Title

Association between external and internal lymphoedema and chronic dysphagia following head and neck cancer treatment

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Abstract

Background: To examine the relationship between chronic external and internal head and neck lymphoedema (HNL) and swallowing function in patients following head and neck cancer (HNC) treatment.

Methods: Seventy-nine participants, 1-3 years post treatment were assessed for external HNL using the MD Anderson Cancer Centre Lymphoedema Rating Scale, and internal HNL using Patterson's Radiotherapy Oedema Rating Scale. Swallowing was assessed via instrumental, clinical and patient-reported outcome measures.

Results: HNL presented as internal only (68%), combined external/internal (29%), and external only (1%). Laryngeal penetration/aspiration was confirmed in 20%. Stepwise multivariable regression models, that accounted for primary site, revealed that a higher severity of external HNL and internal HNL was associated with more severe penetration/aspiration ($p<0.004$ and $p=0.006$ respectively), diet modification ($p<0.001$ both), and poorer patient-reported outcomes ($p=0.037$ and $p=0.014$ respectively).

Conclusion: Increased swallowing issues can be expected in patients presenting with more severe external HNL and/or internal HNL following HNC treatment.

Keywords

Head and neck cancer, radiotherapy, lymphoedema, dysphagia, aspiration

Introduction

Dysphagia is a common and often debilitating sequela of head and neck cancer (HNC) and its management [1]. The extent to which patients experience dysphagia is largely dependent upon the size and location of the tumour, the modality and intensity of the treatment, and the nature of any surgical reconstruction [2, 3]. Dysphagia is known to occur in the acute phases of treatment and can often be attributed to radiation-induced toxicities, such as xerostomia, mucositis, pain and loss of taste and sensation [4, 5]. Three months post treatment, many of these acute toxicities have largely resolved and some patients, over the subsequent months, slowly experience a return to their baseline swallow function [4]. However, other patients may see little or no recovery in their swallow function, with a recent population-based study demonstrating that up to 45% of patients are impacted by chronic dysphagia two years post treatment [6]; whilst a recent longitudinal study showed that up to 50% of patients continued to experience dysphagia three years post treatment [5]. These chronic presentations have historically been attributed to fibrosis and radiation-induced neuropathy [7]. More recently though, emerging evidence has highlighted a potential association between chronic dysphagia and the presence of head and neck lymphoedema (HNL) [8, 9].

HNL is the atypical swelling and accumulation of protein rich fluid within the interstitial spaces, and occurs when lymph fails to drain through the lymphatic vessels or when the lymphatic load exceeds the transport capacity of the lymphatic system [10, 11]. HNL may result from the obstruction of the lymphatic vessels, caused by the presence of tumour bulk, post-operative scar adhesions, or radiation induced fibrosis; or from the direct removal or damage of the lymphatic structures through surgery or radiotherapy [10, 12]. Up to 90% of patients with HNC may experience some form of HNL post treatment [13]. It is well known that HNL may develop externally, on the soft tissues of the face and neck [13, 14], and recent literature has also highlighted that HNL may occur internally, within the oral cavity, pharynx and larynx [13, 14].

HNL that occurs internally has the potential to cause significant thickening and stiffness of the oral, pharyngeal and laryngeal structures. Some authors have speculated that these changes may negatively impact upon the range of movement, contractibility and overall functioning of these important structures [9, 10, 15, 16], and this has led many to consider the potential impact of HNL on swallow function. Jackson et al. [9] showed that HNL that was evident at a number of specific internal sites, such as the epiglottis, arytenoids, and pyriform sinus, was more likely to result in laryngeal penetration and aspiration, and changes in functional diet status. They postulated that the presence of more severe and widespread HNL was more likely to be associated with increasing dysphagia as swallowing compensations may not be possible when one or a number of internal sites are severely compromised. More severe HNL has also been associated with increased self-reported dysphagia, as measured by the Vanderbilt Head and Neck Symptom Survey (VHNSS) [8, 9]. A number of qualitative studies have also shown that patients often perceive a link between their HNL and swallow function [16-18]. One study reported that 11 of 12 participants with long-term HNL felt that that their HNL had altered their swallow function in some way [18]. Participants described feelings of tightness and swelling within their pharynx that had various impacts on swallowing, including negative effects on bolus flow with solid foods.

These preliminary studies have begun to establish an association between the presence of HNL and dysphagia. Chronic dysphagia has the potential to cause significant negative effects on physical function, such as enteral feeding dependence, malnutrition, and an increased risk of hospital admission [19-21], whilst also being one of the most important adverse factors affecting both patient and carer quality of life [19, 22, 23]. It is therefore important that there is a greater understanding of the factors that contribute to chronic dysphagia following HNC treatment. The primary aim of this study was therefore to examine the relationship between chronic external HNL and internal HNL and swallowing function in patients who have undergone definitive radiotherapy (RT), postoperative radiotherapy (PORT), or chemo-radiotherapy (CRT) for HNC. More specifically, it aimed to explore the associations between chronic external HNL and internal HNL and the presence of dysphagia, penetration-aspiration status, functional diet status and patient-reported swallowing outcomes.

Material and Methods

This study utilised a cross sectional study design. Approval was obtained from Hunter New England Human Research Ethics Committee (15/02/18/4.07), University of Queensland Medical Research Ethics Committee (2015000362), and Calvary Mater Newcastle Research Governance Unit (SSA/15/HNE/45). Consent was obtained from all participants.

Participants

Participants were prospectively recruited through the Radiation Oncology Clinic at the Calvary Mater Hospital Newcastle, Australia (1 June 2015 – 12 April 2019). Eligibility included: (1) a diagnosis of oral, nasopharyngeal, oropharyngeal, laryngeal or hypopharyngeal cancer; (2) treatment with curative intent using either RT, PORT, or CRT; and (3) were between one and three years post treatment. Participants were excluded if they were: (1) treated with palliative intent; (2) had experienced cancer recurrence within the head and neck region; (3) had undergone any surgical or laser resection involving the supraglottic or glottic larynx due to its direct impact on airway protection; (4) had pre-existing comorbidity conditions that may result in HNL (e.g., trauma), or impact swallowing, voice or speech function (e.g., neurological injury or insult); or (5) were unable to provide informed consent.

Assessment of Head and Neck Lymphoedema

Participants attended a single assessment visit. External HNL was assessed via head and neck examination and graded using the MD Anderson Cancer Centre (MDACC) Lymphoedema Rating Scale [11]. This is a five-point staging scale based on the International Society of Lymphology Rating Scale [24], where 0 was classified as normal, 1a mild, 1b moderate, 2 severe, and 3 profound external HNL. The location of the participants' external HNL was also noted. Ratings were conducted by the primary investigator (CJ) who was trained in external HNL assessment by two specialist clinicians. As the MDACC Lymphoedema Rating Scale is widely accepted as a valid means of grading external HNL in the HNC population [25], no assessment of reliability was undertaken.

Internal HNL was assessed via transnasal laryngoscopy. This procedure was performed by the participant's treating radiation oncologist and was video-recorded for subsequent rating. Patterson's Radiotherapy Oedema Rating Scale [26] was used to rate the presence, location and severity of internal HNL. The scale includes assessment of 11 laryngopharyngeal structures and two spaces; and uses ratings of normal, mild, moderate or severe to rate the severity of lymphoedema at each structure or space. The scale has demonstrated moderate agreement for inter-rater reliability and very good agreement for intra-rater reliability [26]; although, reliability of individual structures and spaces was more varied. To assist with rating determinations in this study, the following was considered: (1) the presence of structural swelling, thickness or bulkiness; (2) obvious abnormalities in structural shape or loss of anatomical boundaries; (3) structural asymmetry; and (4) mucosa that has a pearl like appearance which may indicate fluid retention.

In addition to the individual assessment ratings of the 11 laryngopharyngeal structures and two spaces, two additional internal HNL summary variables were generated. Firstly, to aide comparison of internal HNL ratings with those of prior studies [8, 9], the maximum rating obtained across the 13 internal sites was used to generate a 'maximum severity score.' That is, if any one structure or space was rated as severe, then the maximum severity score was severe. The second variable to be generated, the 'number of internal sites affected by HNL' was novel and simply counted the number of internal sites identified as having HNL. For example, if three structures and one space were identified as having some degree of HNL, then the number of internal sites affected by HNL would be 4.

Each participant's video-recording was rated by the primary investigator (CJ), who is a practicing speech pathologist. Twenty percent of the recordings were also re-rated by the primary investigator at least three months after the initial rating, and a second speech pathologist to assess intra and inter-rater reliability. The second speech pathologist was blinded to the participant's details and any ratings previously given. The primary investigator was unable to be blinded as she was present for data collection.

Assessment of Swallowing: Penetration-Aspiration, Functional Oral Intake and Patient Reported Outcomes

Swallowing was assessed via instrumental, clinical and patient reported outcome measures. The primary investigator (CJ), a speech pathologist with more than five years clinical experience with head and neck cancer patients, conducted all assessments.

The instrumental assessment was undertaken via fiberoptic endoscopic evaluation of swallowing (FEES), and determined laryngeal penetration and aspiration risk. Participants were observed swallowing two mouthfuls of water, dyed with blue food colouring to optimise visualisation. The size of the mouthfuls were determined by the participant. The Penetration-Aspiration Scale (PAS) [27] was used to describe laryngeal penetration and aspiration events on the worse of the two swallows. The PAS is a validated scale and the score is determined by the depth of material entry into the airway, the patient's response, and whether the material is ejected from the airway. Scores of 1 and 2, indicating that material does not enter the airway or material enters the airway, remains above the true vocal folds and is ejected, were considered normal. Scores of 3 to 8 were considered dysfunctional [28].Twenty percent of the FEES recordings were again re-rated by the primary investigator (CJ) at least three months after the initial rating, and a second speech pathologist to assess intra and inter-rater reliability. The second speech pathologist was blinded to the participant's details and any ratings previously given. The primary investigator was unable to be blinded as she was present for data collection.

The clinical swallowing examination followed a purpose-built assessment protocol that included a diet history, oral musculature and cranial nerve examination, and food and fluid trials. Participants were given three sips of thin fluid, three teaspoons of puree fruit, three teaspoons of soft diced fruit, and three bites of a hard biscuit. This protocol was modified and safe swallowing strategies, such as a fluid wash or instructed cough, were introduced as required for patient comfort and safety. From the clinical assessment observations, the Mann Assessment of Swallowing Ability – Cancer (MASA-C) [29] was used to grade oral musculature, cranial nerve and clinical swallowing ability. The MASA-C has demonstrated strong sensitivity, specificity, and positive predictive value for the identification of dysphagia in the HNC population [29]. It allows a maximum score of 200 which indicates swallowing within normal limits; while a score of 185 or less indicates the presence of dysphagia. The Functional Oral Intake Scale (FOIS) [30] was also used to grade functional diet status, as determined during clinical assessment. The FOIS is a valid and reliable scale that separates diet status into two broad categories: tube dependency (FOIS levels 1-3) and total oral diet (FOIS levels 4-7). Further classifications are made based on the number of diet consistencies tolerated, and the need for special preparations or compensations. A score of 7 indicates a total oral diet with no restrictions; while a score of 1 indicates nothing by mouth.

Finally, the VHNSS (v2.0) Plus General Symptom Scale [31] was given to participants to independently complete and return. The VHNSS is a valid and reliable questionnaire that includes 61-items and examines self-perceived symptom burden. Questions from four symptom subscales, the *swallow general* (questions 5-13), *swallow solids* (questions 5, 7, 8 and 10), *swallow liquids* (questions 6 and 9), and *nutrition* (questions 1-4) were summed, as per prior research [31], and used to determine patient perceptions of swallowing ability and nutritional status. Participants respond to each VHNSS question using a Likert scale, where a score of 0 indicates no symptoms and 10 indicates severe symptoms. As previously done [31], scores of 1-3 were collapsed and classified as mild, 4-6 moderate, and 7-10 severe.

Statistical Methods

Data was entered into the statistical software package Stata 15 [32]. Data validation and cleaning procedures were undertaken prior to analysis. Descriptive statistics were used to describe the cohort, including demographic, disease, treatment and HNL data, and to summarise the instrumental, clinical and patient-reported swallowing outcomes.

Cohen's kappa coefficient, with linear weights (*Kw*) [33], was used to assess the intra and inter-rater reliability of those items re-rated in the 20% subsample (i.e. internal HNL and PAS). The strength of agreement was classified as 0 – 0.20 slight, 0.21 – 0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1 almost perfect [34].

Stepwise multivariable regression models were used to examine associations between the six swallowing outcome variables (i.e. PAS classification of normal or disordered, FOIS score, MASA-C score, and the three VHNSS subscale scores – *swallow solids*, *swallow liquids*, and *nutrition*) and (a) the severity of external HNL, and (b) all of the internal HNL measures (i.e. maximum severity of internal HNL, number of internal sites affected, and the severity of internal HNL at the 11 individual structures and two spaces). A model was fit for each swallowing outcome and HNL variable (i.e. 6 x 16 models). Linear regression models were used to examine the relationships between the HNL variables and the FOIS, MASA-C, and VHNSS subscale scores. Linear models estimate the average FOIS, MASA-C and VHNSS scores and determine the effect of the HNL variables, whilst also accounting for the effects of other significant variables. Primary site, tumour stage, nodal stage and treatment modality were all checked for significance. Logistic regression models were used examine the relationships between the HNL variables and PAS scores, since 80% (n = 63) of participants had a normal PAS score (i.e. scores 1-2). The PAS score was recoded to normal (0; PAS scores 1-2) vs. dysfunctional (1; PAS scores 3-8). Logistic models estimate the probability of a dysfunctional PAS score and determine the effect of the HNL variables, whilst also accounting for the effects of other significant variables. Again, primary site, tumour stage, nodal stage and treatment modality were all checked for significance. Significance was set at $p < 0.05$.

Results

One hundred eighty-four patients were available for recruitment during the study period. Fifty-four declined participation and 51 failed to meet the study criteria. The final cohort contained 79 participants who were predominately male and under 65 years of age (Table 1). The vast majority presented with early-stage oropharyngeal tumours, had HPV-mediated disease, and were treated with CRT. Notably, all participants with oral tumours were treated with PORT, whilst those with tumours at other sites received either RT or CRT. At the time of the study, participants were an average of 17.3 months post treatment (SD = 6.6, range 11.6 – 43.6).

[Insert Table 1 near here]

Intra and Inter-Rater Reliability

The intra-rater reliability of the 13 internal HNL sites was, on average, substantial (*Kw* = 0.72). The sites with the highest agreement (almost perfect) were the true vocal folds, epiglottis and posterior pharyngeal wall (*Kw* = 1, 0.87, 0.86 respectively). The sites with the lowest agreement (moderate) were the valleculae, false vocal folds and anterior commissure (*Kw* = 0.48, 0.55, 0.57 respectively). The intra-rater for PAS was perfect (*Kw* = 1).

Inter-rater reliability for scoring of the 13 internal HNL sites was, on average, fair (*Kw* = 0.28). The sites with the highest agreement (moderate) were the epiglottis, pharyngoepiglottic folds and cricopharyngeal prominence (*Kw* = 0.44, 0.43, 0.42 respectively). The sites with the lowest agreement (slight) were the valleculae, base of tongue and true vocal folds (*Kw* = 0.04, 0.06, 0.15 respectively). The inter-rater reliability for PAS was substantial (*Kw* = 0.73).

Head and Neck Lymphoedema Outcomes: External and Internal

Almost all (99%, n = 78) participants presented with some form of HNL. The majority, 68% (n = 54) had internal HNL only, 29% (n = 23) had combined external and internal HNL, and 1% (n = 1) had external HNL only. External HNL most frequently involved the submental region (28%, n = 22), followed by the neck (11%, n = 9) (Table 2). External HNL was considered moderate or severe in 13% (n = 10) of participants. Of the ten participants who had moderate or severe external HNL, eight also had severe internal HNL (maximum severity score).

[Insert Table 2 near here]

Internal HNL most frequently involved the arytenoids (92%, n = 73), followed by the epiglottis (84%, n = 66), pharyngoepiglottic folds (76%, n = 60), and aryepiglottic folds (76%, n = 60) (Table 3). The sites most frequently rated as severe were the epiglottis (18%, n = 14) and pharyngoepiglottic folds (14%, n = 11). Regarding the maximum severity score, 65% (n = 51) of participants had at least one internal site that was rated as moderate or severe. Regarding the number of internal sites affected, 56% (n = 44) had some degree of HNL that involved eight or more of the 13 internal sites (range 0-13). Of note, 27% (n = 21) had previously undergone some form of external HNL therapy.

[Insert Table 3 near here]

Swallowing Outcomes: Penetration-Aspiration, Functional Oral Intake and Patient Reported Outcome Measures

During the FEES assessment, the majority (80%, n = 63) demonstrated normal PAS scores (i.e. scores 1-2). The remaining (20%, n = 16) had PAS scores of 3-8 (3 = 5%, 4 = 7%, 5 = 5%, 6 = 1%, 7 = 1%, 8 = 1%), indicating some degree of laryngeal penetration and/or aspiration. More than 50% of the penetration-aspiration events occurred after the completion of the swallow, and these events were deemed to be largely the result of residual overflow.

Sixty-seven percent (n = 53) of participants scored 185 or less on the MASA-C, which suggests the presence of dysphagia. All participants were tolerating a total oral diet; although, the majority (76%, n = 60) still required some form of diet modification (FOIS scores 4-6). Thirty-nine percent (n = 31) were able to tolerate multiple food consistencies without special preparation, but had specific food limitations (FOIS score 6); 32% (n = 25) were able to tolerate multiple food consistencies, but required special preparation or compensations (FOIS score 5); and 5% (n = 4) were only able to tolerate a single food consistency (FOIS score 4).

Seventy-one (of the total 79) participants returned the VHNSS questionnaire. The *swallow general*, *swallow solids*, and *swallow liquids* subscales on the VHNSS revealed that 89% (n = 70) of participants felt they had some form of ongoing difficulty swallowing or eating; whilst 56% (n = 44) of participants felt they had some ongoing issues with weight maintenance or appetite. The presence and severity of individual symptoms are reported in Table 4.

[Insert Table 4 near here]

Associations between External Head and Neck Lymphoedema, Internal Head and Neck Lymphoedema and Swallowing Outcomes

Penetration-Aspiration

Logistic regression models were fit with the PAS score (i.e. normal vs. disordered) as the response variable and a HNL variable as the explanatory. A significant positive relationship was found between disordered PAS scores and external HNL ($p < 0.004$) (Table 5, column 1). Significant positive relationships were also found between disordered PAS scores and the maximum severity of internal HNL ($p = 0.006$) and the total number of internal sites affected by HNL ($p = 0.005$). These results indicate that participants with a higher severity of external HNL, internal HNL, and those with HNL at a high number of internal sites were more likely to experience laryngeal penetration and/or aspiration. Eight of the 13 internal sites, when tested independently, were also significant (Table 5, column 1). The anterior commissure was the strongest predictor ($\beta = 1.62$, $p < 0.001$) of all of the internal sites for penetration-aspiration status.

[Insert Table 5 near here]

Functional Oral Intake

Linear regression models were fit with the FOIS score as the response variable and a HNL variable as the explanatory. Primary site was seen to have a significant effect on FOIS scores, and participants with oral tumours had lower (or worse) scores than participants with tumours at other sites. The 15 internal HNL models required adjustment for this effect.

A significant negative relationship was found between FOIS scores and external HNL ($p < 0.001$) (Table 5, column 2). Significant negative relationships were also found between the maximum severity of internal HNL ($p < 0.001$, Figure 1) and the total number of internal sites affected by HNL ($p = 0.001$). These results signify that participants with a higher severity of external HNL, internal HNL, and those with HNL at a high number of internal sites required increased diet modification. Ten of the 13 internal sites, when tested independently, were also significant (Table 5, column 2). The valleculae was the strongest predictor ($\beta = -0.48$, $p < 0.001$) of all of the internal sites for functional diet status. Of note, the pharyngoepiglottic folds, aryepiglottic folds, interarytenoid space, arytenoids and valleculae were highly significant for both penetration-aspiration and functional diet status.

[Insert Figure 1 near here]

Similar modelling was performed on MASA-C scores and the results were broadly similar to those found for the FOIS scores (Table 5, column 3). The R^2 values were notably higher than those in the FOIS models because the presence of an oral tumour accounted for more variability of MASA-C then it did for FOIS.

Patient Reported Outcomes (VHNSS Subscales)

Of the four VHNSS symptom subscales, the *swallow general* and *swallow solids* subscales were highly significantly correlated (r = 0.97). Therefore only the *swallow solids, swallow liquids, and nutrition* subscales will be further discussed. Linear regression models were fit with the VHNSS *swallow solids* score as the response variable and a HNL variable as the explanatory. Primary site was seen to have a significant effect on VHNSS subscale scores, and participants with laryngeal tumours had lower (or better) scores than participants with tumours at other sites. All 16 models required adjustment for this effect.

A significant negative relationship was found between VHNSS *swallow solids* scores and external HNL (p = 0.037) (Table 6, column 1). A significant negative relationship was also found between VHNSS *swallow solids* scores and the maximum severity of internal HNL (p = 0.014). These results indicate that participants with a higher severity of external HNL and internal HNL had higher (or worse) levels of patient-reported symptom burden in relation to swallowing and eating solid foods. Contrary to the findings of swallowing outcomes on the PAS, FOIS and MASA-C scales, the total number of internal sites affected by HNL was not associated with *swallow solid* scores (p = 0.057). There was also little association found between the *swallow solid* scores and HNL that occurred at specific internal sites. Only three of the 13 internal sites, when tested independently, were significant (Table 6, column 1). No significant associations were found between any of the HNL variables and the *swallow liquids* or *nutrition* subscales (Table 6, columns 2 and 3).

[Insert Table 6 near here]

Discussion

This study adds to an emerging evidence base and supports the notion that in a surviving patient cohort between one and three years post HNC treatment, both external HNL and internal HNL are associated with the presence of dysphagia. A series of multivariable regression models were used to confirm that patients with a higher severity of external HNL and internal HNL had more severe dysphagia; and these findings were consistent regardless of whether dysphagia was identified via instrumental assessment, clinical measures, or patient reports. The results of the current study build upon our understanding of the factors contributing to chronic dysphagia symptoms in this patient population, and will ultimately assist with more informed patient education and management.

Specifically, the current study has highlighted that patients with a higher severity of external HNL and those with a higher severity and more diffuse internal HNL were more likely to experience laryngeal penetration and aspiration with thin fluids, and have higher levels of diet modification. These findings are consistent with the results presented by Jackson et al. [9], despite the use of differing outcome measures. Their study demonstrated that both external HNL (rated using the Foldi scale [35]) and internal HNL (rated using the Patterson's Radiotherapy Oedema Rating Scale [26]) were associated with the Dysphagia Outcome and Severity Scale (DOSS) [36] and the National Outcomes Measurement System (NOMS) [37], which were graded following instrumental and clinical swallowing assessments. Jackson et al. [9] also found that the overall severity of internal HNL (i.e. the maximum severity score) was also highly associated with swallowing outcomes, as was observed in the current study. However, slight differences were observed between the two studies regarding the specific internal sites most strongly associated with dysphagia. Jackson et al. [9] found the aryepiglottic folds, pharyngoepiglottic folds, epiglottis, and pyriform sinus were the most highly correlated with their dysphagia outcome measures. In the current study, these internal sites, among others, were identified as significant in the models, but their significance varied across the dysphagia outcome measures used in each regression model. This is likely simply explained by the differences in the two patient cohorts. The current study included patients with chronic HNL, who were between one and three years post treatment; whereas 42% of Jackson et al.'s [9] cohort were assessed less than 12 weeks post treatment. Given that HNL is known to be most prevalent three months post treatment and reach peak severity nine months post treatment [13], this may explain some of the differences found. Furthermore, the current studies cohort was more severe in terms of their internal HNL presentations, with 65% having an overall severity rating of moderate or severe, compared to only 23% in the Jackson et al. [9] study. Natural variability between patient cohorts will ultimately always influence the individual internal site results between studies. However, the consistent message from both of these studies is that patients who present with more severe external HNL and internal HNL, and those with HNL at multiple internal sites, will likely experience greater impacts to swallowing function.

The current study did not describe how internal HNL impacted swallowing leading up to penetration-aspiration risk, however it is logical to expect that patients with more severe and diffuse internal HNL may experience changes to swallowing safety. For example, the presence of more severe HNL in the vallecular space will significantly reduce its depth, and this may impair its capacity to act as a partial barrier to premature spillage. Similarly, more severe HNL in the pyriform sinus will also reduce the depth of these spaces and may impair their capacity to contain food or fluid boluses. More severe HNL at the aryepiglottic folds can also cause these structures to become so thick and bulky that they flatten out and limit the depth of the lateral channels, and this may add to the risk of the bolus entering the laryngeal vestibule and then the airway. Furthermore, more severe internal HNL may also impact the timing and efficiency of the movements of key airway protective structures, such as the epiglottis, arytenoids, and true and false vocal folds. Understanding the impact of internal HNL on swallowing function, and what specific presentations are more associated with penetration-aspiration risk, is an area that requires further systematic consideration.

The results of the current study also showed that patients with higher severities of external HNL and internal HNL were more likely to have higher levels of self-reported dysphagia with solid foods. Interestingly though, no significant associations were found between HNL and the subscales relating to swallowing fluids or nutrition. Again, these results are generally consistent with the findings of other studies. Jackson et al. [9] also found an association between internal HNL and self-reported dysphagia. Although, they found significant relationships across all three VHNSS subscales, and no relationship was confirmed with external HNL. Deng et al. [8] found a relationship between external HNL and self-reported dysphagia with the VHNSS *swallow general* subscale, but no relationship was confirmed with internal HNL. All of these studies have used the VHNSS to examine self-reported symptom burden in relation to swallowing and eating, therefore the fact that the current study found both external HNL and internal HNL to be associated with patient perceptions of swallowing solids may be again explained by simple variability in patient cohorts. As previously mentioned, Jackson et al. [9] and Deng et al. [8] included patients who were in the subacute phase of care, where a number of different radiation-induced toxicities, such as xerostomia, dysgeusia, appetite, and dentition, are having the most perceived impact on swallowing and oral intake [5]. In these earlier stages post treatment, contributors to swallowing dysfunction are therefore both numerous and widespread and it may be difficult for patients to determine the impact of HNL alone [38].

The results of the current study are also consistent with the findings of recent qualitative research; specifically in relation to the presence of more severe dysphagia when patients experience higher severities of external HNL and internal HNL, the need for increased diet modification, and more symptom burden when eating solid foods. Three qualitative studies have concluded that patients often perceive a link between the presence of HNL and swallowing function [16-18]. In one study [18], 11 of 12 patients felt that their HNL made it harder for them to swallow, and these patients spoke of having to modify their diets and use additional compensatory strategies during mealtimes. Patients also reported more difficulties with solid foods, rather than fluids. Two studies have also detailed how temporal changes in HNL corresponded to fluctuations in swallowing function [16, 18]; with HNL often being worse in the morning and making breakfast more difficult to swallow [16]. Many of the patients in these qualitative studies have attributed the changes in their swallow function to altered sensations caused by HNL, such as tightness, stiffness and the feeling of generalised swelling [17, 18].

The high prevalence of HNL within this patient cohort and its association with penetration-aspiration status, functional oral intake and patient-reported swallowing outcomes, further reinforces the need for speech pathology and medical teams to be aware of the association between external HNL and internal HNL and chronic dysphagia. Knowledge of this association is also of high clinical significance as lymphoedema is known to be a chronic inflammatory condition that may ultimately progress and further the development of fibrotic tissue [13, 39, 40]. Literature pertaining to the breast cancer population demonstrates a clear association between lymphoedema, fibrosis and poor function [12], and the same continuum needs to be considered for those patients treated for HNC. Fibrosis is also the leading cause of chronic dysphagia following HNC treatment [7], and dysphagia rehabilitation may not result in any significant functional gains once this process has been activated [41]. External HNL and internal HNL screening, diagnostic and treatment processes therefore need to be prioritised.

Future studies that investigate the threshold severity of external HNL and internal HNL on the severity of dysphagia are needed to further support clinical practice. Determining the radiotherapy dose thresholds in the development of severe HNL and subsequent dysphagia would also be a valuable addition to the literature. Finally, future studies are also needed to determine suitable and effective interventions to minimise the impact of HNL of swallowing outcomes.

Limitations

This study utilised a cross-sectional study design which only allowed HNL and swallowing function to be measured at one time-point. It is possible that the extent of the relationships observed between HNL and swallowing may differ depending on the time periods that patients are assessed post treatment; as highlighted by the differences between the current study and prior studies in this field. Further work with patient populations who are at different time periods post treatment may assist in exploring this further.

It is also acknowledged that the perceptual ratings scales used to measure HNL, particularly the internal HNL rating scale, have limitations. This is highlighted by the lower levels of inter-rater reliability in the current study. The opportunity for greater clinician training in this tool, such as via a training package that includes images of HNL at each internal site and at each severity level, would be beneficial to help enhance clinician reliability and consistency using this tool. Furthermore, an assessment of reliability for the external HNL ratings was also not undertaken in this study.

The limitations of the FEES procedure are acknowledged, and it is recognised that this may increase the risk of low validity. This study did not utilise any form of volumetric control with the water trials and due to clinical time constraints, participants were not trialled with any other food or fluid consistencies. The use of volumetric control in future studies would be beneficial to ensure that all participants complete the same swallowing task, and examining swallowing safety with food trials would be valuable given that external HNL and internal HNL were significantly associated with patient reported symptom burden with solid foods. This study also provided limited detail regarding the physiological events leading up to penetration-aspiration risk. It would be beneficial for future studies to complete a more comprehensive assessment of swallowing and specifically include measures of pharyngeal residue, again given the increased burden with solid foods in this study. Simultaneous FEES and videofluoroscopic assessments may also further our understanding of the specific impact that HNL that occurs at key internal sites has on swallowing physiology. Finally, it is acknowledged that the number of participants who were treated with definitive RT and PORT were low, and this may impact the generalizability of the results to a larger HNC population. However, the included treatment population is reflective of the clinical caseload at the study institution, where more patients are treated with CRT in the era of HPV-mediated disease. As further evidence emerges regarding which treatment modalities have the greatest potential to cause HNL, future work can be done with homogeneous treatment cohorts that refine our understanding of which populations are at greater risk of HNL and its potential impacts to swallowing.

Conclusions

Chronic external HNL and internal HNL are associated with instrumental, clinician and patient-reported measures of dysphagia. Patients who experienced higher severities of external HNL and internal HNL experienced more severe laryngeal penetration and/or aspiration, required increased diet modification, and self-reported more symptom burden in relation to eating solid foods. Further consideration needs to be given to how multidisciplinary teams screen, diagnose and provide ongoing treatment for external and internal HNL, particularly given its high prevalence within surviving HNC populations and its ability to progress and further the development of fibrosis.

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Table 1

Demographic, disease and treatment data

Characteristic	*Parameters*	*CRT* *n = 51* *% (n)*	*RT* *n = 14* *% (n)*	*PORT* *n = 14* *% (n)*	*Total* *n = 79* *% (n)*
Age (years)	Mean (SD)	61.2 (7.7)	71.9 (7.9)	65.0 (8.0)	63.7 (8.7)
Gender	Male	94 (48)	100 (14)	71 (10)	91 (72)
	Female	6 (3)	0	29 (4)	9 (7)
Primary site	Oral	0	0	100 (14)	18 (14)
	Nasopharyngeal	2 (1)	0	0	1 (1)
	Oropharyngeal	90 (46)	36 (5)	0	65 (51)
	Laryngeal	6 (3)	64 (9)	0	15 (12)
	Hypopharyngeal	2 (1)	0	0	1 (1)
T classification	T 1-2	63 (32)	93 (13)	64 (9)	68 (54)
	T 3-4	33 (17)	7 (1)	36 (5)	29 (23)
	T X	4 (2)	0	0	3 (2)
N classification	N 0	6 (3)	64 (9)	43 (6)	23 (18)
	N 1	6 (3)	7 (1)	43 (6)	13 (10)
	N 2-3	88 (45)	21 (3)	7 (1)	62 (49)
	N X	0	7 (1)	7 (1)	3 (2)
HPV status	Positive	80 (41)	29 (4)	7 (1)	58 (46)
	Negative	20 (10)	71 (10)	93 (13)	42 (33)
Radiation treatment	60Gy/30#	0	0	93 (13)	16 (13)
	70Gy/35#	90 (46)	50 (7)	0	67 (53)
	Other	10 (5)	50 (7)	7 (1)	16 (13)
Chemotherapy	Cisplatin	75 (38)	0	0	48 (38)
	Cetuximab	18 (9)	0	0	11 (9)
	Other	8 (4)	0	0	5 (4)
	None	0	100 (14)	100 (14)	35 (28)
Neck dissection	Unilateral	0	0	57 (8)	10 (8)
	Bilateral	0	0	21 (3)	4 (3)
	None	100 (51)	100 (14)	21 (3)	86 (68)
Time post treatment (months)	Mean (SD)	17.3 (6.7)	16.8 (5.6)	17.8 (7.5)	17.3 (6.6)

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy; PORT = postoperative radiotherapy; T = tumour; N = nodal; HPV = human papillomavirus; SD = standard deviation

Table 2

Location and severity of external HNL (n = 79)

External Site	*No visible oedema (0) % (n)*	*Soft visible oedema (1a) % (n)*	*Soft pitting oedema (1b) % (n)*	*Firm pitting oedema (2) % (n)*
None	70 (55)	0	0	0
Submental only	0	14 (11)	4 (3)	1 (1)
Neck only	0	0	1 (1)	1 (1)
Both submental and neck	0	4 (3)	5 (4)	0

Table 3

Location and severity of internal HNL (n = 79)

Internal Site	*Normal* *% (n)*	*Mild* *% (n)*	*Moderate* *% (n)*	*Severe* *% (n)*
Arytenoids	8 (6)	53 (42)	32 (25)	8 (6)
Epiglottis	16 (13)	49 (39)	16 (13)	18 (14)
Pharyngoepiglottic folds	24 (19)	38 (30)	24 (19)	14 (11)
Aryepiglottic folds	24 (19)	47 (37)	22 (17)	8 (6)
Base of tongue	32 (25)	37 (29)	28 (22)	4 (3)
Posterior pharyngeal wall	30 (24)	43 (34)	19 (15)	8 (6)
Interarytenoid space	34 (27)	37 (29)	24 (19)	5 (4)
Valleculae	37 (29)	43 (34)	16 (13)	4 (3)
Cricopharyngeal prominence	52 (41)	23 (18)	16 (13)	9 (7)
False vocal folds	47 (37)	34 (27)	15 (12)	4 (3)
Pyriform sinus	62 (49)	24 (19)	8 (6)	6 (5)
Anterior commissure	63 (50)	24 (19)	13 (10)	0
True vocal folds	91 (72)	5 (4)	4 (3)	0
Maximum severity (across all sites)	3 (2)	33 (26)	37 (29)	28 (22)

Individual sites ordered from the lowest frequency of 'normal' scores

Table 4

Presence and severity of individual symptoms on the VHNSS (n = 71)

VHNSS Questions	*None (0) % (n)*	*Mild (1-3) % (n)*	*Moderate (4-6) % (n)*	*Severe (7-10) %(n)*
Swallow General				
Longer to eat due to swallowing (q13)	31 (22)	24 (17)	17 (12)	28 (20)
Swallowing takes great effort (q12)	49 (35)	30 (21)	13 (9)	8 (6)
Swallow Solids				
Trouble eating certain solid foods (q5)	23 (16)	17 (12)	21 (15)	39 (28)
Food stuck in throat (q8)	31 (22)	34 (24)	15 (11)	20 (14)
Food stuck in mouth (q7)	42 (30)	30 (21)	13 (9)	15 (11)
Choke or strangle on solid foods (q10)	56 (40)	24 (17)	7 (5)	13 (9)
Cough after swallow (q11)	58 (41)	30 (21)	4 (3)	8 (6)
Swallow Liquids				
Choke or strangle on liquids (q9)	75 (53)	20 (14)	6 (4)	0 (0)
Trouble drinking thin liquids (q6)	87 (62)	7 (5)	1 (1)	4 (3)
Nutrition				
Lost appetite (q2)	66 (47)	7 (5)	14 (10)	13 (9)
Use liquid supplements to maintain weight (q3)	70 (50)	13 (9)	13 (9)	4 (3)
Losing weight (q1)	76 (54)	13 (9)	8 (6)	3 (2)
Trouble maintaining weight due to swallowing (q4)	76 (54)	14 (10)	8 (6)	1 (1)

Sorted into subscales and then ordered from the lowest frequency of 'none' scores

Abbreviations: VHNSS = Vanderbilt Head and Neck Symptom Survey (v2.0) Plus General Symptom Scale; q = question number

Table 5

Relationships between swallowing outcomes and HNL via multivariable modelling (n = 79)

Response Variables (range)	*PAS* (1-2 vs. 3-8)*		*FOIS† (1-7)*			*MASA-C† (40-200)*		
Mean (SD)	1.8 (1.6)		5.8 (0.9)			180.4 (12.1)		
Dependent Variables	β	p	β	p	R^2	β	p	R^2
External HNL (severity)	0.96	**0.004**	-0.56	**<0.001**	25%	-4.71	**0.002**	49%
Internal HNL (max severity)	1.11	**0.006**	-0.37	**<0.001**	28%	-4.46	**<0.001**	51%
Number of internal sites	0.32	**0.005**	-0.09	**0.001**	26%	-1.02	**0.001**	50%
Individual internal sites								
Base of tongue	0.57	0.087	-0.23	**0.031**	20%	-2.99	**0.016**	46%
Posterior pharyngeal wall	0.23	0.455	-0.29	**0.004**	24%	-2.11	0.074	44%
Epiglottis	0.53	0.070	-0.32	**0.001**	27%	-3.99	**<0.001**	52%
Pharyngoepiglottic folds	0.71	**0.019**	-0.33	**<0.001**	29%	-3.58	**0.001**	50%
Aryepiglottic folds	1.22	**0.001**	-0.40	**<0.001**	31%	-4.52	**<0.001**	52%
Interarytenoid space	0.80	**0.016**	-0.34	**0.001**	27%	-4.64	**<0.001**	53%
Cricopharyngeal prominence	0.42	0.111	-0.25	**0.005**	23%	-3.70	**<0.001**	51%
Arytenoids	0.82	**0.035**	-0.31	**0.009**	22%	-3.88	**0.006**	47%
False vocal folds	1.16	**0.001**	-0.12	0.256	16%	-3.31	**0.009**	47%
True vocal folds	1.27	**0.028**	0.06	0.789	15%	-1.00	0.689	42%
Anterior commissure	1.62	**<0.001**	-0.13	0.298	16%	-3.25	**0.028**	45%
Valleculae	0.68	**0.046**	-0.48	**<0.001**	34%	-4.01	**0.002**	48%
Pyriform sinus	0.50	0.081	-0.31	**0.002**	25%	-4.02	**0.001**	50%

Bold type indicates statistical significance $p < 0.05$

Abbreviations: PAS = Penetration-Aspiration Scale; FOIS = Functional Oral Intake Scale; MASA-C = Mann Assessment of Swallowing Ability – Cancer; HNL = head and neck lymphoedema; SD = standard deviation; β = regression coefficient

* univariate logistic regression model with normal/dysfunctional PAS as response variable and HNL as explanatory variable

† multivariable linear regression models with FOIS or MASA-C as response variables and oral primary site and HNL as explanatory variables

Table 6

Relationships between VHNSS subscales and HNL via multivariable modelling (n = 71)

Response Variables (range)	*Swallow Solids* (0-50)*			*Swallow Liquids* (0-20)*			*Nutrition* (0-40)*		
Mean (SD)	14.1 (9.3)			2.8 (2.1)			8.0 (5.1)		
Dependent Variables	β	p	R^2	β	p	R^2	β	p	R^2
External HNL (severity)	2.82	**0.037**	14%	0.76	0.331	2%	-0.14	0.674	0%
Internal HNL (max severity)	3.03	**0.014**	16%	0.04	0.959	1%	-0.16	0.601	0%
Number of internal sites	0.6	0.057	13%	0.14	0.440	1%	-0.03	0.730	0%
Individual internal sites									
Base of tongue	2.19	0.083	12%	0.09	0.905	1%	-0.10	0.744	0%
Posterior pharyngeal wall	0.95	0.422	9%	-0.26	0.703	1%	-0.06	0.820	0%
Epiglottis	2.11	0.055	13%	0.50	0.432	1%	0.01	0.987	0%
Pharyngoepiglottic folds	2.6	**0.012**	16%	0.25	0.680	1%	0.03	0.916	0%
Aryepiglottic folds	2.46	**0.045**	13%	0.57	0.422	1%	0.16	0.599	0%
Interarytenoid space	3.03	**0.011**	16%	1.23	0.077	5%	0.36	0.219	0%
Cricopharyngeal prominence	1.55	0.146	11%	0.96	0.117	4%	0.19	0.472	0%
Arytenoids	1.88	0.206	10%	0.54	0.527	1%	0.01	0.993	0%
False vocal folds	1.5	0.283	9%	0.58	0.468	1%	-0.05	0.882	0%
True vocal folds	1.25	0.615	8%	1.11	0.438	1%	-0.49	0.412	0%
Anterior commissure	0.91	0.561	8%	0.56	0.530	1%	0.14	0.702	0%
Valleculae	3.39	**0.011**	16%	0.72	0.357	2%	0.16	0.628	0%
Pyriform sinus	1.44	0.227	10%	0.45	0.513	1%	0.44	0.126	1%

Bold type indicates statistical significance $p < 0.05$

Abbreviations: VHNSS = Vanderbilt Head and Neck Symptom Survey (v2.0) Plus General Symptom Scale; HNL = head and neck lymphoedema; SD = standard deviation; β = regression coefficient

* multivariable linear regression model with VHNSS subscale as response variable and laryngeal primary site and HNL as explanatory variables

Figure 1

Average FOIS scores by primary site and maximum severity of internal HNL