HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2020 May 15.

Published in final edited form as:

Cancer. 2019 May 15; 125(10): 1654–1664. doi:10.1002/cncr.31957.

Single item discrimination of quality of life-altering dysphagia among 714 long-term oropharyngeal cancer survivors: comparison of patient-reported outcomes measures of swallowing

MD Anderson Head and Neck Cancer Symptom Working Group[¥†], **Stephen Richard Grant, MD**[1] **[MR.]**, **Mona Kamal, MD, PhD**[1] **[DR.]**, **Abdallah S. R Mohamed, MD, MSc**[1,4], **Jhankruti Zaveri, MPH**[2], **M.P. Barrow, MPH**[2], **G.B. Gunn, MD**[1], **Stephen Lai, MD, PhD**[2], **Jan S. Lewin, PhD**[2], **David I. Rosenthal, MD**[1], **Xin Shelley Wang, MD, MPH**[3], **Clifton David Fuller, MD, PhD**[1] **[DR.]**, and **K.A. Hutcheson, PhD**[2]

[1.]Departments of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2.]Departments of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3.]Departments of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4.]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Abstract

Background—We compared two patient-reported outcomes (PROs) of swallowing and their relationship to quality of life (QOL) in long-term oropharyngeal cancer (OPC) survivors.

Methods—The single dysphagia item from the 28-item multi-symptom MD Anderson Symptom Inventory—Head and Neck (MDA**S**I-HN-S) was compared to the dysphagia-specific composite

[*]**Corresponding Author:** Katherine Hutcheson, PhD, Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX, 77030, Phone: 713-792-6513 , KArnold@mdanderson.org.

[†]- Co-author specific contributions:

All listed co-authors performed the following:

1. Substantial contributions to the conception or design; or the acquisition, analysis, or interpretation of data
2. Drafting or revising for important intellectual content.
3. Final approval of the version to be published.
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific additional individual cooperative effort contributions to study/manuscript design/execution/interpretation, in addition to all criteria above are listed as follows:

MK, SG –Co-first authors; drafted manuscript, undertook supervised analysis and interpretation of data.

KH - Corresponding author; primary investigator; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, data collection infrastructure, programmatic oversight, direct oversight of classified personnel, manuscript content and editorial oversight and correspondence.

CDF, SYL, GBG, JSL, DIR, ASRM, SW – Co-investigators; direct patient care provision, direct toxicity assessment and clinical data collection; interpretation and analytic support

JZ, MPB, MJ, SG -Data coordination, collection, curation, and analysis

Conflict of interest statement: The authors declare no conflicts of interest.

MD Anderson Dysphagia Inventory (MDA**D**I) and the EuroQol visual analogue scale (EQ-VAS) in 714 patients treated 12 months or more prior with definitive radiotherapy. An MDA**S**I-HN-S score ≥6 and MDA**D**I composite score <60 was considered representative of moderate/severe swallowing dysfunction.

Results—Moderate/severe dysphagia was reported by 17% and 16% of respondents by MDA**S**I-HN-S and composite MDA**D**I, respectively. Both swallow PROs were predictive of QOL, with the MDA**S**I-HN-S model being slightly more parsimonious for discrimination of EQ-VAS scores compared to MDA**D**I (BIC 6062 vs 6076). An MDA**S**I-HN-S cut-point score of ≥6 correlated best with EQ-VAS decline ($p<0.0001$) and was associated with increased radiotherapy dose to several normal surrounding structures.

Conclusion—In this cohort, the single-item MDA**S**I-HN-S performed favorably for discrimination of QOL compared to the multi-item MDA**D**I. A time-efficient model for PRO measurement of swallowing is proposed in which MDA**D**I may be reserved for patients scoring ≥6 on MDASI-HN-S.

CONDENSED ABSTRACT

In a cohort of long-term survivors of oropharyngeal cancer, a single dysphagia item from MDA**S**I-HN (28-item multi-symptom inventory) performed favorably for discrimination of quality of life compared to the multi-item MDA**D**I (20-item swallow QOL). A model of patient-reported outcome measurement of swallowing is proposed in which MDA**D**I may be reserved for those reporting moderate/severe symptoms by a single MDA**S**I-HN dysphagia item.

Keywords

Dysphagia; patient reported outcomes; oropharynx cancer; radiotherapy; quality of life

INTRODUCTION

Definitive radiation therapy (RT) plays an important role in the curative treatment of oropharyngeal cancer (OPC), but carries a risk of long-term toxicity. With an increasing proportion of these cancers related to the human papilloma virus (HPV) that present at an earlier median age of diagnosis and have favorable outcomes compared to non-HPV OPC, there is an enlarging population of long-term survivors in whom late toxicity of treatment is of particular importance [1].

Swallowing dysfunction, or dysphagia, is an important and potentially chronic complication following RT to the oropharynx and has a demonstrated negative impact on quality of life (QOL) [2–4]. Moreover, while highly conformal RT techniques have become standard in the treatment of these cancers with demonstrated improved sparing of the parotid salivary glands and more favorable rates of long-term xerostomia [5], the benefit of conformal treatment with regards to swallowing function is less clear. Dysphagia thus remains commonly cited as a limiting factor in the delivery of curative RT for OPC [6].

Patient-reported outcomes (PRO) questionnaires are increasingly used in clinical practice and research trials to quantify the severity and impact on everyday function of particular

symptoms [7]. There exist a number of general multi-symptom questionnaires for patients undergoing treatment for head and neck cancer (HNC), including the MD Anderson Symptom Inventory Head and Neck Module (MDA**S**I-HN) [8–10]. These instruments assess an array of symptoms and toxicities that may co-exist in patients with HNC. For this reason, multi-symptom inventories offer the most efficient method of querying the patients' perspectives on multiple issues in a single instrument. These instruments, therefore, are attractive for routine use in clinical practice to track symptoms in addition to their value as a research metric. There exist other questionnaires, such as the MD Anderson Dysphagia Inventory (MDA**D**I) [11, 12], that focus solely on a patient's swallowing function. While these dysphagia-specific questionnaires give a narrower snapshot of a patient's overall function as compared to the multi-symptom inventories, they generally provide greater detail with regard to the nature of perceived swallowing dysfunction and ways in which it may impact day-to-day life. Yet, the relative performance of dysphagia-specific inventories to single items from multi-symptom scales is not well known. Likewise, the validity of reporting single dysphagia item scores from multi-symptoms inventories is not established. If a single dysphagia item from multi-symptom questionnaires is a valid representation of global patient-reported swallowing outcome, this may offer practitioners and researchers alike a more efficient way to capture PRO data on dysphagia simultaneously with other symptoms from a single instrument.

In addition, while many multi-symptom and dysphagia-specific inventories have been validated for the measurement of treatment-related swallowing dysfunction in patients with HNC, few have established consensus cut-points or meaningful thresholds at which symptoms likely merit further investigation. In this study, we sought to compare the performance of a single dysphagia question from MDA**S**I-HN (MDA**S**I-HN-S) with the composite MDA**D**I score in a large sample of patients with OPC treated with definitive RT.

The specific aims of this study were to:

1. Examine the performance of a single item dysphagia question from the 28-item multi-symptom instrument (MDA**S**I-HN-S) relative to the widely used dysphagia specific composite MDA**D**I (19-item composite score from 20-item instrument).
2. Validate clinically meaningful cut-points of the two dysphagia PROs examined in Aim 1 (single item dysphagia MDA**S**I-HN-S and 19-item composite MDA**D**I) by examining performance relative to clinical, QOL, and dosimetric parameters.
3. Estimate the prevalence of self-reported RAD using PRO cut-points from Aim 2 among a cross-sectional cohort of long-term OPC survivors treated at the University of Texas MD Anderson Cancer Center.

MATERIALS AND METHODS

Patients

This is a secondary analysis of a cross-sectional survivorship survey. Patients with T1-T4 N0-N3 M0 OPC (per AJCC staging 7th edition) treated with definitive RT at a single institution between January 2000 and April 2014 were sampled from 908 survey respondents

(58% response rate). A total of 194 patients were dropped (148 did not complete of one or more of the surveys of interest, 20 did not receive definitive RT as primary modality, one patient had metastatic disease, and 25 received treatment with one year), leaving 714 available for analysis. Tumor subsites included tonsil, base of tongue, soft palate, pharyngeal wall, glossopharyngeal sulcus, and oropharynx NOS. To focus on chronic toxicities, patients were invited to participate if they completed treatment one year or more prior to the survey administration.

Survey administration

Participants were asked to complete the survey once. The survey was administered using an adapted version of Dillman method [13], including: 1) a letter of invitation via the US postal service to eligible patients 2–3 weeks prior to the initial contact, 2) the survey questionnaire sent to all eligible participants via an online server Qualtrics or US postal service, and 3) two reminders sent to non-responders via US postal service at 2–3 weeks and 4–5 weeks after the initial contact. Participants were contacted by multiple modes of communication, including email (among those with addresses on record) via Qualtrics or myMDAnderson (a secure, personalized patient website), and US postal service via first-class mail with a return envelope.

Patient-reported outcomes

The survey included 3 PROs used in this analysis: the multi-symptom MDA**S**I-HN, the multi-item MDA**D**I, and the EuroQoL visual analogue scale (EQ-VAS) questionnaire.

The 28-item MDA**S**I-HN is a multi-symptom inventory that includes 13 core symptom items (e.g., pain, fatigue), each rated for severity from 0 (“not present”) to 10 (“as bad as you can imagine”) as well as 9 disease-specific head and neck symptom severity items (e.g., dysphagia, mucus, voice/speech), and 6 interference items [8]. There are 2 dysphagia related symptom items on the MDA**S**I-HN, (MDA**S**I-HN-S, “*your difficulty* ***chewing/swallowing*** *at its worst”* and MDA**S**I-HN choke *“your* ***coughing/choking*** *(foods/liquids going down the wrong pipe) at its worst”)*. MDA**S**I-HN-S was selected as the single item dysphagia PRO in this analysis as it represents the more global of the two items, dichotomized for Aims 2 and 3 per published standards [14, 15], with scores 0–5 and 6–10 representing no/mild symptoms and moderate/severe symptoms, respectively.

The MDA**D**I consists of 20 items that assess an individual’s perception of their swallowing ability [11]. MDA**D**I derives a 19-item composite score which summarizes performance across three individual subscales (physical, emotional, and functional) and ranges from 20 (extremely low functioning) to 100 (high functioning). The 19-item composite MDA**D**I score was selected as our MDA**D**I metric in this analysis as it represents the summary measure combining responses from all domains. An MDA**D**I score of 60 has previously been suggested to meaningfully stratify individuals [16–18], and was selected as a cut point to investigate for Aims 2 and 3 in this study.

The EQ-5D questionnaire is a standardized instrument designed to assess the generic status of one’s overall health, and has been widely used to measure health-related QOL in many

populations [19]. EQ-5D is separated in two sections. The first includes five questions or dimensions that assess one's mobility, ability to care for self, level of pain, participation in usual activities, and psychological status. The second section is the visual analogue scale (EQ-VAS) that allows a patient to rate the state of his or her own health on a visual scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Only EQ-VAS estimate of health state were available for this analysis as a surrogate of health-related QOL.

Treatment and planning

While a small subset of patients were treated with 3D conformal therapy (3D-CRT) or proton therapy, the large majority were treated with IMRT. The authors' institutional IMRT approach from this time period in the treatment of OPC has previously been described in detail [20].

Dosimetric correlates (subset analysis)

Out of 714 patients included in this analysis, a total of 320 treatment plans and dosimetric data were located and restored using Pinnacle 9.6 software (Phillips Medical Systems, Andover, MA). These 320 patients were included in subgroup analysis with PROs as a covariate for validation of the PRO cut points in Aim 2. Planning CT DICOM files were exported into a deformable registration/segmentation software (Velocity AI 3.0.1, Velocity Medical Solutions, Atlanta, GA). Candidate dysphagia-related structures were auto-segmented using a custom region of interest (ROI) library, with dose volume histograms (DVHs) generated for the inferior, middle and superior pharyngeal constrictors (IPC, MPC, and SPC), anterior digastrics (ADM), intrinsic tongue muscles (ITM), mylo/geniohyoid complex (MHM), genioglossus (GGM), cricopharyngeus (CPM), submandibular (SM) and parotid glands (PG), larynx (LX), and esophagus (ESG).

Clinical variables

Clinical variables are listed in Table 1. Patients with unknown HPV status and no history of tobacco use were considered likely HPV positive for the purpose of this analysis. Baseline dysfunction included PEG tube dependence, inability to tolerate solid food, poor airway protection, or impaired mobility of the tongue, soft palate, or true vocal cord at diagnosis, as determined in the medical record by the treating providers.

Statistical analysis

Summary statistics, chi-squared, and t-tests were used to describe clinical characteristics. Correlations between MDA**S**I-HN-S, composite MDA**D**I, and EQ-VAS were assessed using Spearman's correlation coefficient. The Bayesian information criteria (BIC) were used to test the discriminant ability of MDA**S**I-HN-S and composite MDA**D**I for QOL as measured by EQ-VAS. This method for use of BIC in predicting model performance has been described previously [14].

To identify the possible score of the MDA**S**I-HN-S and composite MDA**D**I at which a detrimental poor QOL could be reported, we used the modified Breiman recursive partitioning analysis (RPA). Training, test and validation sets for optimization of the MDA**S**I-swallowing score RPA were conducted using MDA**S**I-HN-S as a continuous

variable. The RPA (decision tree-based partitioning) was performed with 20% verification "holdback" and a minimum split size of 15% per split/partition. A total of 571 patients were including in the training set and 143 in the validation set. Post hoc K-fold cross validation (n=10) was performed to evaluate for over-fitting. Regression analysis was used to confirm the threshold effect size. The ROI mean dose differentials were then stratified by the derived MDA**S**I-HN-S and composite MDA**D**I scores cut-points as a measure of validity to represent dose-dependent thresholds of swallowing muscle (region) injury.

A p value ≤0.05 was considered to be statistically significant, with statistical tests based on a two-sided significance level. Data analysis was performed using STATA/IC statistical software (version 12.1: STATA, College Station, TX), MatLab (R2011a, Mathwork, Natick, MA), JMP (version 12Pro, SAS Institute, Cary, NC), and IBM SPSS (version 22.0, Chicago, IL).

RESULTS

Patient and treatment characteristics

A total of 714 survey respondents with a mean survival time at survey response of 6.7 years (range 1.5 years to 15.6 years) were included in this analysis. Patient and disease characteristics, treatment details, and follow up data are summarized in Tables 1 and 2.

Patient-reported dysphagia per MDA**S**I-HN-S and MDA**D**I and QOL

There was a strong inverse relationship between MDA**S**I-HN-S and composite MDA**D**I scores, indicating that both tools capture a similar symptom burden of dysphagia (Spearman's $p = -0.65$, $p<0.0001$) (Figure 1a). Bivariate analyses showed an expected inverse relationship between EQ-VAS and MDA**S**I-HN-S (Spearman's $p = -0.48$, $p<0.0001$) (Figure 1b) and similarly a direct relationship between EQ-VAS and composite MDA**D**I (Spearman's $p = 0.50$, $p<0.0001$) with similar effect size between each dysphagia PRO and QOL (per EQ-VAS) (Figure 1c).

Using the Bayesian information criteria to assess performance of MDA**S**I-HN-S and composite MDA**D**I in predicting EQ-VAS, model performance was superior for MDA**S**I-HN-S compared to MDA**D**I (BIC of 6062 vs 6076). While the difference between MDA**S**I-HN-S and MDA**D**I BIC models is "very strong" (posterior probability >99%), the R-squared for these two models were similar, 0.21 and 0.19, respectively. Thus, while this data suggests improved parsimony for discrimination of QOL-altering swallowing dysfunction for MDA**S**I-HN-S as compared to MDA**D**I, dysphagia symptoms as captured by either tool significantly correlated with QOL scores in similar magnitude. Figure 2 displays EQ-VAS scores as boxplots stratified by MDA**S**I-HN-S (0–10) and by composite MDA**D**I (0–100) groupings with a line of best fit demonstrating that, in general, QOL declines with more significant self-reported dysphagia symptoms.

Swallowing PRO cut-point validation by QOL

Using the modified Breiman RPA, an MDA**S**I-HN-S score of ≥6 was verified as the threshold for EQ-VAS decline in the training set ($p<.0001$)(Figure 3a). These results were

maintained after 10-fold cross validation. Assessing this cut-point as a binary split across the entire cohort (n=714) yielded mean (SD) EQ-VAS scores of 63.4 (23.1) vs. 83.5 (15.7) for those with MDA**S**I-HN-swallowing scores ≥6 (n=119) vs. <6 (n=595), respectively (p<0.001). A similarly designed modified Breiman RPA for EQ-VAS based on composite MDA**D**I scores demonstrated MDA**D**I cut-points of 60, 75.8, and 88.4 (p<.0001)(Figure 3b). Assessing these across the entire cohort (n=714) yielded mean (SD) EQ-VAS scores of 64.5 (22.9), 75.2 (17.3), 81.3 (17.8), and 88.0 (12.7) for those with composite MDA**D**I scores of <60, ≥60 but <75.8, ≥75.8 but <88.4, and ≥88.4, respectively.

Clinical covariate validation of swallowing PRO cut-points

Moderate/severe dysphagia was reported by 17% and 16% of respondents by MDA**S**I-HN-S ≥6 and composite MDA**D**I <60, respectively. In univariate analysis, patient demographic, disease, and treatment characteristics significantly associated with moderate/severe dysphagia by both MDA**S**I-HN-S and by composite MDA**D**I score included baseline swallowing dysfunction (p=0.008 and p=0.001 for MDA**S**I-HN-S and composite MDA**D**I, respectively), T4 tumor stage (p=<0.001 for both inventories), 3D-CRT (<0.001 for both inventories), accelerated fractionation schedule (p=0.024 and p=0.006), higher radiation dose (p=0.017 and p=0.003) and fraction number (p=0.001 and p<0.001), and concurrent platinum-based chemotherapy (p<0.001 for both inventories). Those with unfavorable MDA**S**I-HN-S and composite MDA**D**I scores displayed a higher rate of feeding tube placement and more significant mean weight loss from baseline to survey response.

Dosimetric validation of PRO thresholds

Moderate/severe symptoms by MDA**S**I-HN-S ≥6 was significantly associated with a higher mean dose to the contralateral ADM (p=0.019), ITM (p=0.035), and LX (p =0.032) (Table3). Similarly, moderate/severe dysphagia by MDA**D**I score < 60 was significantly associated with a higher mean dose to the contralateral ADM (<0.001), ITM (p=0.003), MHM (p=0.028), ESG (p=0.038), LX (p=0.005), and contralateral SM (p=0.010).

DISCUSSION

This report demonstrates that patient-reported dysphagia as captured by the single item MDA**S**I-HN-S (from a multi-symptom inventory) performs favorably in distinguishing QOL-altering dysphagia symptoms as compared to the widely used 19-item dysphagia-specific MDA**D**I inventory. Both MDA**S**I-HN-S and composite MDA**D**I models, however, correlated with EQ-VAS scores and similar clinical/dosimetric factors, suggesting that dysphagia symptoms as captured by either inventory are valid measures. Indeed, these results should not imply that one inventory universally replace the other. Rather, they demonstrate the potential role of the single-item MDA**S**I-HN-S as a time-efficient initial screening tool for QOL-altering dysphagia. For patients with an MDA**S**I-HN-S score ≥ 6, MDA**D**I may then be used to explore with greater detail and granularity the patient's swallowing symptoms (Figure 4).

With a median follow-up of nearly 7 years, this study highlights that greater than 15% of patients may experience long-term QOL-altering dysfunction in swallowing following

treatment. While not analyzed longitudinally in this study, patients have previously demonstrated marked worsening in swallowing function at 6 months to 1 year following definitive IMRT for OPC, with partial recovery by 2 years [16]. By limiting our cohort to those who completed treatment 1 year or more prior, we largely exclude those with acute or sub-acute symptoms of dysphagia that may recover. In our cohort, patients reporting moderate/severe dysphagia tended to have a longer time since treatment interval, which may suggest continued and persistent deterioration in function many years after treatment, or be a surrogate for older and less conformal treatments techniques.

MDA**S**I-HN is a compelling candidate as a screening tool in patients with OPC following RT for reasons beyond only swallowing. It was designed and validated with the aim to assess, in a single instrument, the burden of 22 distinct symptoms specific to oncology patients and HNC treatment [8]. Further, previous analyses similar to the present study have shown single-item MDA**S**I-HN questions to perform favorably to multi-item inventories in predicting the severity of radiation-induced mucositis and xerostomia (compared to the Functional Assessment of Cancer Therapy—Head and Neck (FACT—HN) module and multi-question Xerostomia Questionnaire (XQ), respectively) [14, 21]. Routine use of MDA**S**I-HN following RT for OPC may thus accurately and efficiently screen for an array of common symptoms, after which patients may be triaged to more detailed questionnaires, clinical referrals, imaging tests, or other work up as needed.

If MDA**S**I-HN is to be used as a routine screening tool, clinically relevant single-item cut-points must be established. While these have been explored for other symptoms of MDA**S**I-HN (dry mouth score of ≥6 for xerostomia [14]), a clinically meaningful MDA**S**I-HN-S cut-off point has, to the best of our knowledge, not yet been validated. As no consensus cut-point for MDA**S**I-HN-S has previously been identified, a value of ≥6 to represent moderate/severe symptoms was chosen based on published data of optimal cut-points from composite and other single item MDA**S**I-HN items [14, 15]. By RPA, an MDA**S**I-HN-S cut-point of ≥ 6 was validated to best distinguish QOL-altering dysphagia symptoms as measured by EQ-VAS. Regarding MDA**D**I, a score of 60 has previously been proposed as a clinically meaningful cut-off point [16, 22] and is used as an endpoint for patient reported swallowing dysfunction in NRG HN-002, a recent randomized trial of IMRT in OPC [23]. These findings support this cut-point as RPA confirmed an MDA**D**I score of less than 60 to be associated with worse QOL by EQ-VAS. Two additional MDA**D**I cut-points of 75.8 and 88.4 were found to distinguish QOL, suggesting that further partitioning of MDA**D**I may be of clinical relevance. In a subset analysis exploring dose/PRO correlates, several structures of swallowing were found to correlate with moderate-severe dysphagia by both MDA**S**I-HN-S and composite MDA**D**I per the pre-specified cut-off points of ≥6 and <60, respectively. These relationships further support the validity of the proposed MDA**D**I and MDA**S**I-HN-S cut-points as well the use of self-reported swallowing outcomes as a dose-dependent measure of RT toxicity.

This study highlights a wide EQ-VAS differential by PRO dysphagia scores (an absolute difference of more than 20 EQ-VAS points between patients scoring <6 vs ≥6 on MDA**S**I-HN-S). While there is an abundance of literature on the clinical relevance and meaning of EQ-VAS scores, there exists no consensus interpretation. Studies, however, consistently

demonstrate an association between EQ-VAS and the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [24, 25]. Thus, while it is difficulty to encapsulate a person's perceived quality of life in a single number, such wide differences in EQ-VAS may suggest meaningful differences in overall health, independence in daily activities, and psychosocial functioning. These survey results, therefore, further highlight the large impact of dysphagia symptoms on overall QOL in OPC survivorship.

Several limitations exist in this study, including those inherent to secondary analysis of a cross-sectional survey from a single cancer center, including lack of longitudinal follow up. Second, while this series includes over 700 patients, only 320 DICOM files were attainable for review to correlate PRO responses with dose. Third, dysphagia was determined in this study solely on basis of patient reported outcomes. While an objective measurement such as modified barium swallow or endoscopy may have offered additional useful information, these were not available in a similar time to the survey response. Moreover, we analyzed MDA**S**I-HN-S out of context from its original place as only part of a larger inventory. It is thus possible that responses to a stand-alone single dysphagia would differ than what is observed here. Fourth, while we intended to allow all RT types into this study to enhance generalizability, due to institutional practices in the study period, the large majority received IMRT.

In conclusion, this comparison of a single-item dysphagia question from the multi-symptom MDA**S**I-HN to the dysphagia-specific 20-item MDA**D**I instrument in over 700 patients and with a mean follow up of nearly 7 years marks, to the best of our knowledge, the largest study measuring long-term self-reported swallowing dysfunction following RT for OPC. These results show that although the single item MDA**S**I-HN-S performed slightly better in predicting QOL as compared to the multi-item MDA**D**I score, both models successfully captured QOL-altering dysphagia. Moreover, an MDA**S**I-HN-S score of 6 or greater and an MDA**D**I score less than 60 were associated with worse QOL scores, known clinical risk factors for dysphagia, and higher swallowing region RT dose. A model in which MDA**D**I is reserved for patients scoring ≥6 on MDA**S**I-HN-S may thus be used a time-efficient method to effectively capture patients experiencing QOL-altering dysphagia symptoms following RT for OPC. As additional single item cut-points are explored and validated in future studies, MDA**S**I-HN may become an increasingly valuable clinical tool.

Acknowledgments

Funding sources and financial disclosures: This research is supported by the Andrew Sabin Family Foundation; Dr. Fuller is a Sabin Family Foundation Fellow. Dr. Fuller receives funding and salary support from the National Institutes of Health (NIH), including: the National Institute for Dental and Craniofacial Research Award (1R01DE025248–01/R56DE025248–01); a National Science Foundation (NSF), Division of Mathematical Sciences, Joint NIH/NSF Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant (NSF 1557679); the NIH Big Data to Knowledge (BD2K) Program of the National Cancer Institute (NCI) Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Award (1R01CA214825–01); NCI Early Phase Clinical Trials in Imaging and Image-Guided Interventions Program (1R01CA218148–01); an NIH/NCI Cancer Center Support Grant (CCSG) Pilot Research Program Award from the UT MD Anderson CCSG Radiation Oncology and Cancer Imaging Program (P30CA016672) and an NIH/NCI Head and Neck Specialized Programs of Research Excellence (SPORE) Developmental Research Program Award (P50 CA097007–10). Dr. Fuller has received direct industry grant support and travel funding from Elekta AB.

REFERENCES

1. Gillison ML, et al., Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol, 2015 33(29): p. 3235–42. [PubMed: 26351338]
2. Goepfert RP, et al., Symptom burden as a driver of decisional regret in long-term oropharyngeal carcinoma survivors. Head Neck, 2017 39(11): p. 2151–2158. [PubMed: 28736965]
3. Hunter KU, et al., Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. Int J Radiat Oncol Biol Phys, 2013 85(4): p. 935–40. [PubMed: 23040224]
4. Langendijk JA, et al., Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol, 2008 26(22): p. 3770–6. [PubMed: 18669465]
5. Nutting CM, et al., Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol, 2011 12(2): p. 127–36. [PubMed: 21236730]
6. Hutcheson KA, et al., Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer, 2012 118(23): p. 5793–9. [PubMed: 23640737]
7. Deshpande PR, et al., Patient-reported outcomes: A new era in clinical research. Perspect Clin Res, 2011 2(4): p. 137–44. [PubMed: 22145124]
8. Rosenthal DI, et al., Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head Neck, 2007 29(10): p. 923–31. [PubMed: 17358040]
9. Bjordal K, et al., Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. J Clin Oncol, 1999 17(3): p. 1008–19. [PubMed: 10071296]
10. Murphy BA, et al., Reliability and validity of the Vanderbilt Head and Neck Symptom Survey: a tool to assess symptom burden in patients treated with chemoradiation. Head Neck, 2010 32(1): p. 26–37. [PubMed: 19626644]
11. Chen AY, et al., 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, 2001 127(7): p. 870–6. [PubMed: 11448365]
12. McHorney CA, et al., The SWAL-QOL outcomes tool for oropharyngeal dysphagia in adults: I. Conceptual foundation and item development. Dysphagia, 2000 15(3): p. 115–21. [PubMed: 10839823]
13. Dillman DA, Smyth JD, and Christian LM, Internet, phone, mail, and mixed-mode surveys : the tailored design method 4th edition. ed. 2014, Hoboken: Wiley xvii, 509 pages.
14. Kamal M, et al., Patient reported dry mouth: Instrument comparison and model performance for correlation with quality of life in head and neck cancer survivors. Radiother Oncol, 2017.
15. Eraj SA, et al., Long-term patient reported outcomes following radiation therapy for oropharyngeal cancer: cross-sectional assessment of a prospective symptom survey in patients >/=65 years old. Radiat Oncol, 2017 12(1): p. 150. [PubMed: 28888224]
16. Goepfert RP, et al., Long-Term, Prospective Performance of the MD Anderson Dysphagia Inventory in “Low-Intermediate Risk” Oropharyngeal Carcinoma After Intensity Modulated Radiation Therapy. Int J Radiat Oncol Biol Phys, 2017 97(4): p. 700–708. [PubMed: 27485284]
17. Chen PH, et al., Prevalence of perceived dysphagia and quality-of-life impairment in a geriatric population. Dysphagia, 2009 24(1): p. 1–6. [PubMed: 18368451]
18. Bhide SA, et al., Correlation between dose to the pharyngeal constrictors and patient quality of life and late dysphagia following chemo-IMRT for head and neck cancer. Radiother Oncol, 2009 93(3): p. 539–44. [PubMed: 19883951]
19. Balestroni G and Bertolotti G, [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. Monaldi Arch Chest Dis, 2012 78(3): p. 155–9. [PubMed: 23614330]
20. Garden AS, et al., Patterns of disease recurrence following treatment of oropharyngeal cancer with intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys, 2013 85(4): p. 941–7. [PubMed: 22975604]

21. Rosenthal DI, et al., The M. D. Anderson symptom inventory-head and neck module, a patient-reported outcome instrument, accurately predicts the severity of radiation-induced mucositis. Int J Radiat Oncol Biol Phys, 2008 72(5): p. 1355–61. [PubMed: 18501527]

22. Hutcheson KA, et al., What is a clinically relevant difference in MDADI scores between groups of head and neck cancer patients? Laryngoscope, 2016 126(5): p. 1108–13. [PubMed: 26542529]

23. NRG Oncology. Reduced-Dose Intensity-Modulated Radiation Therapy With or Without Cisplatin in Treating Patients With Advanced Oropharyngeal Cancer Available from: https://clinicaltrials.gov/ct2/show/NCT02254278.

24. Jelsma J and Ferguson G, The determinants of self-reported health-related quality of life in a culturally and socially diverse South African community. Bull World Health Organ, 2004 82(3): p. 206–12. [PubMed: 15112009]

25. Whynes DK, Does the correspondence between EQ-5D health state description and VAS score vary by medical condition? Health Qual Life Outcomes, 2013 11: p. 155. [PubMed: 24034630]

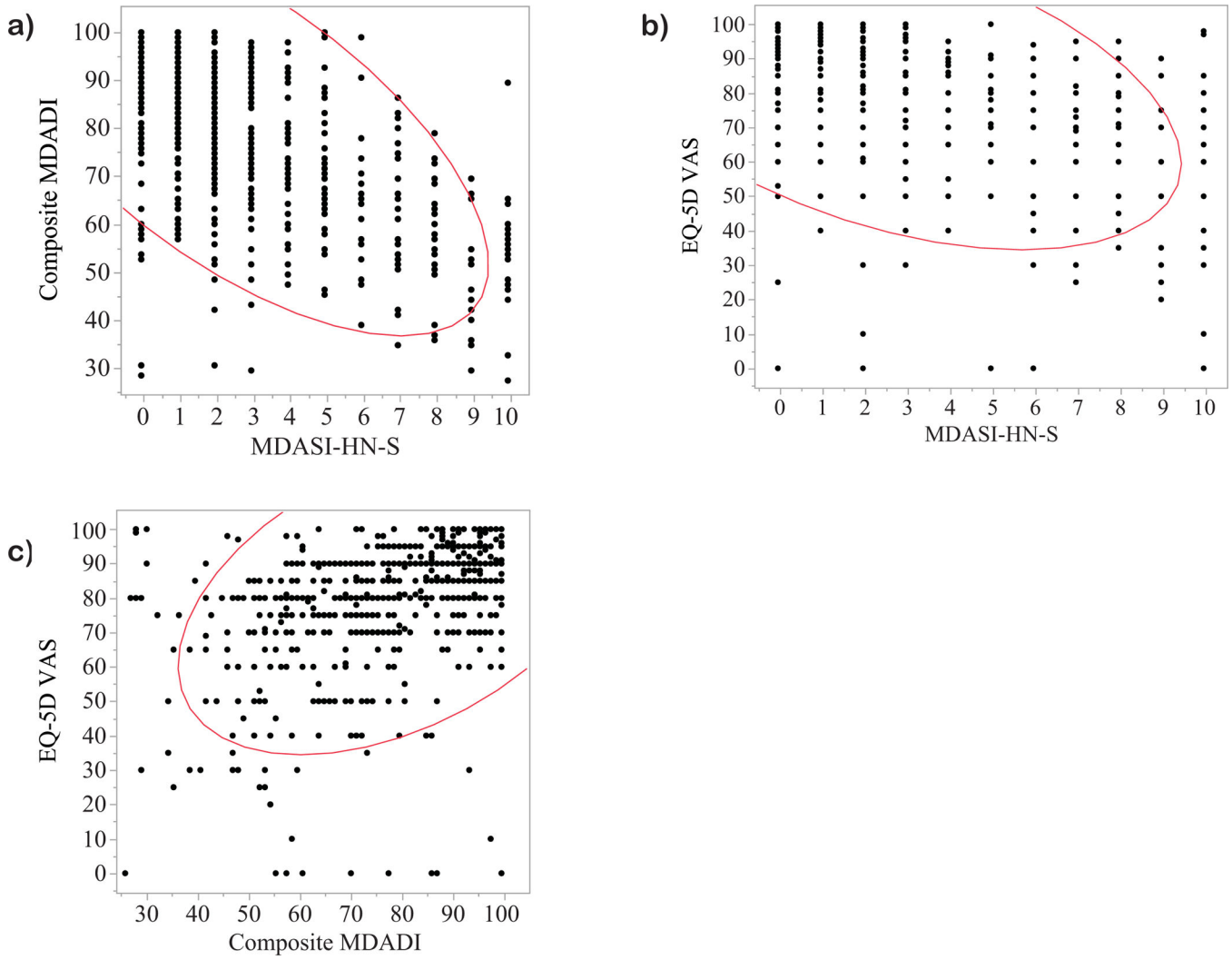

Figure 1:

Bivariate analyses demonstrating a) an inverse relationship between composite MDA**D**I and MDA**S**I-HN-S (Spearman's p = p = −0.65, p<0.0001), b) an inverse relationship between EQ-5D VAS and MDA**S**I-HN-S (Spearman's p = −0.48, p<0.0001) and c) a positive relationship between EQ-5D VAS and composite MDA**D**I (Spearman's p = 0.50, p<0.0001).

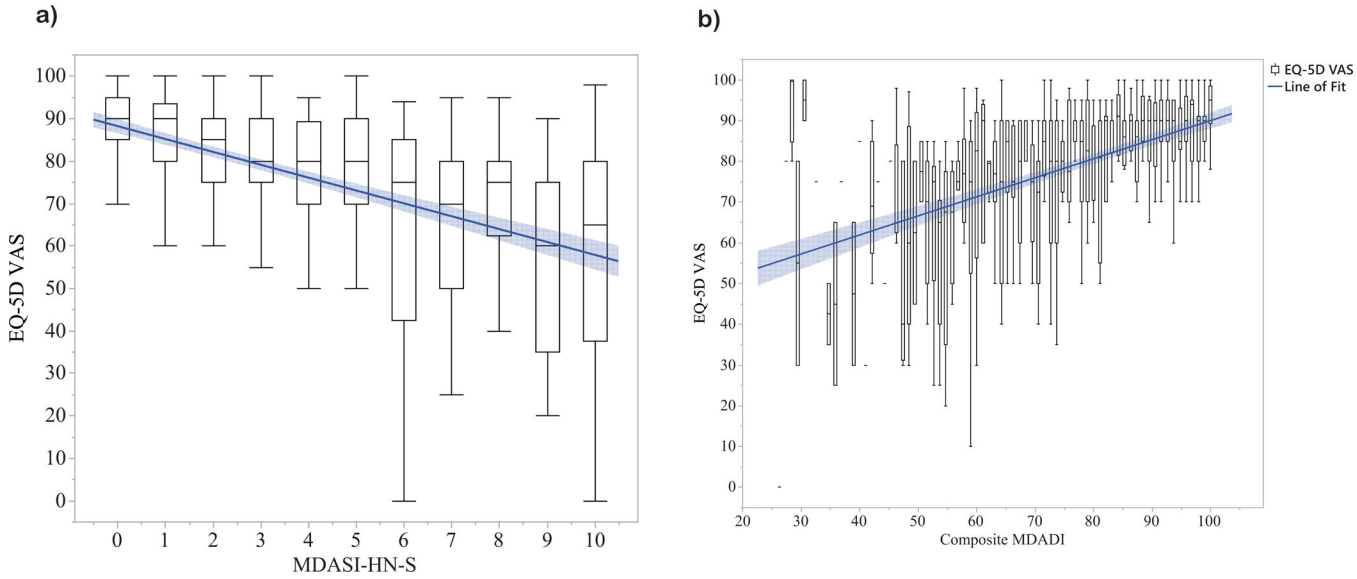

Figure 2:

EQ-5D VAS scores displayed as boxplots stratified by a) MDA**S**I-HN-S and b) composite MDA**D**I, with lines of best fit shown in blue.

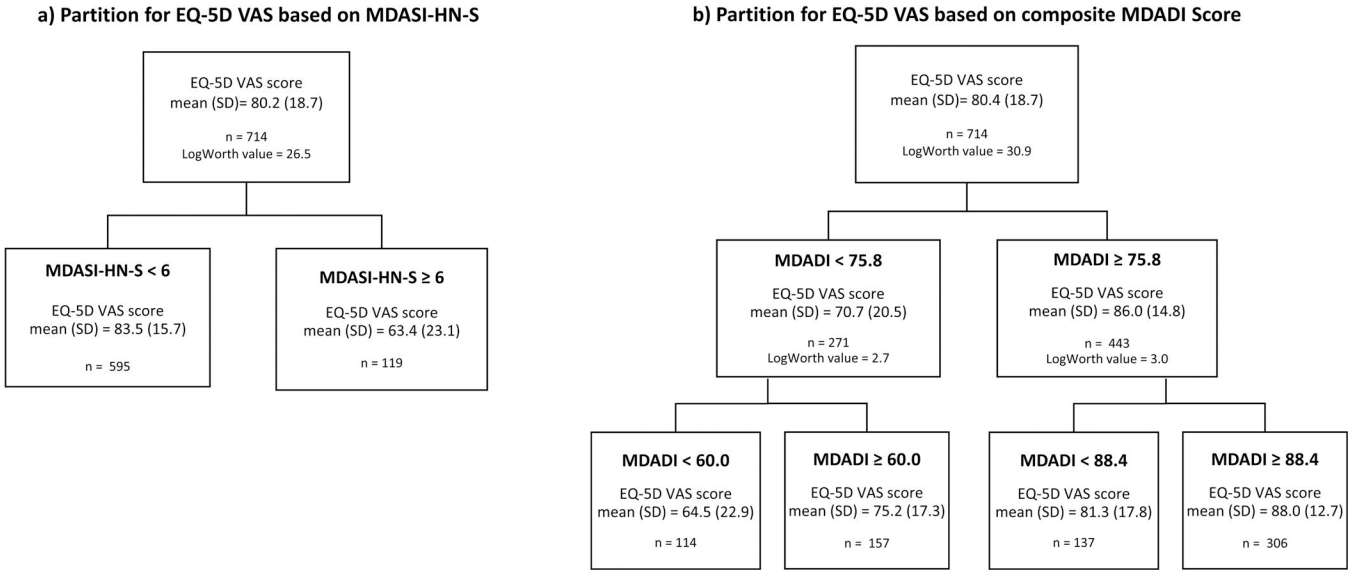

Figure 3:

Modified Breiman RPA for EQ-5D VAS score by dysphagia PRO, showing a) an MDA**S**I-HN-S cut-point of 6 ($p<0.0001$) and b) composite MDA**D**I cut-points of 60, 75.7, and 88.4 ($p<0.0001$)

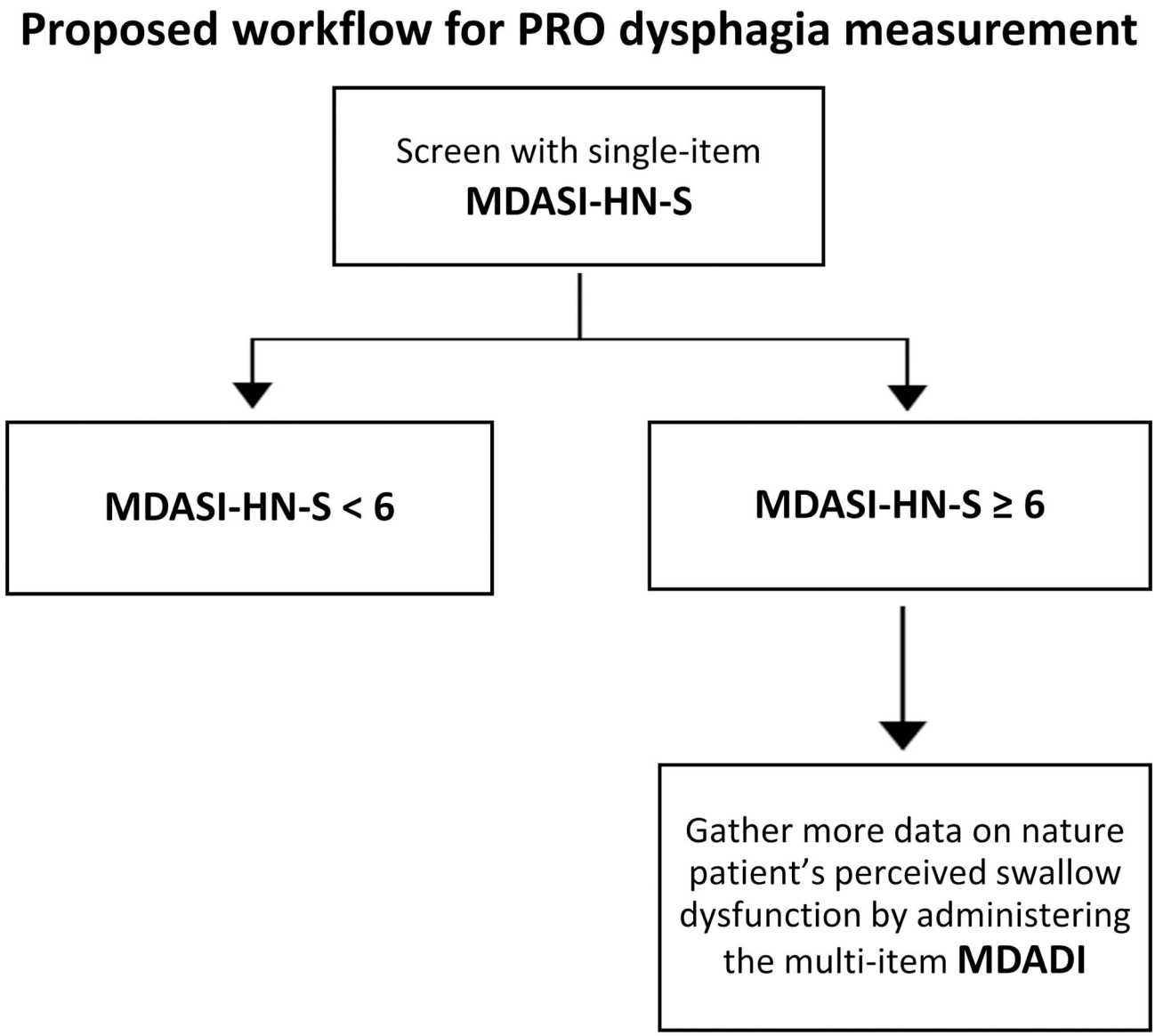

Figure 4:
Proposed workflow to capture QOL-altering dysphagia in clinic using MDA**S**I-HN-S and MDA**D**I.

Table 1:

Patient and disease characteristics, treatment details, and follow up data

		Proportion of patients by MDASI-HN-S			Proportion of patients by composite MDADI		
	All patients (%)	**0–5**	**6–10**	**p value**	**<60**	**≥60**	**p value**
All patients	714 (100%)	0.17	0.83	N/A	0.16	0.84	N/A
Gender							
Male	602 (84.3%)	0.83	0.17	0.854	0.15	0.85	0.381
Female	112 (15.7%)	0.84	0.16		0.19	0.81	
HPV *							
Negative	217 (30.4%)	0.82	0.18	0.536	0.19	0.81	0.102
Positive	497 (69.6%)	0.84	0.16		0.15	0.85	
Smoking †							
No	327 (45.8%)	0.85	0.15	0.190	0.13	0.87	0.036
Yes	387 (54.2%)	0.82	0.18		0.19	0.81	
Baseline dysfunction ‡							
No	677 (94.8%)	0.84	0.16	0.008	0.15	0.85	0.001
Yes	37 (5.2%)	0.68	0.32		0.35	0.65	
Tumor subsite							
Tonsil	326 (45.7%)	0.85	0.15	0.560	0.15	0.85	0.658
Base of tongue	354 (49.6%)	0.82	0.18		0.17	0.83	
Other	34 (4.8%)	0.82	0.18		0.15	0.85	
Tumor staging							
T1	257 (36.1%)	0.86	0.14		0.11	0.89	
T2	280 (39.3%)	0.86	0.14	<0.001	0.13	0.87	<0.002
T3	106 (14.9%)	0.79	0.21		0.21	0.79	
T4	69 (9.7%)	0.65	0.35		0.38	0.62	
Nodal staging				0.014			0.001

		Proportion of patients by MDASI-HN-S				Proportion of patients by composite MDADI		
	All patients (%)	0–5	6–10	p value	<60	≥60	p value
N0	65 (9.0%)	0.78	0.22		0.19	0.81	
N1	100 (14.0%)	0.85	0.15		0.11	0.89	
N2a	89 (12.5%)	0.79	0.21		0.11	0.89	
N2b	319 (44.7%)	0.88	0.12		0.13	0.87	
N2c	120 (16.8%)	0.76	0.24		0.26	0.74	
N3	22 (3.1%)	0.77	0.23		0.36	0.64	
Radiation modality							
3D-CRT	42 (5.9%)	0.52	0.48	<0.001	0.45	0.55	<0.001
IMRT	656 (91.9%)	0.85	0.15		0.14	0.86	
Proton	16 (2.2%)	1.00	0.00		0.06	0.94	
Radiation schedule							
Standard fractionation	632 (90.5%)	0.84	0.16	0.024	0.14	0.86	0.006
Accelerated fractionation	66 (9.5%)	0.73	0.27		0.27	0.73	
Concurrent therapy							
None	340 (47.6%)	0.89	0.11		0.12	0.88	
Platinum chemotherapy	251 (35.2%)	0.76	0.24	<0.001	0.24	0.76	<0.001
Cetuximab	123 (17.2%)	0.84	0.16		0.10	0.89	
Induction chemotherapy							
No	487 (68.2%)	0.83	0.17	0.541	0.14	0.86	0.010
Yes	227 (31.8%)	0.85	0.15		0.21	0.79	
Salvage neck dissection							
No	540 (75.6%)	0.83	0.17	0.815	0.15	0.85	0.315
Yes	174 (24.4%)	0.84	0.16		0.18	0.82	
Feeding tube placement							
No	377 (52.8%)	0.90	0.10	<0.001	0.09	0.91	<0.001
Yes	337 (47.2%)	0.76	0.10		0.24	0.76	
Swallowing exercises[§]							

		Proportion of patients by MDASI-HN-S			Proportion of patients by composite MDADI		
	All patients (%)	0–5	6–10	p value	<60	≥60	p value
Partial or full adherence	226 (48.7%)	0.83	0.17	0.906	0.15	0.85	0.458
Minimal or no adherence	238 (51.3%)	0.83	0.17		0.18	0.82	

*Patients with unknown HPV and no history of smoking considered HPV positive

†Any history of smoking at time of diagnosis

‡Baseline dysfunction as reported by patient

§Adherence assessed at time of follow up

Table 2:

Patient and disease characteristics, treatment details, and follow up data

		Mean value by MDASI-HN-S			Mean value by composite MDADI		
		0–5	6–10	p value	<60	≥60	p value
Age (years)							
Mean	56.5	56.4	56.4	0.939	56.5	56.4	0.907
Radiation dose (Gray)							
Mean	68.2	68.1	68.7	0.017	68.8	68.0	0.003
BED with time							
Mean	55.3	54.5	58.6	0.085	59.7	54.3	0.003
Radiation fractions							
Mean	32.5	32.3	33.3	0.001	33.5	32.3	0.000
Time since treatment (years)							
Mean	6.7	6.6	7.4	0.026	7.4	6.6	0.027
Weight change *							
Mean	−7.2	−6.2	−11.8	<0.001	−10.9	−6.5	<0.001
EQ-5D VAS							
Mean	80.2	83.5	63.4	<0.001	64.5	83.2	<0.001

*Weight change from diagnosis to time of survey

Table 3:

Normal tissue dose by swallowing inventory score

	Mean dose by MDASI-HN-S			Mean dose by composite MDADI		
	0–5	**6–10**	**p value**	**<60**	**≥60**	**p value**
Inferior pharyngeal constrictors	30.9	34.8	0.160	35.8	30.8	0.076
Middle pharyngeal constrictors	56.5	57.1	0.756	57.8	56.4	0.540
Superior pharyngeal constrictors	61.3	64.2	0.056	64.3	61.3	0.054
Ipsilateral anterior digastric	57.2	58.5	0.413	60.1	57.0	0.060
Contralateral anterior digastric	45.3	51.2	0.019	53.7	45.1	<0.001
Intrinsic tongue muscles	54.3	58.2	0.035	59.7	54.2	0.003
Mylogeniohyoid	48.3	53.3	0.095	54.8	48.1	0.028
Genioglossus	58.7	60.7	0.293	62.0	58.6	0.066
Cricopharyngeal muscle	18.0	19.9	0.415	20.7	17.9	0.254
Ipsilateral parotid gland	35.6	37.9	0.253	38.1	35.6	0.342
Contralateral parotid gland	20.2	24.0	0.052	24.4	20.2	0.057
Ipsilateral submandibular gland	68.5	68.9	0.892	69.7	68.4	0.074
Contralateral submandibular gland	55.1	55.9	0.133	57.7	49.9	0.010
Larynx	25.5	29.9	0.032	30.1	25.4	0.005
Esophagus	26.8	29.0	0.277	30.8	26.6	0.038