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ORIGINAL ARTICLE

Modeling symptom drivers of oral intake in long-term head and neck cancer survivors

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Abstract

Purpose This study examined the relationship between self-reported symptom severity and oral intake in long-term head and neck cancer (HNC) survivors.

Methods An observational survey study with retrospective chart abstraction was conducted. HNC patients who had completed an MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) questionnaire and also had clinician graded oral intake ratings (Functional Oral Intake Scale [FOIS]) were included. Correlation coefficients were computed. FOIS scores were regressed on MDASI-HN symptom items using stepwise backwards elimination for multivariate models.

Results One hundred and fifty-two survey pairings were included in the analysis (median 44 months follow-up, range 7–198). Per FOIS, 28% of survivors maintained a total oral diet with no restrictions, 67% reported a restricted oral diet (without tube), 3% were partially tube-dependent with some oral intake, and 2% were NPO. Of the 22 symptom items, the most severe items in decreasing order were dry mouth, difficulty swallowing\chewing, problems with mucus, tasting food, and choking/coughing. Significant bivariate correlations, after Bonferroni correction for multiple comparisons, were present for 8 of 22 symptoms with FOIS. On multivariate analysis, symptom severity for difficulty swallowing and problems with teeth/gums remained significantly associated with FOIS.

Conclusions Oral intake in HNC survivorship is a multidimensional issue and functional outcome that is impacted not only by dysphagia but also by dental status. Symptom drivers of oral intake likely differ in acute survivorship. Nonetheless, these findings highlight the lack of specificity in this end point and also the need for multidisciplinary supportive care to optimize oral intake in survivors.

Keywords Oral intake · Head and neck cancer · Survivors · Symptom drivers · Toxicity · Functional outcomes

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Introduction

Radiotherapy (RT), which may be delivered as a primary modality, concurrently with chemotherapy, or adjuvant to surgical resection, is a mainstay of treatment for head and neck cancer (HNC). Although HNC cases make up a small percentage of all new cancers in the USA (3%), the survival rates have been steadily increasing in recent years with 5-year survival estimated at 65% for oral and pharyngeal cancers and 60% for laryngeal cancers [1, 2]. With an increase in survival and intensification of RT with concurrent chemotherapy, there is heightened awareness of the supportive care needs of HNC survivors [3]. A safe and efficient swallow is required for optimal quality of life, nutrition, and to prevent aspiration. There are a variety of validated clinical instruments to assess

oral intake and also validated patient-reported outcomes (PRO) instruments that assess symptoms affecting oral intake, but no single method is accepted as standard.

Oral intake of HNC survivors is often impaired due to effects of the tumor as well as short- and long-term side effects associated with cancer therapy. Relevant acute toxicities of radiation therapy include dysgeusia, mucositis, odynophagia, dysphagia, aspiration, fatigue, and pain [4, 5]. Chemotherapy has been reported not only to cause nausea and vomiting, leading to dehydration, but also to enhance the above side effects of RT [5]. While many acute toxicities improve in the months immediately following RT, a number of salivary and neuromuscular toxicities may linger, progress, or have delayed onset as consequential late effects of therapy. The most commonly cited chronic symptoms of multimodality therapy include xerostomia, trismus, and soft tissue fibrosis, leading to pharyngo-esophageal strictures and stenosis, dysphagia, and aspiration [5, 6].

Acute and chronic toxicities and their associated symptoms cause functional impairments, such as restrictions in oral intake in HNC survivorship. Swallowing disorders [7], mucosal sensitivity [8], and xerostomia [8] have been shown to significantly relate to oral intake, as have clinical factors such as age, tumor location, tumor staging, and treatment. Limited published data exist, however, on the relationship between clusters of symptoms as they relate to functional impairments in oral intake after treatment. The negative consequences of altered oral intake include treatment interruptions, increased recovery times, impaired immunity, weight loss, increased risk of complications, poor quality of life (QOL), and reduced survival rates [9, 10]. Up to 57% of HNC patients present with significant malnutrition, manifested by greater than 10% weight loss from baseline body mass [11]. During multimodality therapy, the percentage of malnourished patients rises as high as 88% [12]. After the completion of treatment, HNC survivors continue facing challenges with oral intake due to the long-term side effects of cancer therapy.

Various PRO and clinician-graded scales exist to measure oral intake in HNC patients. Although there is a lack of consensus on one predominant oral intake scale, the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) and Functional Oral Intake Scale (FOIS) are the most commonly reported validated scales in published literature. FOIS was originally developed and validated in stroke patients, and the psychometric properties were subsequently confirmed in other populations such as HNC patients [13]. FOIS is reliable, valid, and sensitive to change in functional oral intake [12]. PSS-HN was specifically designed to assess three areas of dysfunction in HNC patients including understandability of speech, normalcy of diet, and eating in public [13]. Unlike FOIS, which takes into account the use of a feeding tube with oral intake, PSS-HN focuses more on the complexity of the patient's diet regardless of feeding tube status. Other non-validated oral intake classifications (e.g., regular diet versus blended/pureed versus liquids) are also regularly reported as an outcome in HNC publications [14, 15]. The MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) is a PRO instrument that takes 2 min to complete to rate the severity of symptoms that may affect oral intake and other functions.

The objective of this pilot study is to examine the relationship between self-reported symptom severity (per MD Anderson Symptom Inventory-Head and Neck, MDASI-HN) and oral intake (per FOIS) in long-term HNC survivors. Primary symptoms of interest included surrogates of mucosal toxicity, salivary dysfunction, and dysphagia.

Methods

Study design and eligibility

An observational study was conducted at the University of Texas MD Anderson Cancer Center to identify symptom drivers of oral intake in long-term HNC survivors. HNC patients who completed MDASI-HN questionnaire and also had prospective clinician graded quantitative oral intake ratings using the Performance Scale of Head and Neck Cancer (PSS-HN) available for retrospective analysis were eligible for inclusion in the study. Inclusion criteria were (1) diagnosis of oral cavity, oropharyngeal, nasopharyngeal, laryngeal, or unknown primary HNC; (2) history of RT with or without chemotherapy; (3) at least 18 years of age; (4) MDASI-HN questionnaire in the study database; and (5) prospective clinical oral intake ratings per PSSHN using the normalcy of diet scale in the study database or clinical record.

A total of 952 eligible patients with 2422 MDASI-HN were identified in the MDASI-HN database. One hundred and sixty-three HNC patients were excluded according to the following criteria: radical or salvage surgery; re-irradiation; skin, sinonasal, or skull base cancers; active disease at the time of MDASI-HN completion; and less than 18 years of age. Of the 789 eligible HNC patients with MDASI-HN scores, only 123 also had clinical PSS-HN assigned in proximity to the MDASI-HN survey, i.e., within 6 months. Thus, a final sample size of 152 survey pairings (MDASI-HN + PSS-HN) from 123 patients was included in this analysis.

Study instruments

MDASI-HN [16]

The MDASI-HN questionnaire permits patients to self-report and grade their symptom burden via 28 items: 22 items rate the severity of symptoms and 6 items rate how symptoms interfere with daily life. Symptoms are graded on a 0–10 scale, 0 representing "not present" and 10 indicating "as bad as you

can imagine." Interference items are also graded on a 0–10 scale, 0 indicating the item "did not interfere" and 10 indicating the item "interfered completely." MDASI-HN were prospectively collected by phone or mailing as part of a prospective HNC survivorship study. MDASI-HN symptom severity items were the primary independent variables of interest in the statistical analysis.

PSS-HN [17]

The PSS-HN is clinician-graded based on a semi-structured interview with three subscales: normalcy of diet, understandability of speech, and eating in public. Only the normalcy of diet subscale was utilized in this study. The normalcy of diet subscale is arranged hierarchically where 100 indicates a regular, fully unrestricted diet and 0 indicates non-oral nutrition. This subscale takes into account the complexity of the patient's diet according to various food textures. The PSS-HN normalcy of diet scores >0 do not take into account the feeding tube status of the patient. Feeding tube status was prospectively documented at the time of PSS-HN completion using four standardized questions ascertaining presence, type of use (sole use [i.e., no or minimal oral intake], supplementation, liquids only, or not currently used), number of cans, and proportion of intake by tube. PSS-HN and feeding tube use were routinely documented using a standardized clinical form, at clinical encounters with the speech pathology service. PSS-HN was considered as a secondary oral intake measure in sensitivity analyses.

FOIS [13]

The FOIS is a psychometrically validated clinician-graded ordinal scale of oral intake that consists of seven levels with level 1 representing nothing by mouth and level 7 representing total oral diet with no restrictions. As a distinction from PSS-HN, FOIS includes ordinal rankings to account for various degrees of partial oral intake with tube supplementation (levels 2 and 3), but specific food avoidances are not graded as in the PSS-HN normalcy of diet subscale (PSSHN 60–80). The PSS-HN normalcy of diet scores and tube status were converted to the FOIS scale for this analysis; conversion criteria are listed in Supplementary Table 1. FOIS was considered as the primary measure of oral intake for statistical analyses.

Pairing measures (MDASI-HN and oral intake)

The source of MDASI-HN (symptom instrument) and PSS-HN/FOIS (oral intake instruments) differed. That is, MDASI-HN was collected from a prospective survey study administered longitudinally outside of clinic whereas PSS-HN (converted to FOIS) was collected at clinical encounters within the Head and Neck Center. The authors allowed a maximum 6-month window in which the patient was NED, with no cancer treatment or rehabilitation rendered to pair instruments. Six months was felt to reflect a fairly stable window for symptoms and functional status at this point given that most survivors included were years out from cancer treatment.

Table 1 Patient, tumor, and treatment characteristics

	No.	Percentage
Sex		
Male	94	75
Female	29	24
Age		
Median (range)	60 (32–83)	
Tumor Site		
Oropharynx	70	57
Nasopharynx	7	6
Larynx or hypopharynx	46	37
T classification		
TX/1/2	79	64
T3/4	44	36
N classification		
NX/0	48	39
N1/2	72	59
N3	3	2
Therapeutic combination		
RT alone	36	29
IC → RT alone	10	8
Concurrent ChemoRT	43	35
IC → ChemoRT	33	27
RT → Adjuvant chemotherapy	1	1

IC induction chemotherapy, *RT* radiotherapy, American Joint Commission on Cancer 7th Edition staging

Statistical methods

Descriptive statistics were calculated. Mean MDASI-HN summary scores (total symptom burden, local symptom burden, systemic symptom burden, and interference) were computed. Statistical analyses of the categorical variables were performed using chi-square test and *t* tests for continuous outcomes. Symptom clusters were defined by hierarchal cluster analysis and displayed via heat map, by which each patient's individual item ratings were identified, to provide a pictorial representation of how symptoms clustered. Symptom clusters are groups of symptoms, which centered together and may share specific underlying dimensions relatively independent of other clusters. The symptoms that join with others were rated by patients more similarly and could be interrelated. The heat map for the hierarchal cluster analysis is accompanied with a dendrogram to show the relative distances between clusters, i.e., those symptoms that join with others earlier

Table 2 Mean individual MDASI-symptom item and symptom interference ratings by order of decreasing severity

Symptom	Entire study cohort $n = 152$		Regression coefficient—univariate analysis*	p value	Regression coefficient—multivariate analysis**	p value
	Mean	SD				
Local items						
Dry mouth*	4.14	3.16	− 0.121	0.000*		
Swallow**	3.56	3.28	− 0.149	0.000*		0.000**
Mucus	3.09	3.06				
Taste*	2.43	3.23	− 0.102	0.000*		
Choking*	2.40	3.00	− 0.099	0.001*		
Voice/speech*	2.36	2.73	− 0.111	0.001*		
Teeth/gum**	1.27	2.37	− 0.182	0.000*		0.004**
Constipation	1.17	2.13				
Sores	0.90	2.15				
Skin	0.56	1.51				
Systemic items						
Fatigue	2.40	2.62				
Sleep	2.02	2.69				
Memory	1.99	2.48				
Drowsy	1.95	2.49				
Appetite*	1.61	2.66	− 0.159	0.000*		
Breath	1.34	2.31				
Numbness	1.33	2.38				
Distress	1.28	2.07				
Sad	1.14	2.05				
Pain*	1.13	2.15	− 0.128	0.002*		
Nausea	0.28	1.14				
Vomiting	0.15	0.87				
Total (all 22 symptom items)		38.17	33.85			
Symptom interference						
Activity	1.78	2.50				
Work	1.68	2.54				
Enjoyment	1.46	2.25				
Mood	1.36	2.20				
Walking	1.13	2.28				
Relations	0.97	2.00				
Total (6 symptom interference items)	1.40	1.96				

FOIS Functional Oral Intake Scale, *MDASI-HN* MD Anderson Symptom Inventory-Head and Neck questionnaire

*Significant correlations between MDASI-HN symptom items and the FOIS dietary scale in univariate analysis after Bonferroni correction for multiple comparisons

**Significant correlations between MDASI-HN symptom items and the FOIS dietary scale in multivariate analysis

within small relative distance were rated by patients more similarly. Spearman correlation coefficients were computed for ordinal variables. For the primary analysis, FOIS scores were regressed on MDASI-HN symptom items. To control for multiple comparisons of each of the 22 MDASI-HN symptom items, a Bonferroni correction was performed with a p value of ≤ 0.002 (i.e., 0.05/22, accounting for $n = 22$ items) deemed significant. Eight MDASI items with significant p value ($p \leq 0.002$) were entered the multivariate models using stepwise backward elimination per methods of Hosmer and Lemeshow; the final model retained confounders that were independently associated ($p \leq 0.006$, i.e., 0.05/8) with FOIS. Univariate generalized linear regression models were first examined for each MDASI symptom item and clinical variables (T-classification, N-classification, sex, age, treatment modalities, surgery, and primary site). Multivariable models retained confounders that were independently associated ($p < 0.05$) with FOIS. A p value of < 0.05 was considered statistically significant. Statistical

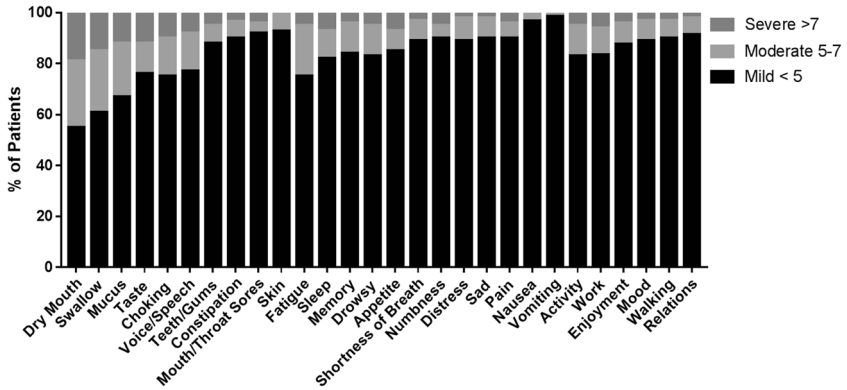


Fig. 1 Percentage of patients with MDASI-HN symptoms. Abbreviations: MDASI-HN MD Anderson Symptom Inventory-Head and Neck

analyses were performed using the STATA data analysis software, version 14.0 (StataCorp LP, College Station, TX, USA) and JMP, version 12 (Pro, SAS Institute, Cary, NC, USA).

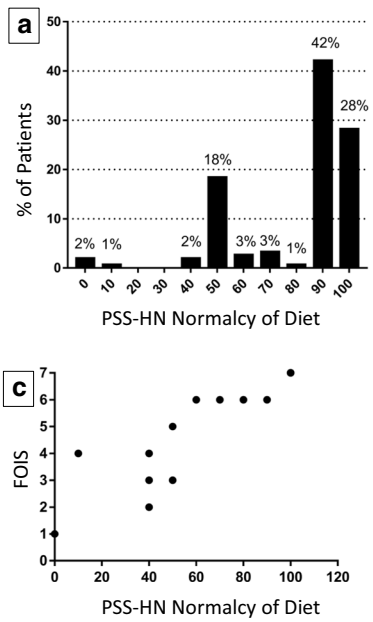
Results

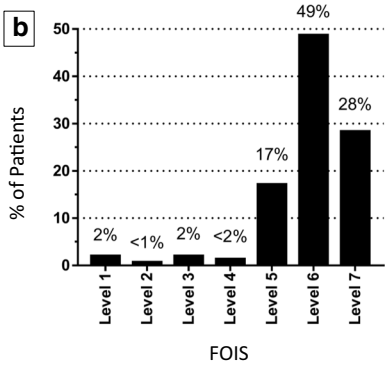
Patients

Table 1 lists the demographic and disease-related characteristics for the patients contributing 152 surveys included in this study. The median age was 60 years (range 41–83) and 75% were male. The most common disease sites were the oropharynx (55%) and larynx/hypopharynx (40%). Only 13 surveys were collected after surgery (8.5%), which included procedures such as selective neck dissection, neck skin wide local excision, transoral robotic surgery, and marginal mandibulectomy. All 152 surveys post-dated radiation therapy: 30% radiation alone and 70% with chemotherapy.

MDASI-HN

The average time from the end of treatment to completion of MDASI-HN was 44 months (range 7–198 months). The mean individual and composite MDASI-HN symptom and symptom interference item ratings are shown in Table 2. Of the 10 local symptom items, the three most severe items in order of decreasing

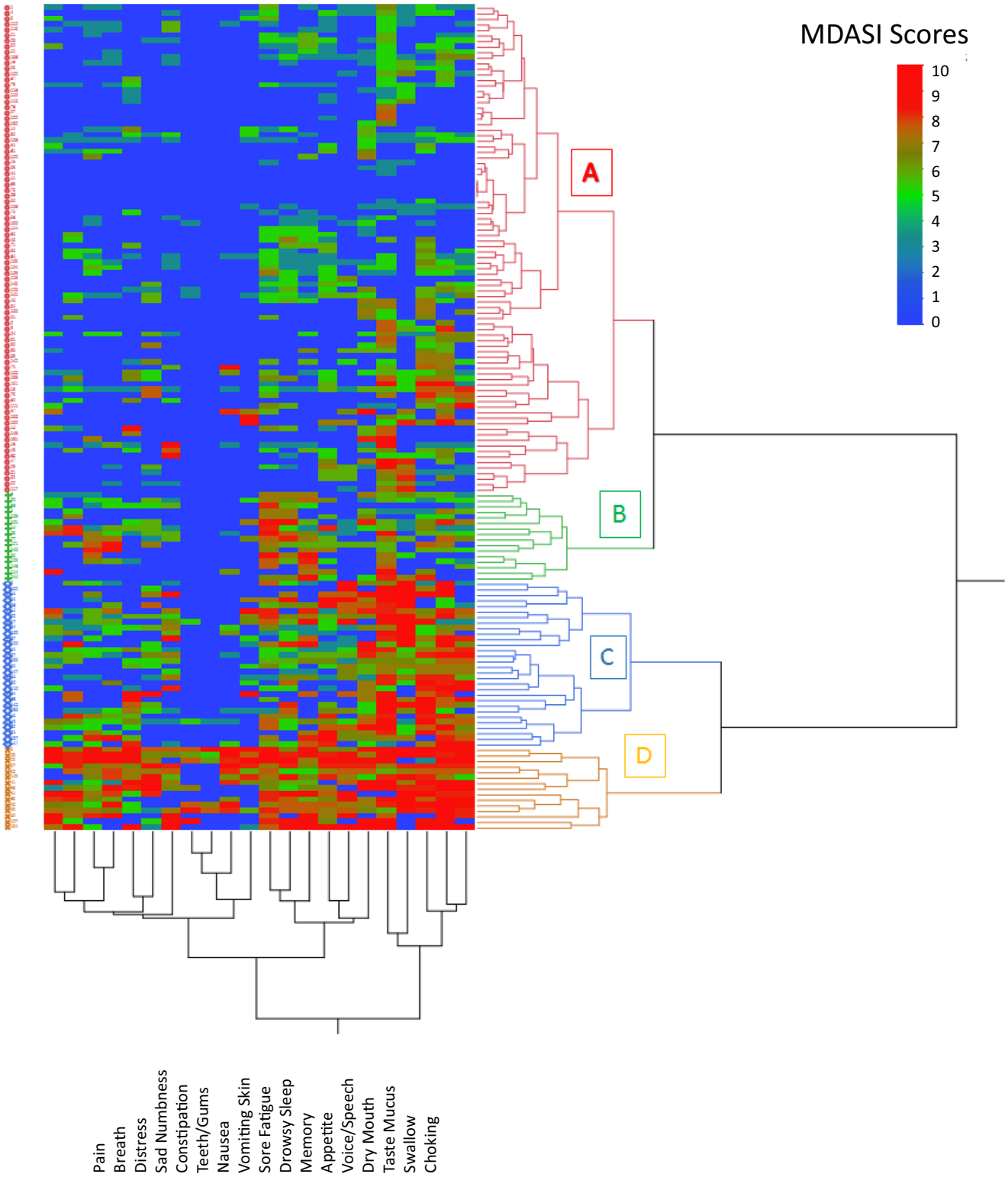




d

PSS-HN Score	FOIS score							Total
	1	2	3	4	5	6	7	
100-80	0	0	0	0	0	65	43	108
79-60	0	0	0	0	0	9	0	9
59-40	0	1	3	1	26	0	0	31
39-0	3	0	0	1	0	0	0	4

Fig. 2 **a** PSS-HN normalcy of diet subscale. **b** FOIS outcome summary. **c** Comparison of FOIS and PSS-HN dietary scales. **d** Number of patients in each group per FOIS and PSS-HN normalcy of diet subscale. Abbreviations: PSSHN the Performance Scale of Head and Neck Cancer, FOIS Functional Oral Intake Scale



severity were dry mouth, difficulty swallowing\chewing, and problems with mucus. Of the 12 systemic items, the three most severe items in order of decreasing severity were fatigue, sleep, and memory. The total mean of both local and systemic symptom severity items (22 items) was 1.74, representing low symptom burden among long-term survivors who participated in the survey study. For symptom interference, the three most severe items in order of decreasing severity were activity, work, and enjoyment. The total mean of symptom interference items (6 items) was 1.40. The percentage of patients experiencing each level of symptom severity reported as mild, moderate, or severe is shown in Fig. 1 and Supplementary Table 2. Overall, the

◀ **Fig. 3** Heat map representing the symptom burden of 22 individual MDASI-HN symptom items, for each individual patient, and grouped by hierarchal cluster analysis of patients with dendrogram. The *X*-axis represents symptom clusters, and the *Y*-axis represents the patients' grouping. Solid red squares denote high MDASI-HN scores (high symptom burden), while solid blue squares indicate low MDASI-HN scores. Four patient clusters labeled A, B, C, and D and four symptom clusters have been categorized; 1st cluster includes choking, swallow, mucous, taste, and dry mouth; 2nd includes voice, appetite, sleep, drowsy, and fatigue; 3rd includes oral sores, skin, vomiting, nausea, constipation, and numbness, and 4th includes teeth, sad, breath, distress, and pain. Groups A, B, C, and D include 88(55%), 16(10%), 30(19%) and 15(9%) patients, respectively. The dendrogram, on the *X*-axis, illustrates the clustering of various symptoms and shows the relative distances between clusters, i.e., those items that join with others earlier within small relative distance scale were rated by patients more similarly and could be interrelated. For example, the symptoms choking, swallow, mucous, taste, and dry mouth joined together quickly, indicating that patients perceived and rated these symptoms similarly. Of note, the red squares are more abundant and represent the severity of 1st symptom cluster which is centered around and represents oral morbidity symptoms across patient groups D, C, B, and A in order. Abbreviations: MDASI-HN MD Anderson Symptom Inventory-Head and Neck

majority of patients reported mild symptom severity for all 28 symptom and interference items included in the MDASI-HN questionnaire.

PSS-HN

The average time from the end of treatment to completion of PSS-HN was 43 months (range 6–197 months). The distribution of diet ratings and median for the normalcy of diet subscale is noted in Fig. 2. Twenty-eight percent were eating a regular, unrestricted diet, 42% required liquid assistance to wash down solid foods, and 28% were eating a restricted diet. Complete feeding tube dependence was rare (2%).

FOIS

FOIS distribution of diet ratings is noted in Fig. 2. Twenty-eight percent had a total oral diet with no restrictions, 67% had a total oral diet with restrictions, and 3% were tube dependent with some oral intake. As expected, the FOIS scale and the PSS-HN normalcy of diet scale were highly correlated (Spearman's rho = 0.9760, $p < 0.001$). The distribution of patients, per FOIS and diet score of PSS-HN, is shown in Fig. 2.

Cluster analysis (symptoms)

Hierarchical cluster analysis results are presented in Fig. 3, categorizing the patients into four district groups. In general, group D

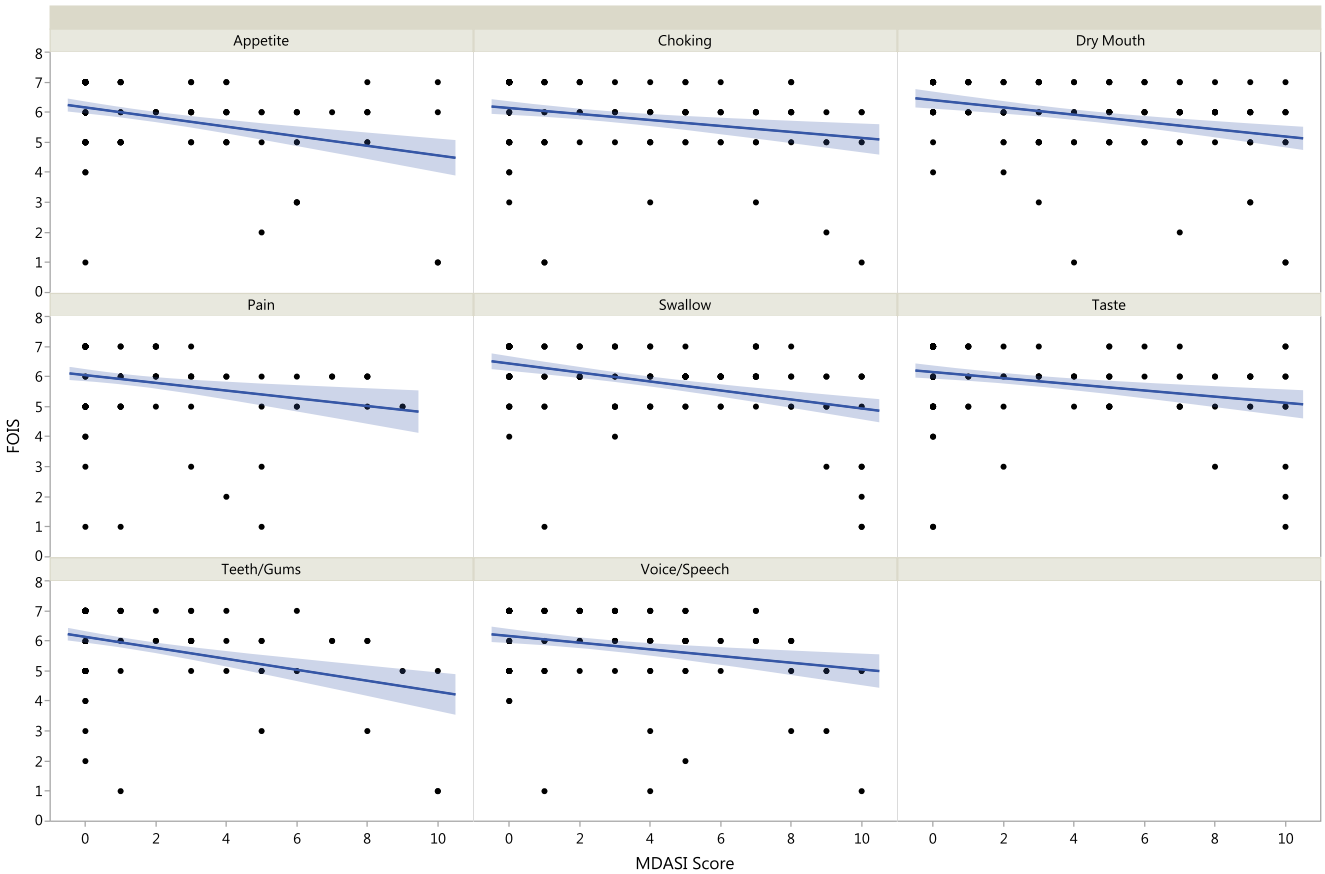


Fig. 4 MDASI-HN symptom items with significant correlations to FOIS dietary scale. Abbreviations: FOIS Functional Oral Intake Scale, MDASI-HN MD Anderson Symptom Inventory-Head and Neck questionnaire

and group A experienced the highest and lowest symptom burden, respectively. The dendrogram, on the *X*-axis, illustrates the clustering of various symptoms and shows the relative distance between the clusters. Those symptoms that join with others were rated by patients more similarly. For example, the symptoms choking, swallow, mucous, taste, and dry mouth joined together quickly, indicating that patients perceived and rated these symptoms similarly. Groups C and D had poor oral intake per FOIS, with mean scores of 4.8 and 5.7, respectively. The other two groups (A and B) had near normal intake with mean FOIS score of 6.12 ± 0.9 compared to groups C and D ($p < 0.01$). Groups C and D had 30 (20%) and 15 (10%) patients with a median age of 60 and 63 years, respectively. In group C, difficulty swallowing/chewing, dry mouth, problems with tasting food, and problems with mucus represent the highest symptom burdens, per MDASI-HN. Difficulty swallowing\chewing, problems with mucus, choking/coughing, and dry mouth were the highest MDASI-HN scores in group D, similar to group C with dysphagia and salivary symptoms but not experiencing high dysgeusia symptoms. In groups C and D, 50% and 33% patients received concurrent chemotherapy (CCRT), while 27% and 40% had combined induction (IC) + CCRT, respectively; additionally, 80 and 67% presented with the nodal positive disease. The patient groups with poor oral intake (groups D and C) shared the same symptom profile/severity and the oral morbidity symptoms clustered together. This finding suggests a link between the symptom cluster grouping and oral intake status and at the same time suggests interrelated oral morbidity symptoms found within the same cluster.

Correlation of clinical characteristics with oral intake

Advanced T-category (i.e., T3–4) ($p = 0.0004$), presentation with positive lymph nodes ($p = 0.0001$), location of primary site (oropharynx rather than larynx or nasopharynx) ($p = 0.0005$), and intensified treatment modalities (IC ± CCRT) ($p = 0.007$) were significantly associated with poor oral intake, per FOIS, while age ($p = 0.649$), gender ($p = 0.177$), and surgery ($p = 0.591$) failed to demonstrate an association with oral intake status. Larger T stage and intensified treatment maintained significantly associated with poor oral intake in the multivariate analysis ($p = 0.0089$ and 0.004, respectively).

Correlation of MDASI-HN symptom items with oral intake

On bivariate analysis, significant correlations, after Bonferroni correction for multiple comparisons, were identified between eight MDASI-HN patient-reported symptom items and the FOIS clinician-graded dietary scale ratings as shown in Table 2 and Fig. 4. Multivariate models found severity of difficulty swallowing/chewing and problems with gums/teeth were independently associated with poor oral intake as measured by FOIS. Sensitivity analysis examining symptom severity and oral intake as measured by PSS-HN found similar relationships, Supplementary Fig. 1.

Discussion

The current study is a part of a continued interdisciplinary effort at MD Anderson Cancer Center to simultaneously improve survival and functional outcomes in HNC survivors. In the scenario in which disease control and organ preservation can be achieved, maintaining optimal function becomes the ultimate endpoint of HNC treatment. Thus, we aim to involve patients in clinical decisions and rehabilitation strategies by integrating symptom reporting into clinical care. This requires understanding of the functional relevance of various symptom items. In a sample of 123 HNC survivors, we identified the functional relevance of self-reported severity of swallowing and oral morbidity symptoms to impaired oral intake in long-term survivorship. On univariate analysis, symptom severity for difficulty swallowing and oral-related morbidities, diminished appetite, dry mouth, problems with teeth/gums, choking, voice/speech changes, diminished appetite, and pain were correlated with poor oral intake. While many symptoms significantly correlated with oral intake on univariate analysis, swallowing impairment and injured gums/missing teeth were identified as independent drivers for poor oral intake per FOIS among long-term HNC survivors in multivariate analysis.

Oral intake profiles during the survivorship period have been previously studied. However, the multisymptom focus of this work represents a departure from the previously reported single symptom focus. The long-term promise of this work is that multisymptom tracking may help clinicians and patients to develop more standardized, proactive toxicity management paradigms that accelerate the recovery of oral intake during the surveillance period after RT. By considering the functional impact of multiple symptoms acting in clusters, our approach represents a departure from the status quo of single symptom methodology that does not align with the complexity of the clinical reality either during HNC treatment or the survivorship period.

Abnormal oral intake is a critical manifestation of unavoidable radiotherapy (RT) effects to mucosal, salivary, and soft tissue, previously published to persist in up to 33% of HNC survivors after RT. In long-term survivorship, restricted oral intake, avoidance of social eating, and weight loss have a detrimental influence on the QOL [18] and can also have a negative influence on survival [19]. Using standardized clinical tracking of oral intake, we identified only 28% of survivors reporting fully unrestricted oral intake (i.e., 72% with impaired oral intake) suggesting a potentially greater prevalence of this problem than previously published. Oral intake was also significantly associated with symptom severity. Thus, standardized tracking of oral intake-related symptoms in

HNC survivors may help to provide appropriate interventions to maintain the patient's health and improve QOL.

These data and others demonstrate that persistent dysphagia is one of the primary symptom drivers of impaired oral intake after RT in HNC survivors. For instance, in a cross-sectional study, at a median of 44 months, the severity of patient-reported dysphagia significantly correlated with greater oral intake restrictions ($r = 0.41$) [20]. Late dysphagia is mainly thought to impair the range of motion of swallowing structures either by fibrosis [21] or neuropathy [22]. These results and others [23] also suggest that oral morbidities significantly influence restricted oral intake in long-term survivorship. Acute mucositis is commonly accepted as a functionally limiting toxicity. However, there is less known about functional relevance of long-term oral morbidities on oral intake.

The severity of oral symptoms (the MDASI-HN item "difficulty with my teeth/gums") was one of two symptoms that retained in the multivariate model for poor oral intake. This symptom item is rather non-specific, so it is not entirely clear what physical oral morbidity it reflects. Indeed, tooth loss, which could be related to these perceived symptoms as well as periodontal or mucosal oral toxicities that damage the gum [23], may significantly decrease functional mastication [24] and lead to deterioration of the efficiency of food absorption [25] and nutritional status. Patients with injured gums or missing teeth are often forced to modify their diet to include moist, soft foods to facilitate mastication and swallowing. A limitation of this study is the inability to specify the most functionally relevant oral morbidity.

A somewhat surprising outcome was that the severity of xerostomia symptoms did not significantly associate with oral intake in multivariate models. RT-induced xerostomia (RIX) has been associated with dysphagia, dysphonia, alterations in taste, and poor dental health [23, 26]. Additionally, RIX is commonly implicated as the source of altered intake in survivorship. Xerostomia leads to desiccated mucosal tissues and exacerbates thick mucus secretions. Salivary enzymes initiate the process of digestion of starches and fats during oral intake. When food enters the oral cavity, it is softened and lubricated by salivation and mastication, permitting the food bolus to be propelled easily into the oropharynx. While not an independent driver of oral intake in this model, results of the cluster analysis supported the common clinical observation that HNC patients have substantial individual differences in the severity of their treatment-related symptoms, and they could be grouped [27] as those with either high or low symptom severity based on the symptom cluster profiles [28]. Dry mouth symptoms retained in clusters associated with poor oral intake.

The limitations of the current study include those inherent to biases of a single-institution, cross-sectional study in a tertiary cancer hospital. Notable limitations include potential selection biases of our convenience sample of survivors with available data in existing databases, as well as lack of baseline data regarding symptom burden and nutrition status. Historically, prophylactic gastrostomy was often considered mandatory to maintain the nutritional status of patients during and after RT and to minimize treatment interruptions [29, 30]. Although beneficial for nutritional status, the use of gastrostomy tubes may have a negative impact on long-term swallowing recovery [30], prompting more frequent adoption of reactive feeding tube models in many practices. Simultaneously, many have also adopted proactive swallowing therapy [31] (i.e., "use it or lose it") models of service. These data support also the functional relevance of integrating dental services not only to oral health but also to oral intake. While not variables in the analysis, all patients were treated in a time in which a reactive feeding tube model as well as proactive speech pathology and dental oncology referrals were standard in HNC RT at the authors' institution. Finally, symptoms and functional outcomes are recognized as dose-dependent toxicities of RT in HNC. The probability of restricted oral intake depends on the dose delivered to the non-target irradiated normal structures, especially with the modern RT techniques [32] that allow radiation oncologists to meet normal tissue constraints without compromising the target coverage. While critical covariates, regional doses to normal structures were not available for covariate adjustment.

Conclusions

The current research effort aimed to identify the functional relevance of self-reported symptoms burden on the oral intake status of long-term HNC survivors. We hypothesized that multiple symptoms could share specific underlying dimensions and act as a cluster that could drive the functional outcomes of the cancer survivors. Our approach is aligned with the complexity of the clinical reality either during HNC treatment or the survivorship period. Our study showed that oral intake in HNC survivorship is a multidimensional issue and functional outcome that is impacted not only by dysphagia but also by dental symptoms. Symptom drivers of oral intake likely differ in acute survivorship. Nonetheless, these findings highlight the lack of specificity of oral intake as a dysphagia endpoint as well as the need for multidisciplinary supportive care to optimize oral intake in survivors.

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Author contributions All listed co-authors performed the following:

1. Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work
2. Drafting the work or revising it critically 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, MPB, AE—Drafted manuscript and 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

GBG, JSL, DIR, QS, TH, CDF—Co-investigators; direct patient care provision, direct toxicity assessment and clinical data collection; interpretation and analytic support

MPB, MK, AE—Data coordination, collection, curation, and analysis

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68:7–30
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017
3. Mason H, DeRubeis MB, Burke N, Shannon M, Karsies D, Wolf G et al (2016) Symptom management during and after treatment with concurrent chemoradiotherapy for oropharyngeal cancer: a review of the literature and areas for future research. World J Clin Oncol 7:220–226
4. Samim F, Epstein JB, Zumsteg ZS, Ho AS, Barasch A (2016) Oral and dental health in head and neck cancer survivors. Cancer Head Neck 1:14
5. Xiao C, Hanlon A, Zhang Q, Ang K, Rosenthal DI, Nguyen-Tan PF, Kim H, Movsas B, Bruner DW (2013) Symptom clusters in patients with head and neck cancer receiving concurrent chemoradiotherapy. Oral Oncol 49:360–366
6. Kubrak C, Olson K, Jha N, Jensen L, McCargar L, Seikaly H, Harris J, Scrimger R, Parliament M, Baracos VE (2010) Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. Head Neck 32:290–300
7. Pauloski BR, Rademaker AW, Logemann JA, Newman L, MacCracken E, Gaziano J, Stachowiak L (2006) Relationship between swallow motility disorders on videofluorography and oral intake in patients treated for head and neck cancer with radiotherapy with or without chemotherapy. Head Neck 28:1069–1076
8. Ganzer H, Touger-Decker R, Parrott JS, Murphy BA, Epstein JB, Huhmann MB (2013) Symptom burden in head and neck cancer: impact upon oral energy and protein intake. Support Care Cancer 21:495–503
9. Cacicedo J, Dal Pra A, Alongi F, Navarro A (2015) Impact of weight loss in patients with head and neck carcinoma undergoing radiotherapy: is it an underestimated phenomenon? A radiation oncologist's perspective. Eur J Clin Nutr 69:757–760
10. Varkey P, Tang W-R, Tan N (2010) Nutrition in head and neck cancer patients. Semin Plast Surg 24:325–330
11. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME (2005) Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head Neck 27:659–668
12. Alshadwi A, Nadershah M, Carlson ER, Young LS, Burke PA, Daley BJ (2013) Nutritional considerations for head and neck cancer patients: a review of the literature. J Oral Maxillofac Surg 71:1853–1860
13. Crary MA, Mann GDC, Groher ME (2005) Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil 86:1516–1520
14. Righini CA, Timi N, Junet P, Bertolo A, Reyt E, Atallah I (2013) Assessment of nutritional status at the time of diagnosis in patients treated for head and neck cancer. Eur Ann Otorhinolaryngol Head Neck Dis 130:8–14
15. Newman LA, Vieira F, Schwiezer V, Samant S, Murry T, Woodson G, Kumar P, Robbins KT (1998) Eating and weight changes following chemoradiation therapy for advanced head and neck cancer. Arch Otolaryngol Head Neck Surg 124:589–592
16. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC (2000) Assessing symptom distress in cancer patients. Cancer 89:1634–1646
17. List MA, Ritter-Sterr C, Lansky SB (1990) A performance status scale for head and neck cancer patients. Cancer 66:564–569
18. Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL (2011) Malnutrition and quality of life in patients treated for oral or oropharyngeal cancer. Head Neck 33:490–496
19. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME (2005) Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head Neck 27:659–668
20. van den Berg MGA, Rütten H, Rasmussen-Conrad EL, Knuijt S, Takes RP, van Herpen CML, Wanten GJA, Kaanders JHAM, Merkx MAW (2014) Nutritional status, food intake, and dysphagia in long-term survivors with head and neck cancer treated with chemoradiotherapy: a cross-sectional study. Head Neck 36:60–65

21. Martin M, Lefaix J, Delanian S (2000) TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? Int J Radiat Oncol Biol Phys 47:277–290
22. Awan MJ, Mohamed ASR, Lewin JS, Baron CA, Gunn GB, Rosenthal DI, Holsinger FC, Schwartz DL, Fuller CD, Hutcheson KA (2014) Late radiation-associated dysphagia (Late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol 50:746–752
23. Beumer J 3rd, Curtis T, Harrison RE (1979) Radiation therapy of the oral cavity: sequelae and management. part 1 Head Neck Surg 1:301–312
24. Kimura Y, Ogawa H, Yoshihara A, Yamaga T, Takiguchi T, Wada T, Sakamoto R, Ishimoto Y, Fukutomi E, Chen W, Fujisawa M, Okumiya K, Otsuka K, Miyazaki H, Matsubayashi K (2013) Evaluation of chewing ability and its relationship with activities of daily living, depression, cognitive status and food intake in the community-dwelling elderly. Geriatr Gerontol Int 13:718–725
25. Ranawana V, Clegg ME, Shafat A, Henry CJ (2011) Postmastication digestion factors influence glycemic variability in humans. Nutr Res 31:452–459
26. Bjordal K, Ahlner-Elmqvist M, Hammerlid E, Boysen M, Evensen JF, Biorklund A et al (2001) A prospective study of quality of life in head and neck cancer patients. Part II: longitudinal data. Laryngoscope 111:1440–1452
27. Shi Q, Mendoza TR, Gunn GB, Wang XS, Rosenthal DI, Cleeland CS (2013) Using group-based trajectory modeling to examine heterogeneity of symptom burden in patients with head and neck cancer undergoing aggressive non-surgical therapy. Qual Life Res 22: 2331–2339
28. Rosenthal DI, Mendoza T, Cleeland C (2009) Identifying head and neck cancer patients at risk for high symptom burden during treatment. J Clin Oncol 27:15_suppl, 6066
29. Beaver ME, Matheny KE, Roberts DB, Myers JN (2001) Predictors of weight loss during radiation therapy. Otolaryngol Head Neck Surg 125:645–648
30. Mick R, Vokes EE, Weichselbaum RR, Panje WR (1991) Prognostic factors in advanced head and neck cancer patients undergoing multimodality therapy. Otolaryngol Head Neck Surg 105: 62–73
31. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS (2008) Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope 118:39–43
32. MD Anderson Head and Neck Cancer Symptom Working Group (2016) Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. Radiother Oncol 118:304–314