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# Changes in patient-reported swallow function in the long term following chemoradiotherapy for oropharyngeal carcinoma

## Declarations of Interest

None.

## Abstract

**Objectives:** To assess long term patient-reported swallow function following chemoradiotherapy for oropharyngeal carcinoma, and to evaluate the frequency of deterioration/improvement over years.

**Materials and Methods:** 59 patients with oropharyngeal carcinoma treated with parotid-sparing intensity modulated radiotherapy and concurrent chemotherapy between 2010-2012 had previously completed the MD Anderson Dysphagia Inventory (MDADI) at a median of 34 months (range 24-59) post-treatment. An MDADI was posted to 55 alive and disease-free patients after a 30 month interval. 52/55 replies were received, median of 64 months (range 52-88) post-treatment. 27/52 (52%) had been managed with a prophylactic gastrostomy. A 10-point or greater change of the MDADI scores was defined as clinically significant.

**Results:** Overall in the whole cohort, patient reported swallow function showed a small absolute improvement in MDADI composite score on the second MDADI questionnaire (>5 years post-treatment) compared with the first MDADI (>2 years post-treatment), mean 68.0 (SD 19.3) versus 64.0 (SD 16.3),  $p=0.021$ . Using the composite score, swallow function was stable over time in 29/52 (56%) of patients; a clinically significant improvement in swallow function over time was noted in 17/52 (33%) patients; conversely 6/52 (12%) of patients experienced a clinically significant deterioration with time. Abnormality of pre-treatment diet and a prophylactic gastrostomy correlated with an inferior MDADI composite score on the later questionnaire ( $p=0.029$  and  $p=0.044$  respectively).

**Conclusions:** Long term dysphagia is prevalent >5 years post-treatment. Although long term swallow function is stable in the majority of patients, it is not static in a minority. On MDADI composite summary scores 33% of patients experienced an improvement whilst 12% deteriorated with time. Further investigation is needed to determine underlying mechanisms behind these divergent outcomes.

## **Keywords**

Head and neck cancer; oropharynx cancer; radiotherapy; chemotherapy; patient reported outcomes; swallow function; late toxicity

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This research did not receive any specific funding.

## Introduction

Definitive (chemo)radiotherapy for head and neck cancer is a standard of care with the aim of locoregional tumour control with organ preservation. Chemoradiotherapy can impair all phases of swallowing [1] and long term dysphagia is recognised as a major late toxicity [2-4]. Dysphagia has been shown to have a major impact upon health-related quality-of-life (QoL) [5-8], and remains a priority concern for patients one year post treatment [5]. Early side effects impacting upon swallow function are well recognised may be attributed to mucositis and oedema; these improve gradually following completion of treatment. The pathogenesis of long term dysphagia is less well understood and is likely to relate to mechanisms including fibrosis, oedema, cranial neuropathy, trismus and osteoradionecrosis [2]. Radiation-induced nerve and muscle dysfunction can develop slowly and may not be apparent for years following treatment [9].

The majority of series examining dysphagia have focussed upon dysphagia occurring after only limited period of time post treatment (eg. 1-2 years) [5, 10-12]. Dysphagia over a much longer time period of >5 years post treatment is only occasionally reported [3, 13]. These data demonstrate that persistent dysphagia is prevalent; for example in a retrospective analysis of 78 patients with oropharyngeal carcinoma, 50% of patients had experienced a severe late dysphagia event after a median follow up of over 5 years [3].

A key issue is how often swallow function can be expected to improve, remain stable, deteriorate over multiple years following treatment. There is very little data upon how dysphagia may change with increasing time from completion of treatment. Hutcheson et al. [12] found a modest deterioration in swallow function 2 years post treatment compared with baseline in 47 patients using range of functional measures, with increased pharyngeal residue on videofluoroscopic swallowing study (VFSS). Feng et al. [11] found that VFSS measured swallow function did not change between 3 months and 2 years. A retrospective study of 83 patients with median follow up of 3 years using the Sydney Swallow Questionnaire found no correlation between dysphagia severity and time from therapy [14]. In a series of 39 patients assessed using the Australian Therapy Outcome Measures Frowen et al. [13] showed that patient-reported swallowing activity for solids significantly improved

for all patients between 6 months and 5 years; however, by contrast the semi-solid swallowing measure deteriorated over time.

The aim of the current study is to assess patient-reported swallow outcomes in the long term (>5 years) post-chemoradiotherapy for oropharyngeal carcinoma, and to evaluate changes with time following chemoradiotherapy, including determination of how commonly swallow function may improve/deteriorate. We have previously evaluated patient reported swallow function at least 2 years post-chemoradiotherapy for oropharyngeal carcinoma using the MD Anderson Dysphagia Inventory (MDADI) [15] in a cohort of 59 patients with returned questionnaires [16]. The MDADI was re-administered to the same patients after a further 30 month interval (at least 4 ½ years post-chemoradiotherapy).

## Methods

### *Study design*

The study was registered with the Institutional Quality Improvement Board.

The aim of the study was to evaluate changes patient-reported swallow function at least 5 years post-chemoradiotherapy using the MDADI tool in a cohort of patients who had previously completed the MDADI at least 2 years post-chemoradiotherapy.

The MDADI is a validated reliable self-administered questionnaire which uses 20 questions which are designed to assess patients' perception of their swallowing ability and how this may impact upon their quality of life [15, 17]. Each question is scored on a 5-point scale ranging from 'strongly agree' to 'strongly disagree'. Questions are divided into emotional, functional and physical subscales. Two summary scores are obtained; the global scale is a single question scored individually and the composite is a score summarising the remaining 19 questions. Summary and subscale scores are normalised to a range from 20-100; a higher score indicates superior swallow-related quality of life/function.

Patients were identified in a prior study in which patients were asked to complete the MDADI at least 2 years post-chemoradiotherapy [16]. In this prior study, patients with locally advanced squamous cell carcinoma of the oropharynx were identified who had received definitive concurrent chemoradiotherapy between October 2010-December 2012. Inclusion criteria were: oropharyngeal primary, squamous cell carcinoma, stage III/IV, non-surgical treatment with curative intent, concurrent chemotherapy, IMRT including treatment of bilateral neck, disease free for at least 2 years following completion of radiotherapy. Patients were excluded for recurrent disease, prior neck dissection, and for therapeutic enteral feeding prior to treatment. As previously described [16], 94 patients were identified and exclusions were: 18 due to disease recurrence, 3 deaths without disease recurrence, 5 received therapeutic feeding pre-treatment. The remaining 68 patients were posted the MDADI along with an explanatory letter in January 2014. Completed MDADI forms were received from 59 (87%) of these patients. Pre-treatment diet was categorized

using prospectively collected pre-treatment dietitian and nursing assessments into: nil by mouth, sips, pureed, soft, normal.

In this current study, electronic notes records were reviewed for the 59 patients who had returned a completed MDADI in the original study. 4 patients were excluded from being sent a further MDADI in the event of death or disease recurrence; 2 patients had died of unrelated causes, one patient was receiving chemotherapy for distant metastases and one patient had undergone salvage surgery for regional recurrence.

The MDADI was sent with an explanatory letter to the remaining 55 patients in June 2017. All patients were a minimum 4 ½ years post-chemoradiotherapy and were disease free with no prior recurrence. Completed MDADI questionnaires were received from 52 patients.

#### *Pre- and post-treatment support*

All patients routinely underwent dietetic, nursing and speech and language therapy (SLT) assessments pre-treatment. During this period of time the institutional policy regarding a prophylactic or reactive approach to enteral nutritional support was to consider either a prophylactic gastrostomy or reactive nasogastric tube approach based upon clinician + patient preference. During treatment patients were routinely reviewed twice weekly by medical and nursing teams with additional dietetic and SLT input as required. Post-treatment rehabilitation was offered to all patients in dedicated combined nursing, dietetic and SLT post-treatment clinics.

#### *Treatment details*

##### *Induction chemotherapy*

Induction chemotherapy in this era was delivered to selected patients based upon clinician preference, patients and disease factors. Induction chemotherapy constituted either TPF (docetaxel 75mg/m<sup>2</sup>, cisplatin 75mg/m<sup>2</sup>, 5-fluorouracil (5-FU) 750mg/m<sup>2</sup> days 2-5) [18] or PF (cisplatin 80mg/m<sup>2</sup> and 5-FU 800mg/m<sup>2</sup>) [19].

##### *Concurrent chemotherapy*

Standard concurrent chemotherapy was cisplatin 100mg/m<sup>2</sup> days 1 and 29. Carboplatin AUC4 was substituted in the event of a contraindication to cisplatin.

### *Radiotherapy*

Intensity modulated radiotherapy (IMRT) was delivered as previously described according to an institutional protocol [16, 20] using a compartmental approach to primary and lymph node levels was used for target volume delineation, to include the whole oropharynx and whole involved lymph node levels within the high dose volume. During this period outlining was performed by one of four radiation oncologists (outlining 15, 15, 12, 10 cases each). There were no formal prospective arrangements for contour peer review during this period although ad hoc informal review was commonly undertaken. The standard dose was 70Gy in 35 fractions over 7 weeks. The dose to the elective target volume was 57Gy in 35 fractions with an intermediate dose level of 63Gy in 35 fractions available at clinician discretion. Treatment was delivered using a 5-7 angle step and shoot technique.

### *Statistics*

Descriptive statistics and correlations were performed using SPSS 24(Chicago, IL). Follow up was calculated from the final date of radiotherapy. The Shapiro-Wilk method was used to assess for normality in distribution (using a significance level at the 0.05 level) of the difference in composite MDADI scores on the first and second questionnaires (composite  $p=0.83$ , global  $p<0.01$ , emotional  $p=0.59$ , functional  $p=0.06$ , physical 0.07); parametric and non-parametric tests were selected appropriately. The paired t test was used to compare swallow function at both questionnaire time points for composite, emotional, functional and physical subscales; the Wilcoxon signed rank test was used for the global subscale. A difference in MDADI scores of  $\geq 10$  points was considered clinically significant [17]. In order to examine potential associations between patient/tumour/treatment factors, the composite MDADI score was chosen as it reflects the overall performance [17]. The Shapiro-Wilk method was performed to assess normality of the composite summary score of the MDADA at each questionnaire timepoint and was non-significant ( $p=0.22$  and  $p=0.29$  for first and second questionnaires respectively indicating a normal distribution). Factors included in the analysis were: age, gender, T stage (T1/2 versus T3/4), use of prophylactic gastrostomy, use of enteral feeding during/shortly after treatment, pre-treatment swallow function (according to 5 point scale), mean contralateral parotid dose. Smoking and alcohol

consumption were not included as accurate information on long term follow up was not available. Depending on type of variable independent t tests, Pearson's correlation coefficient and Spearman's rho was used to examine factors potentially associated with swallowing outcomes as assessed by the composite summary MDADI score at each questionnaire timepoint. An exploratory analysis using Spearman's correlation was performed examining the same factors with a change of +/-10 points on the composite MDADI score. Correlations were considered significant at the 0.05 level (2-tailed).

## Results

Patient and treatment characteristics for the 52 patients who had returned the first and second MDADI questionnaires are shown in Table 1. 27 (52%) had had a prophylactic gastrostomy inserted pre-chemoradiotherapy; the remaining patients were treated with the intention of management with a nasogastric tube as required. Overall 41/52 (79%) of patients received enteral feeding support during chemoradiotherapy. 25/27 (93%) patients who had received a prophylactic gastrostomy received enteral feeding. 16/25 (64%) without a prophylactic gastrostomy received enteral feeding (14 via a nasogastric tube and 2 via radiologically inserted gastrostomy following difficulties with nasogastric tube feeding).

The first MDADI questionnaire was completed at a median of 34 months (range 24-59) post-chemoradiotherapy. The second MDADI questionnaire was requested after an interval of 30 months from the initial questionnaire, at a median of 64 months (range 54-89) post-treatment.

2 (4%) patients were using a gastrostomy for enteral feeding at the time of the first MDADI questionnaire. 4 (8%) patients were using gastrostomy feed at the time of the second questionnaire. 2 of these 4 patients had documented osteoradionecrosis of the mandible. 3 of 4 of these patients had a prophylactic gastrostomy and the remaining patient received NG feeding during treatment.

### *Patient reported swallow function on long term follow up*

Patient reported swallow function as measured using the MDADI are shown in Table 2 and illustrated for the composite and global scores and each subdomain domain in Figure 1. The distribution of changes in MDADI scores between the first and second questionnaires is illustrated in Figure 2. Comparing MDADI scores at the two different timepoints, swallow function was significantly superior at the later timepoint for composite and global scores, and on emotional and functional domains, with a non-significant difference for the physical domain. However, as seen in Table 2, absolute differences in median scores between the two questionnaire timepoints were small.

A difference in MDADI of  $\geq 10$  points is considered clinically significant [17]. Table 3 summarises how many patients had either a clinically significant deterioration or improvement or a difference of  $< 10$  points (stable) in their reported swallow function for the composite summary score and for each MDADI domain. In terms of the composite summary score, 29/52 (56%) of patients had stable swallow function over time with no clinically significant change. 6/52 (12%) and 17/52 (33%) patients had a clinically significant deterioration or improvement in swallow function respectively between the two questionnaires. 20/52 (38%), 20/52 (38%) and 28/52 (54%) of patients did not have a clinically significant change in emotional, functional and physical domains respectively. 10 (19%), 12 (23%) and 15 (29%) experienced a clinically significant deterioration and 22 (42%), 20 (38%) and 9 (17%) a clinically significant improvement in emotional, functional and physical domains respectively between the two MDADI questionnaires.

#### *Risk factors for swallowing function*

Potential associations between multiple clinical factors (age, sex, T stage, contralateral parotid dose, use of induction chemotherapy, number of concurrent chemotherapy cycles, pre-treatment diet, insertion of a prophylactic gastrostomy, enteral feeding during treatment (by any route)) and the composite summary score of the MDADI were assessed (Table 4). For the initial questionnaire ( $> 2$  years post-treatment) there was a significant but weak correlation with pre-treatment diet ( $p=0.048$ , Spearman's  $\rho=0.30$ ). At 5 years the composite summary MDADI score showed a significant association with pre-treatment diet ( $p=0.029$ ,  $\rho=0.33$ ) and with the insertion of a prophylactic gastrostomy with a mean MDADI for patients who received a prophylactic gastrostomy of 63.0 (SD 11.2) versus 73.8 (SD 19.3) for those who did not ( $p=0.044$ ). An exploratory analysis did not demonstrate any correlations between the same factors and a clinically significant improvement or deterioration of  $\pm 10$  points between the composite MDADI scores (all  $p$  values  $> 0.3$ ); however these results should be interpreted with caution in view of the exploratory nature of the analysis.

## Discussion

Late dysphagia is increasingly recognised as an important long term morbidity of chemoradiotherapy. Survivorship issues have become particularly important in the era of human papilloma virus (HPV)-related oropharyngeal carcinoma with a more favourable prognosis and many patients are living for many years with the long term sequelae of treatment . There is a paucity of data available to determine the impact of dysphagia upon patients >2 years post-treatment, and very little information available regarding how dysphagia may change over many years post treatment. We [10, 16] and others [21] have previously evaluated swallow function using the MDADI at least 2 years post-treatment on the basis that it is likely to be stable and reflect long term outcomes after this length of time post-treatment. However, it may be hypothesised that progressive radiotherapy fibrosis and superimposed age-related changes [13] may cause a progressive deterioration in swallow function. Conversely, compensatory adaptation may lead to an improvement in swallow related QoL [13].

The assessment of swallow outcomes is complex with a host of potential tools, including physician assessed toxicity scores, physical outcomes including videofluoroscopy and multiple patient reported measure [1]. It has been shown that these do not necessarily correlate, with data suggesting that patients may rate dysphagia more severely [13, 22, 23]. Therefore, patient reported outcome measures are key tools in assessment of dysphagia. The MDADI is a well used, reliable and validated patient reported outcome measure [15, 17].

In this study 52 patients had completed the MDADI at two different timepoints at least 2 and 5 years post-chemoradiotherapy and separated an interval of 30 months for each patient. These data therefore provide the opportunity to evaluate the impact of extended time post-treatment upon dysphagia. Overall changes in median MDADI scores were small (Table 2) although there was a statistically significant improvement in MDADI scores overall, and in the global, emotional and functional domains, with non-significant improvement in the physical domain (Table 2, Figure 1); these small changes are of debatable clinical significance overall. However, such summary measures conceal the experience of individual

patients. Using a change in MDADI score of  $\geq 10$  as being clinically significant [17], the data shown in Table 3 reveals that swallow function was stable with time in the majority of patients (composite MDADI change  $< 10$  points in 29/52 (56%) of patients. Overall 33% of patients report an improvement in swallow function based upon composite scores (42%, 38%, 17% improve in emotional, functional and physical subscales). By contrast, overall 12% of patients report a deterioration in swallow function (19%, 23%, 29% deteriorate in emotional, functional and physical subscales). Therefore, these data suggest that dysphagia can be a dynamic process, with stable function in the majority in the long term, with a subset of patients improving and another subset of patients deteriorating. No patient, tumour or treatment related factors were identified which correlated with an improvement or deterioration in swallow function between the two questionnaire timepoints.

A prior study by Frowen et al. [13] has also informed on changes in swallow function over long term follow up using paired data at 6 months and 5 years post-treatment in a series of 39 patients using the swallowing scale of the Australian Therapy Outcome Measures (AusTOMs) relating to patient reported swallowing activity along with the MDADI and videofluoroscopy in a subset 21 of these patients. This study found that patient-reported swallowing activity for solids, but not liquids, significantly improved for all patients between 6 months and 5 years. However, the semi-solid swallowing measure deteriorated over time, with a significant difference between 6 months and 5 years post treatment. In the videofluoroscopy, pharyngeal residue significantly increased between 6 months and 5 years post treatment (19% versus 31%). One important finding of this study is the discrepancy between swallow dysfunction on videofluoroscopy which was either stable or deteriorated whilst patient-reported activity which improved. The authors considered that this may relate to patient adaptation over time.

By contrast with our data and that of Frowen et al. [13] suggesting a time dependence to the severity of dysphagia, a retrospective study of 83 patients evaluated using the Sydney Swallow Questionnaire at a mean of 3 years (range 0.5-8) post-treatment found a prevalence of dysphagia of 59% and that severity was not predicted by time from therapy [14].

Some [16, 21, 24], but not all [25], prior studies have suggested that the use of a prophylactic gastrostomy may be detrimental to long term swallow function. In our centre the decision to place a prophylactic gastrostomy was based upon clinician and patient preference ie. patients commonly offered a choice. In this cohort 52% of patients had a prophylactic gastrostomy placed. We have previously reported a matched pair analysis performed to account for confounding factors based upon the first MDADI questionnaire timepoint [16] finding significantly inferior MDADI scores in the group with a prophylactic gastrostomy. Although that matched pair analysis did not include all of the patients reported here, a correlation between the insertion of a prophylactic gastrostomy and inferior MDADI scores was seen here on the second MDADI questionnaire >5 years post-treatment. As previously discussed [16], there are potential confounding factors which may influence this correlation and this observation is hypothesis generating. Consistent with other data that acute dysphagia requiring enteral tube feeding is not related to risks of long term dysphagia [26], the use of enteral feeding during treatment did not correlate with MDADI scores at either timepoint.

Limitations of this study include the variable timepoints post-treatment at which patients completed the first and second MDADI questionnaires. However, these were a minimum of 2 and 4 ½ years post-treatment respectively with a fixed interval of 30 months between administration of questionnaires. Swallow function was assessed only by the MDADI; although patient reported outcomes are key outcome measures, it is not possible to determine from these data how swallow function based on objective assessment (eg. videofluoroscopy) compares. The patients in this study were treated in the early days of IMRT within our institute; the mean contralateral parotid dose is higher than would currently be expected and the compartmental approach of including the whole oropharynx within the high dose target volume is no longer our standard of care. It is possible that these factors may negatively impact upon long term swallow function. Dose to the pharyngeal constrictor muscles is recognised as a factor in long term swallow function [1,27] and pharyngeal constrictor organs at risk were not outlined. The approach of including the whole oropharynx as a high dose compartment does not allow for pharyngeal constrictor sparing. Although it is possible that there may have been inter-clinician variability in outlining, with a lack of formal contour peer review in this era, it is therefore unlikely that

this would have impacted upon dose to pharyngeal constrictors and hence swallow outcomes. In addition, HPV data is not available for this historical cohort of patients; however, there is no data to suggest that HPV-status would impact upon treatment-related long term dysphagia rates. 23% of patients received induction chemotherapy in this era; this is no longer our standard approach.

In summary, this study shows that long term dysphagia continues to have an impact upon patients many years following chemoradiotherapy, and is a major survivorship issue. Long term dysphagia is not a static process. Based upon composite MDADI scores, long term swallow function was stable in 56% of patients, whilst 33% experienced an improvement, and 12% of patients experienced continued deterioration in swallow function over many years follow up. No factors were identified which predicted which patients may improve or deteriorate. Further evaluation of these patients having divergent outcomes is important to determine the underlying mechanisms and to guide potential therapeutic interventions.

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## Figure Legends

**Figure 1: Patient reported outcomes from MDADI in long term.** 52 patients with oropharyngeal carcinoma completed MDADI at first timepoint at median 34 months post-chemoradiotherapy (dark grey) and at second timepoint 30 months later (median 64 months post-chemoradiotherapy) (light grey). A=composite score. B=global score. C=emotional domain. D=functional domain. E=physical domain. Count=number of patients.

**Figure 2: Summary of changes in MDADI scores between first and second questionnaires.** Boxplots: A=composite score, B= global score, C=emotional domain, D=functional domain, E=physical domain. Paired t test used when difference between scores was normally distributed (composite, emotional, functional, physical scales). Wilcoxon signed rank test used when difference between scores not normally distributed (global). Note emotional, functional and physical questionnaires contain questions also contained within the composite score. Therefore caution is required in interpretation of statistical significance of overlapping data.