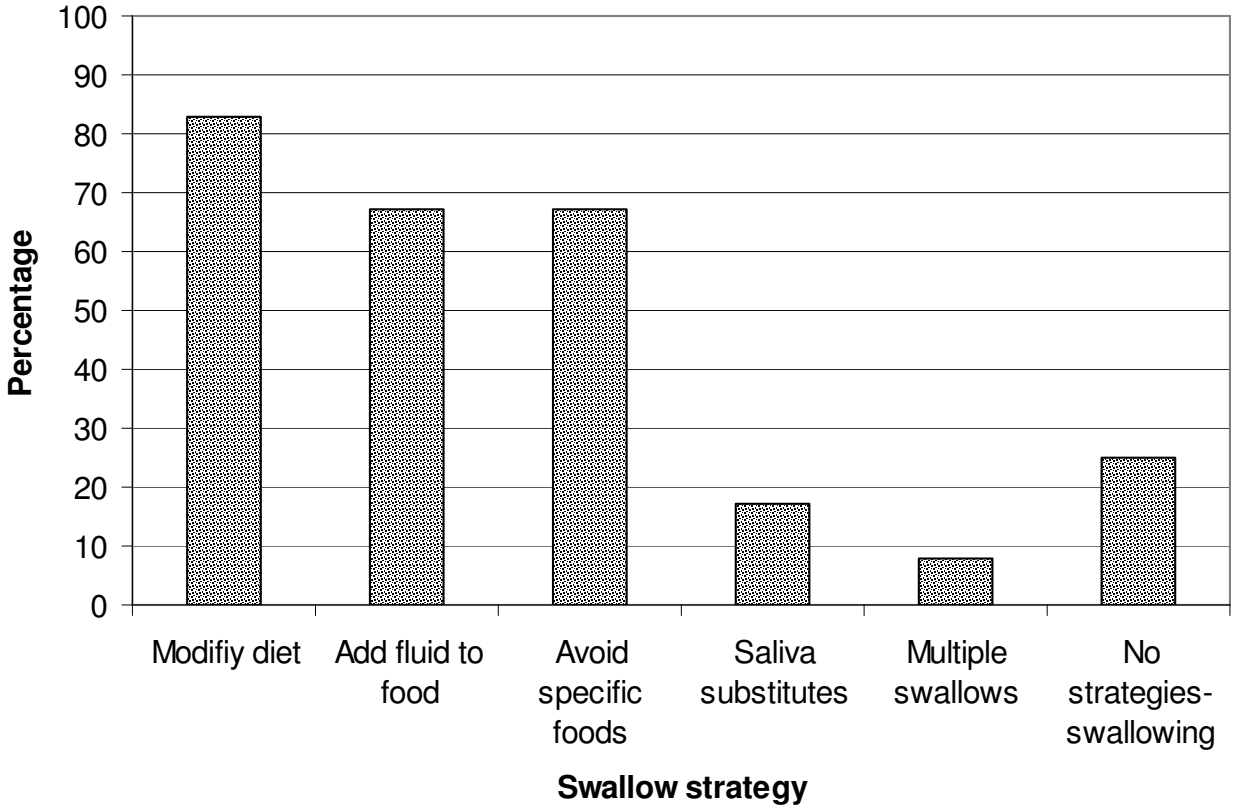

Figure 2. Frequency of patient-reported strategies used to overcome swallow-related side effects at 2 years post-treatment with AFRT-CB

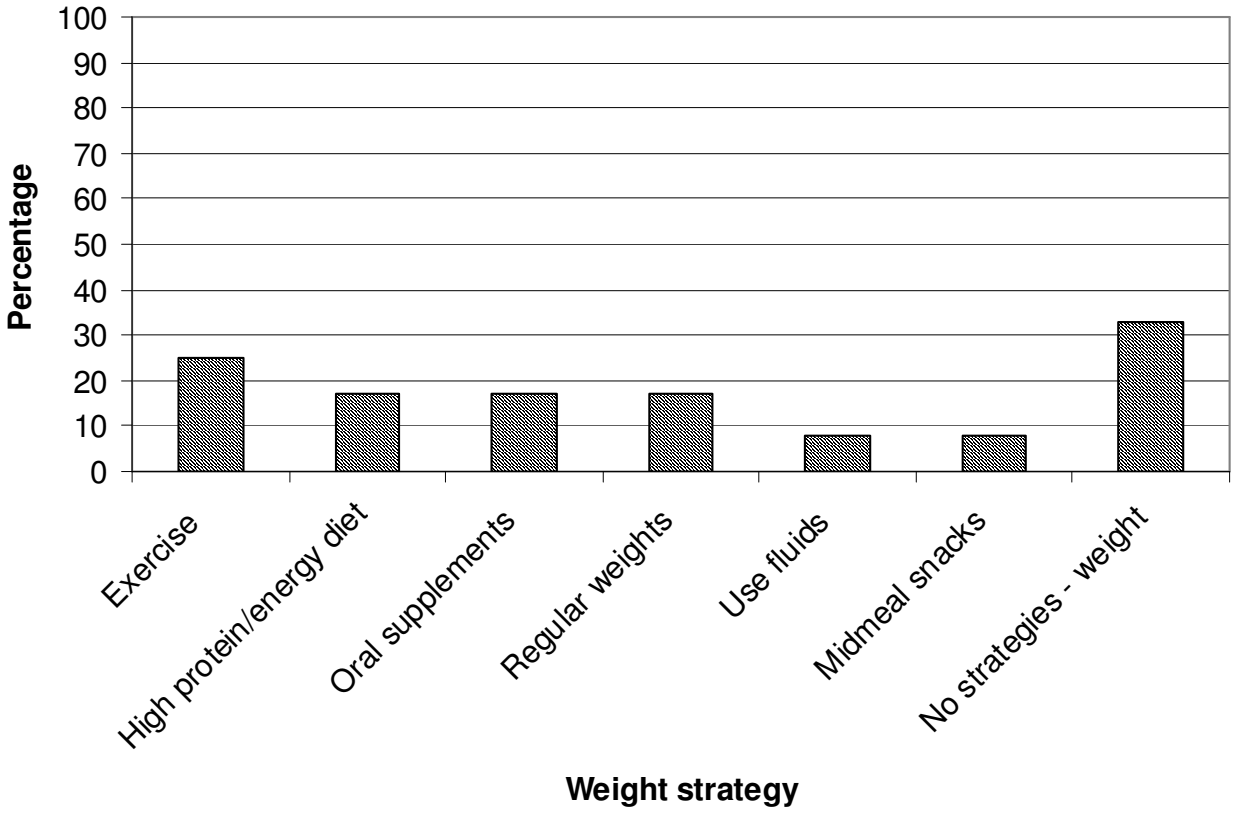

Figure 3. Frequency of patient-reported strategies used to maintain weight at 2 years post-treatment with AFRT-CB