Head and Neck Lymphatic Obstruction and Dysphagia Following Chemo-radiotherapy for Head and Neck Cancer A Retrospective, Linear, and Experimental Research

Corresponding Author
Tshetiz Dahal (MBBS)

General Physician, Clinical Researcher and Writer
Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine

Co-Authors
Anusiyan Alagan

Audiologist and Speech Language Pathologist
Naseema Institute of Speech and Hearing, Bangalore

Subarna Rizal (MBBS)

Junior Resident
Central Referral Hospital
5th Mile, Upper Tadong,, Gangtok, Sikkim 737101

Manoj Kharka (MPT)

Neurophysiotherapist
New STNM Multi-Specialty Hospital, Sochakgang
Gangtok 737101 - Sikkim, India

Abstract: **The study's objectives were to investigate (a) the development of external and internal head and neck lymphoedema (HNL) in head and neck cancer (HNC) patients up to 12 months after chemo-radiotherapy (CRT), and (b) the association between HNL and swallowing performance. External/internal HNL and swallowing were assessed in 33 patients using a prospective longitudinal cohort study at 3, 6, and 12 months after CRT. Using the MD Anderson Cancer Center Lymphoedema Rating Scale and the Assessment of Lymphoedema of the Head and Neck, external HNL was evaluated. Using Patterson's Radiotherapy Oedema Rating Scale, internal HNL was evaluated. Clinical, instrumental, and patient-reported assessments were used to evaluate swallowing. Multi-variable regression models were used to evaluate the relationships between HNL and swallowing. External HNL was prevalent at 3 months (71%), improved by 6 months (58%) and largely resolved by 12 months (10%). In contrast, moderate/severe internal HNL was prevalent at 3 months (96%), 6 months (84%) and at 12 months (65%). More severe penetration/aspiration and increased diet modification were associated with higher severities of external HNL (p=0.006 and p=0.031, respectively) and internal HNL (p<0.001 and p=0.007, respectively), and more diffuse internal HNL (p=0.043 and p=0.001, respectively). Worse patient-reported swallowing outcomes were associated with a higher severity of external HNL (p=0.001) and more diffuse internal HNL (p=0.002). External HNL largely resolves by 12 months post CRT, but internal HNL persists. Patients with a higher severity of external and/or internal HNL and those with more diffuse internal HNL can be expected to have more severe dysphagia.**

Keywords: ***Head and Neck Cancer, Radiotherapy, Lymphoedema, Dysphagia, Deglutition, Deglutition disorders, Swallowing, Chemotherapy, Radiotherapy, Speech pathology, Lymphatic obstruction*.**

Introduction:

Patients with locally advanced head and neck cancer (HNC) are being treated more frequently with chemo-radiotherapy (CRT) regimens [1]. In patients with HNC, the addition of concomitant chemotherapy, improved radiation delivery strategies, and tumor-related variables have improved tumour response and survival rates [2]. Nevertheless, despite improved disease control, patients receiving CRT continue to have significant acute and chronic side effects [3, 4], which can be severely devastating for those in the survival phase of care [5] in terms of both functional ability and psychological well-being. Following HNC treatment, head and neck lymphoedema (HNL) is extremely common [6] and develops when lymph does not drain through lymphatic vessels or when the lymphatic burden exceeds the lymphatic system's transport capacity [7, 8]. Up to 90% of those with HNC may also have some form of HNL [6]; this infection can manifest itself in one or more of the following ways: outwardly on the soft tissues of the face and neck; internally in the oral cavity; internally in the pharynx or larynx; or both [9]. Historically, surgical procedures have been blamed for the emergence of HNL, including the removal of lymphatic nodes, arteries, and structures. However, the presence of significant tumour bulk and management via non-surgical treatment options, such as high-dose radiotherapy and concurrent chemotherapy,may also damage the lymphatic structures and disrupt the normal flow of lymph fluid [10, 11]. Patients are less likely to have HNL as time passes after treatment, according to research [11]. This idea is in line with the anecdotal theory that HNL will eventually become better under prudent management. Recent research, however, suggests that HNL might not fully resolve [6, 12]. In a prospective study of 83 HNC patients who had had some type of multimodal treatment, Ridner et al. [6] discovered that HNL was most common three months after treatment, with 90% of the group having external HNL and 86% experiencing internal HNL. From 12 to 18 months, the severity of both exterior and internal HNL seemed to progressively lessen. At the end of the research, however, 82% and 80% of participants still had exterior and internal HNL, respectively.

Similar outcomes were observed by Tribius et al. [12] in a longterm trial involving 280 HNC patients who had additionally received postoperative radiation (+/ chemotherapy) and surgery. At 3 months after therapy, 80% of their cohort still had some degree of external and/or internal HNL, and 38% still did at the end of the observation period (time varies). It is alarming that HNL is so common in individuals who have undergone HNC treatment because HNL has been linked to a variety of medical, functional, and psychological problems [13–17]. Increased dysphagia has been observed in patients with more severe exterior and internal HNL in particular [13, 16–19]. They suffer more pharyngeal residue, need more diet modification, have more severe laryngeal penetration and/or aspiration, and report greater symptoms while consuming solid foods [13, 16–19].

However, only cross-sectional datasets with different populations have been used to study the association between HNL and dysphagia, and it is unknown if the relationship persists at various time periods after therapy. Therefore, the main goal of this study was to investigate the course of external and internal HNL in HNC patients who had had CRT and to outline the changes in HNL location and severity over a 12-month period. It also aimed to explore the relationship between external and internal HNL and the presence of dysphagia, including penetration–aspiration status, functional diet status and patient reported swallowing outcomes during this time period.

Materials and Methods:

It employed a longitudinal cohort study design. It is a component of a bigger investigation that has been extensively discussed elsewhere [16]. The University of Lugansk Medical Research Ethics Committee and the Ukraine Kyiv Human Research Ethics Committee both granted their clearance.

Participants:

Using a convenience sample technique, participants were prospectively selected from the Radiation Oncology Clinic at the Kyiv Hospital in Kyiv, Ukraine. From September 2019 to July 2020, candidates were recruited, and candidates were followed up with until November 2021. The following requirements were required for eligibility: Having received a recent diagnosis of oral, nasopharyngeal, oropharyngeal, laryngeal, or hypopharyngeal cancer and intending to undergo curative CRT. The following was listed as an exclusion criterion: Any of the following conditions precludes consent: (1) treatment with palliative intent; (2) recurrent or metastatic disease; (3) preexisting comorbidity conditions that may cause HNL (such as trauma); or (4) conditions that have an impact on swallowing, voice, or speech function (such as neurological injury or insult).

Procedure:

Measures were taken 3, 6, and 12 months after the end of the treatment. Prior to each time point, a review of each participant's chart was done to make sure they were still disease-free. At each time point, swallowing, internal HNL, and external HNL were evaluated.

Evaluation of Head and Neck Lymphoedema:

Two evaluations were used to measure external HNL. The MD Anderson Cancer Centre (MDACC) Lymphoedema Rating Scale [8] was initially used to rate it. This scale employs five points to classify HNL along the continuum from gentle swelling to fibrosis. For the objectives of this investigation, external HNL was classified as normal when 0, mild when 1, moderate when 1, severe when 2, and profound when 3. The secondary evaluation comprised a MoisureMeterD (MMD; Delfn Technologies Ltd, Kuopio, Finland) tissue dielectric constant (TDC) measurement and the Assessment of Lymphoedema of the Head and Neck (ALOHA) [20] which uses surface tape measurements. Additionally, the participant's weight is noted. Tape measures were obtained at the lower neck circumference, upper neck circumference, and length from ear to ear using the normal setup placement methodology. The 2.5-mm MMD probe was positioned on the skin's surface eight centimeters below the lower lip's edge, and three measurements were collected. Strong inter-rater reliability has been shown for the TDC measure and the ALOHA tape measurement method [21]. Additionally included as benchmark data were the normative values for the TDC [22]. When external HNL was identified, it was standard clinical practise to refer patients to the physiotherapy department for additional evaluation and management. Transnasal laryngoscopy was used for internal HNL assessment. The Patterson's Radiotherapy Oedema Rating Scale [23] was used to assess the existence, location, and severity of internal HNL (scale recently revised [24]). There are 13 laryngopharyngeal sites on this scale, and each site can be rated as normal, mild, moderate, or severe.

The scale has demonstrated very strong agreement within-rater reliability and modest agreement between-rater reliability [23]. An education package was created with photographs of HNL at various severity levels and at each site to help with rating determinations. In order to evaluate intra- and inter-rater reliability, the principal investigator and a second speech pathologist related 20% of the total recordings at least three months following the initial rating. In addition to the 13 site ratings, three internal HNL summary variables were also generated: (1) a 'maximum severity score' which reflected the maximum severity rating obtained across the 13 internal sites; (2) a 'sum severity score' which was generated by allocating each severity rating a score (i.e. normal = 0, mild = 1, moderate = 2, severe = 3) and adding the scores across the 13 internal sites; and (3) the 'number of internal sites affected by HNL was generated by counting the number of internal sites identified as having HNL (three severity variations—any severity; moderate or severe; or severe). The 'maximum severity score' and 'number of internal sites affected by HNL have previously been used in the literature [6, 9, 16, 18]. The 'sum severity score' was novel.

Evaluation of Swallowing:
Measures of clinical, instrumental, and patient-reported outcomes were included in the assessment of swallowing. Oral musculature, cranial nerve, and clinical swallowing abilities were rated using the Mann Assessment of Swallowing Ability—Cancer (MASA-C) [25]. A score of 185 or below shows the presence of dysphagia, while a maximum score of 200 suggests swallowing within normal limits [25]. Functional diet status was evaluated using the Functional Oral Intake Scale (FOIS) [26]. The FOIS evaluates the number of food consistencies tolerated as well as the requirement for extra preparations or compensations before classifying diet status as non-oral (scores 1-3) or oral (scores 4-7). A fiberoptic endoscopic evaluation of swallowing (FEES) was carried out for instrumental assessment. The Penetration-Aspiration Scale (PAS) [27] was used to rate laryngeal penetration and aspiration occurrences on the worse of the two swallows after participants inhaled two mouthfuls of blue-colored water. Normal PAS scores ranged from 1-2, which indicate that either no material enters the airway or that material enters the airway, remains above the actual vocal folds, and is expelled. Scores between 3 and 8 were deemed dysfunctional [28]. Twenty percent of all FEES recordings were related in accordance with the dependability protocol previously mentioned. Finally, the self-perceived symptom load in connection to nutritional status and swallowing abilities was examined using the Vanderbilt Head and Neck Symptom Survey (VHNSS) (v2.0) Plus General Symptom Scale [29]. Participants were required to independently complete and return it.

The VHNSS uses a Likert scale for its questions, with a score of 0 denoting no symptoms and a score of 10 denoting severe symptoms. According to earlier research [29], questions from four symptom sub-scales, including nutrition (questions 1-4), swallow general (questions 5-13), swallow solids (questions 5, 7, 8, and 10), swallow liquids (questions 6 and 9), were added up, then collapsed, and classified as mild (scores 1-3), moderate (scores 4-6), and severe (scores 7-9). (7–10). All participants received routine clinical care at the study centre, including regular speech pathology evaluations and management of their swallowing, voice, and speech function during CRT and for up to three months after treatment. Review was only conducted after then on an as-needed basis.

Statistical Methods:
Analyses were conducted by the primary investigator Tshetiz and study statistician Manoj using the statistical software package Stata 16 [30]. Cohen's kappa coefficient was used to assess the intra- and inter-rater reliability of the Patterson Radiotherapy Oedema Rating Scale and PAS ratings, which were observed via the transnasal laryngoscopy and FEES assessments (20% sub-sample). Linear weights (Kw) were applied [31] and the strength of agreement was classified as slight (Kw 0–0.20), fair (Kw 0.21–0.40), moderate (Kw 0.41–0.60), substantial (Kw 0.61–0.80) and almost perfect (Kw 0.81–1) [32].

The differences in continuous variables between time points (i.e., 3 vs. 6 months and 6 vs. 12 months) were examined using paired t-tests. The Wilcoxon signed-rank test was performed to look at how categorical variables changed over time. The relationships between weight changes and ALOHA tape measurement system time points were investigated using linear regression models. To determine whether the residuals were normal, Shapiro-Wilk was utilized. The relationships between the swallowing and the HNL characteristics were investigated using regression models. For each HNL and swallowing variable, a model was fitted (i.e., 6 × 17 models—all reported in Table 1) The associations between the FOIS, MASA-C, and VHNSS sub-scale scores and the HNL variables (explanatory) were investigated using linear regression models (response).

Since 56% of the total observations (n = 48/86) had a normal PAS score, logistic regression models were employed to investigate the correlations between the HNL variables (explanatory) and PAS scores (response) (i.e. scores 1–2). These models were fit using a backwards stepwise approach to account for potential effects of other factors such age, tumour and nodal stage, and external HNL treatment. To produce the primary dataset, data from the 3, 6, and 12 month time points were combined (i.e. 86 observations on 33 participants). Due to the small sample size at each time point and the low variability of the HNL and swallowing results, this was conducted (i.e. most outcomes were tightly clustered around the mean). Since each participant was the subject of many observations, which accounted for the time point variable, clustered standard errors were employed in the models [33]. $P < 0.05$ was used to determine significance.

Table 1: Relationships between swallowing outcomes and HNL via regression modelling.

Response variables (possible range)	PAS (1–2 vs. 3–8)a	FOIS (1–7)b	MASA-C (40–200)2	VHNSS solids (0–50)2	VHNSS liquids (0–20)2	VHNSS nutrition (0–40)2

Explanatory variables	Odds ratio	p	β	p	β	p	β	p	β	p	β	p
External HNLc	3.5	**<0.01**	− 0.7	**0.04**	−9.4	**<0.01**	4.5	**<0.01**	1.8	**0.04**	3.7	**0.05**
Max internal HNL	5.2	**<0.01**	− 0.4	**0.01**	−5.6	**<0.01**	2.1	0.19	−0.3	0.44	0.4	0.76
Sum internal HNL	1.2	**<0.01**	− 0.1	**0.01**	−0.7	**<0.01**	0.4	**0.02**	0.0	0.46	0.1	0.35
Number of internal sites	1.6	**0.04**	− 0.2	**<0.01**	− 1.7	**<0.01**	1.1	**<0.01**	0.3	**0.04**	0.7	**0.03**
Individual internal sites												
Base of tongue	1.2	0.57	0	0.95	− 1.5	0.27	−1.0	0.41	−0.3	0.17	0.2	0.86
Posterior pharyngeal wall	2.1	0.07	− 0.2	0.24	− 2.4	0.12	1.2	0.43	−0.6	0.15	− 0.5	0.70
Epiglottis	2.5	**<0.01**	− 0.3	0.10	− 3.6	**0.02**	2.3	0.07	− 0.3	0.53	− 0.2	0.87
Pharyngoepiglottic folds	2.4	**<0.01**	− 0.4	**0.02**	− 4.5	**0.01**	2.5	**0.02**	0.1	0.87	0.7	0.49
Aryepiglottic folds	4.3	**<0.01**	− 0.6	**<0.01**	− 6.6	**<0.01**	3.0	**0.02**	0.5	0.22	1.7	0.12
Interarytenoid space	2.3	**0.01**	− 0.5	**0.01**	− 5.5	**0.01**	3.1	**0.01**	0.5	0.22	1.2	0.18
Cricopharyngeal prominence	3.3	**<0.01**	− 0.5	0.01	− 5.9	**<0.01**	3.4	**<0.01**	0.6	0.09	1.5	0.14
Arytenoids	3.4	**<0.01**	− 0.4	**0.03**	− 5.2	**0.01**	3.4	**0.01**	0.6	0.12	1.6	0.25
False vocal folds	2.3	0.05	− 0.3	0.09	− 4.9	**0.01**	2.8	**0.02**	0.5	0.12	1.2	0.34
True vocal folds	1.9	0.33	− 0.8	0.28	− 13	0.18	4.1	0.61	4.0	0.28	− 3.6	0.49
Anterior commissure	2.8	−	−	0.52	− 3.5	0.10	0.2	0.86	0.3	0.56	− 0.1	0.96
Valleculae	1.8	0.14	− 0.2	0.15	− 3.1	**0.02**	− 0.5	0.62	− 0.5	0.16	0.7	0.45
Pyriform sinus	3.9	**<0.01**	− 0.5	**0.01**	− 5.8	**<0.01**	3.2	**<0.01**	0.4	0.29	0.7	0.41

PAS penetration-aspiration scale, FOIS functional oral intake scale, MASA-C mann assessment of swallowing ability—Cancer, VHNSS vander-bilt head and neck symptom survey, p = p-value

Bold type indicates statistical significance $p < 0.05$

a Logistic regression with response PAS=1 or 2, with standard errors clustered on participant

b Linear regression, with standard errors clustered on participant

c Determined by the MDACC Scale rating only

Results:

At the commencement of CRT, 42 volunteers were recruited. (Fig. 1). Two participants dropped out because of recurrent or residual illness, and three dropped out because of comorbidity-related complications. Participants who have finished. In the analysis, data for at least two of the three follow-up time points were present, requiring the elimination of four participants with only one time point of data. Of the 20 of the 33 remaining subjects had full data at all three sites. At two of the time points, 13 had complete data. A total of 86 observations were made (n = 24 at 3 months, n = 31 after 6 months and at 12 months. The total attrition rate was 21%, while the participation rates at 3 months, 6 months, and 12 months were 73% and 94%, respectively. Be aware that if a time point was missed, individuals were still included in the study. The majority of participants were male and younger than 65 years old (Table 2). The majority of patients who had early-stage oropharyngeal tumours when they were first diagnosed also had advanced nodal metastases and HPV-positive illness. Intensity-modulated radiation treatment (IMRT) or volumetric-modulated arc therapy was used to treat each subject (VMAT). The majority got three cycles of high-dose cisplatin and conventional radiation therapy at a dose of 70 Gy/35#. At the time of participation, every individual was healthy.

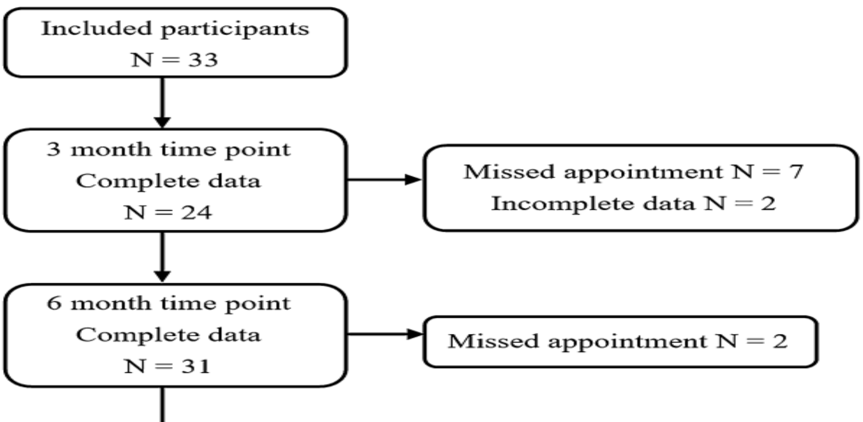

Fig. 1 : Number of participants by time point. Recruitment occurred at the start of CRT. Participation in the 3-month time point was low. Participants often declined this study appointment due to the recency of treatment and some anxiety surrounding their post-treatment PET-CT scan results. In such cases, their first participation was at 6 months.

Patterson Radiotherapy Oedema Rating Scale and Penetration-Aspiration Scale Inter- and intra-rater Reliability:
Re-ratings were done on 18 of the 86 transnasal laryngoscopy and FEES examinations. The Patterson Radiotherapy Oedema Rating Scale ratings (13 internal sites) had an average high level of intra-rater reliability (Kw = 0.83). The real vocal folds, cricopharyngeal prominence, and posterior pharyngeal wall had the highest agreement (nearly perfect) (Kw = 1, 0.95, 0.91, respectively). False vocal folds, anterior commissure, and Interarytenoid space had the lowest levels of agreement (substantial) (Kw = 0.60, 0.74, and 0.74, respectively). The PAS ratings had perfect intra-rater reliability (Kw = 1). The Patterson Radiotherapy Oedema Rating Scale evaluations have an average inter-rater reliability of moderate (Kw = 0.44). The aryepiglottic folds, epiglottis, and cricopharyngeal prominence had the highest levels of agreement (substantial) (Kw = 0.69, 0.68, and 0.64, respectively). The real vocal folds, base of tongue, and false vocal folds had the lowest levels of agreement (Kw = 0, 0.12, and 0.15, respectively). The PAS has a high level of inter-rater reliability (Kw = 0.78).

Table 2 : Demographic, disease and treatment data

Characteristic		**n = 33**
Age (years) (mean (SD))		**59.9 (7.7)**
		% (n)
Gender	Male	91 (30)
	Female	9 (3)
Primary site	Nasopharyngeal	3 (1)
	Oropharyngeal	91 (30)
	Laryngeal	6 (2)
T classification	T 1–2	67 (22)
	T 3–4	30 (10)
	T X	3 (1)
N classification	N 0	6 (2)
	N 1	6 (2)
	N 2–3	88 (29)
TNM staging	Stage 0	3 (1)
	Stage I	3 (1)
	Stage III	9 (3)
	Stage VI A	82 (27)
	Stage VI B	3 (1)
HPV status	Positive	76 (25)
	Negative	24 (8)
Radiation treatment	70Gy/35#	94 (31)
	Other	6 (2)
Chemotherapy	Cisplatin	70 (23)
	Cetuximab	24 (8)
	Other	6 (2)
Baseline FOIS	Levels 4–6	27 (9)
	Level 7	73 (24)

Percentages may not total 100 due to rounding
T tumour, N nodal, HPV human papilloma virus, SD standard deviation, FOIS functional oral intake scale

Lymphoedema of the External Head and Neck: Prevalence, Location, and Severity:
According to the MDACC Scale, external HNL peaked in prevalence at 3 months (71%), improved little at 6 months (58%) and significantly at 12 months (10%) (Table 3). Between 6 and 12 months, the MDACC Scale score significantly decreased ($z = 3.873$, $p < 0.001$), whereas between 3 and 6 months, it did not ($z = 1.698$, $p = 0.089$). When present across the three time points, external

HNL was typically regarded as modest (MDACC Scale rating 1a). The submental region was the most frequently affected site, according to the descriptive analysis, and it was affected in all patients with external HNL at 3 and 12 months, and in all but one participant at 6 months. Both statistical and clinical improvements were also evident in the ALOHA's TDC value and the tape measurements of the upper and lower neck circumferences (Table 3).

Significant improvements in the TDC were found between 6 and 12 months ($t_{26} = -3.376$, $p = 0.002$, 95% confidence interval (CI) = [− 10.0, − 2.4], although still slightly outside the normal range at 12 months [22]), but not between 3 and 6 months ($t_{19} = -1.436$, $p = 0.167$, 95% CI = (− 7.2, 1.3)). In contrast to the MDACC Scale and TDC,significant improvements in the tape measurement of the upper and lower neck circumference were found between 3 and 6 months ($t_{19} = -2.553$, $p = 0.019$, 95% CI = (− 3.0, − 0.3) and $t_{19} = -3.142$, $p = 0.005$, 95% CI = (− 1.8, − 0.4), respectively), but not between 6 and 12 months ($t_{27} = 1.254$, $p = 0.220$, 95% CI = (− 0.8, 3.2) and $t_{27} = 1.478$, $p = 0.151$, 95% CI = (− 0.4, 2.7), respectively). However, between 6 to 12 months, an increase in body weight was significantly related to an increase in upper and lower neck circumferences ($F(1,26) = 6.07$, $p= 0.021$ and $F(1,26) = 7.16$, $p = 0.013$, respectively), an effect unseen in the other external HNL measurements.

Although the study group's external HNL generally improved over time, individual case analysis showed that 6% of the cohort as a whole had lower MDACC Scale scores between three and six months. Additionally, 9% of people experienced a worse TDC between 3 and 6 months, and 3% experienced a worse TDC between 6 and 12 months. At three months, all participants who had external HNL were referred to the physiotherapy department for additional evaluation and care. Only 39% of patients who had external HNL that was still being treated at 6 months underwent external HNL therapy, nevertheless (Table 3). Of the three participants who still had external HNL at \s12 months, all had previously had therapy and were continuing self-management at home.

Head and Neck Lymphoedema: Basic Presentation:

At each time point, all subjects had some degree of HNL (Table 3). Most people (71%) had mixed external and internal HNL at 3 months, and most people (58%) still had combined HNL at 6 months. But after a year, the majority of subjects (90%) only had internal HNL.

Table 3 : Head and neck lymphoedema prevalence and outcome measures by time point

HNL type	3 mths, *n = 24*	6 mths, *n = 31*	12 mths, *n = 31*	p, 3 vs. 6 mths	p, 6 vs. 12 mths
No HNL	0	0	0		
Both external and internal HNLa	71 (17)	58 (18)	10 (3)		
Internal HNL only	29 (7)	42 (13)	90 (28)		
External HNL only a	0	0	0	0.059	**<0.001b**
External HNL outcome measures					
MDACC Scale (% (n))					
No visible oedema (0)	29 (7)	42 (13)	90 (28)		
Soft visible oedema (1a)	63 (15)	48 (15)	6 (2)		
Soft pitting oedema (1b)	8 (2)	10 (3)	3 (1)	0.089	**<0.001b**
TDC (Mean (SD))	29.8 (8.7)	27.7 (9.6)	21.3 (8.8)	0.167	**0.002c**
Tape measurements (cm) (Mean (SD))					
Lower neck	42.3 (4.6)	41.6 (3.7)	40.5 (4.6)	**0.005**	**0.151c**
Upper neck	44.9 (5.2)	43.6 (4.5)	42.2 (4.9)	**0.019**	0.220c
Ear to ear	25.5 (1.9)	26.0 (2.7)	25.1 (2.1)	**0.028**	**0.032b**
Weight (kg) (Mean (SD))	74.9 (16.1)	76.3 (14.4)	80.3 (12.4)	0.903	**0.010b**
External HNL treatment (% (n))					
Yes	13 (3)	26 (8)	10 (3)		
No	88 (21)	77 (24)	90 (28)	0.083	**0.059b**
Internal HNL outcome measures					
Maximum severity (all sites) (% (n)					
Normal	0	0	0		
Mild	4 (1)	16 (5)	35 (11)		
Moderate	38 (9)	48 (15)	48 (15)		
Severe	58 (14)	35 (11)	16 (5)	**0.011**	**0.013b**
Sum severity (all sites)					
Mean (SD)	18.9 (5.9)	15.8 (7.7)	9.7 (6.5)		
Range	10–28	6–32	2–29	**0.009**	**<0.001b**
Number of sites (any severity)					
Mean (SD)	10.5 (1.5)	9.9 (2.2)	7.0 (2.9)		
Range	7–12	5–13	2-12	**0.022**	**<0.001c**

Number of sites (moderate/severe)					
Mean (SD)	6.4 (3.1)	4.5 (4.0)	2.2 (2.9)		
Range	0–11	0–13	0–10	**0.017**	**<0.001c**
Number of sites (severe)					
Mean (SD)	2.0 (2.2)	1.4 (2.3)	0.5 (1.4)		
Range	0–6	0–9	0–7	0.053	**0.007c**
Internal site severity (Mod or Severe % (n))					
Arytenoids	67 (16)	52 (16)	29 (9)	0.083	**0.007b**
Epiglottis	63 (15)	52 (16)	35 (11)	**0.046**	0.317b
Pharyngoepiglottic folds	63 (15)	45 (14)	26 (8)	**0.020**	**0.002b**
Aryepiglottic folds	67 (16)	42 (13)	19 (6)	**0.020**	**<0.001b**
Valleculae	67 (16)	26 (8)	10 (3)	**0.003**	**0.004b**
Posterior pharyngeal wall	54 (13)	58 (18)	29 (9)	0.739	**0.001b**
Interarytenoid space	58 (14)	42 (13)	23 (7)	0.096	**0.006b**
Pyriform sinus	50 (12)	29 (9)	10 (3)	**0.003**	**<0.001b**
Base of tongue	42 (10)	35 (11)	23 (7)	0.698	**0.006b**
Cricopharyngeal prominence	58 (14)	35 (11)	16 (5)	**0.002**	**0.010b**
False vocal folds	29 (7)	26 (8)	0	0.364	**<0.001b**
Anterior commissure	17 (4)	10 (3)	3 (1)	0.216	**0.021b**
True vocal folds	4 (1)	3 (1)	0	0.583	**0.317b**

Percentages may not total 100 due to rounding

HNL head and neck lymphoedema, MDACC MD Anderson cancer centre, TDC tissue dielectric constant, mths months, SD standard deviation, p p-value

a Determined by the MDACC Scale rating only
b Wilcoxon signed-rank test
c Paired t-test

Lymphoedema of the internal head and neck: occurrence, position, and intensity:

All participants had some degree of internal HNL at each time point (Table 3). The maximum severity score indicates that most participants had moderate or severe internal HNL at 3 months (96%), 6 months (84%) and 12 months (65%). The number of internal sites affected by moderate or severe internal HNL also improved over time. At 3 months, participants had on average 6.4 of 13 internal sites that were moderate or severe, but this reduced to 4.5 sites at 6 months, and 2.2 sites at 12 months. Significant improvements in the maximum severity score and number of internal sites affected by moderate or severe HNL were found between 3 and 6 months ($z = -2.530$, $p = 0.011$ and $t21 = -2.584$, $p= 0.017$, 95% CI = (− 3.1, − 0.3), respectively), and 6 and 12 months ($z = -2.496$, $p = 0.013$ and $t28 = -4.838$, $p < 0.001$, 95% CI = (− 2.5, − 1.0), respectively). Again, despite the fact that internal HNL was generally improving, 12% of the entire group had more internal sites involving HNL between 3 and 6 months and 3% between 6 and 12 months. Between 3 and 6 months, 9% of participants had a worse sum severity score and 3% had a worse maximum severity score. Fig. 2 displays the location and severity of internal HNL at certain places. It's noteworthy that just four out of the 13 locations had a significant improvement ($p < 0.05$) over the three and six-month and twelve-month periods. These comprised the aryepiglottic folds, the Pharyngoepiglottic folds, the pyriform sinus, the cricopharyngeal prominence, and the valleculae.

Swallowing Outcomes:

The dysfunctional PAS score of one-third of the cohort (i.e. scores 3-8) at three months, suggesting some laryngeal penetration or aspiration with thin filaments during the FEES evaluation (Table 4). Only 13% had a by 12 months unhealthy PAS score. 92% achieved a score of 185 or above at three months, the MASA-C score was lower, indicating the existence dysphagia, but after a year, only 55% had a score of 185 or above less. Most individuals (79%) needed to follow a diet of some kind 3 months after modification (FOIS scores 4-6), 68% were still there needed to modify their diet after a year. There are 74 (of the A total of 32 participants returned 86) VHNSS questionnaires. the existence and seriousness of specific symptoms Those are included in Table 4.

Exterior and Interior Head and Neck Lymphoedema and the Implications of Swallowing:

Table 1 shows the connections between the exterior and internal HNL factors and the results of swallowing. Backward stepwise techniques failed to uncover any additional significant variables, and the model residuals retained their normal distribution. Significant ($p < 0.05$) associations between dysfunctional PAS scores (i.e., scores 3-8), FOIS scores, MASA-C scores, and external HNL were found by regression modelling. Additionally, significant correlations ($p < 0.05$) were discovered between the three internal HNL summary variables and the dysfunctional PAS, FOIS, and MASA-C scores. According to these findings, individuals were, if someone had more severe exterior and/or internal symptoms, they were more likely to experience dysphagia, have laryngeal penetration and/or aspiration, and need to modify their diet more. HNL and diffuse internal HNL if they had more. Internal HNL that took place at the aryepiglottic folds is noteworthy. Additionally, the cricopharyngeal prominence and pyriform sinus among the most reliable indicators of dysfunctional PAS scores, FOIS scores, and MASA-C scores all declined.

The correlation between the VHNSS swallow general and swallow solids sub-scales was highly significant (r = 95%). Therefore, the regression modelling only looked at the VHNSS swallow solids, swallow liquids, and nutrition sub-scales. Compared to the PAS, FOIS, and MASA-C scores, there was less of a connection between the VHNSS sub-scales and the HNL variables in these models. But noteworthy are the significant associations (all $p < 0.05$) discovered between the swallow solids sub-scale and the sum severity score for internal HNL, external HNL, and the total number of internal locations affected by HNL. These findings show that patient-reported symptom load for swallowing and eating solid foods was higher (or worse) in participants with more severe exterior HNL and diffuse internal HNL. The aryepiglottic folds, pyriform sinus, and cricopharyngeal prominence were once again some of the best predictors of symptom burden with solid foods, along with the PAS, FOIS, and MASA-C scores.

Discussion:

The progression of external and internal HNL and its relationship to dysphagia in a homogeneous sample of HNC patients receiving CRT are described in this study. The findings show that both exterior and internal HNL are common after CRT and that two distinct trajectory patterns exist in the first twelve months following treatment. External HNL was most noticeable at 3 months, started to get better at 6 months, and was mostly gone by 12 months. Internal HNL, on the other hand, continued for the full 12 months, and despite modest improvement in its severity and diffuseness during the research period. As a result, it is to be anticipated that HNC patients who are 12 months post-CRT may present with internal HNL in the absence of external HNL. In addition to having more severe exterior and/or internal HNL in the first 12 months following therapy, patients with more widespread internal HNL may also have more severe dysphagia.The results of the current investigation are in line with earlier studies that showed a high frequency of both exterior and internal HNL in HNC patients following treatment [6, 9, 10, 12, 19]. Contrary to the homogeneous cohort of the present investigation, earlier studies have studied both surgical and non-surgical treatment techniques. However, using a homogeneous sample of just HNC patients who received CRT can also be considered as a strength because it has shown that these non-surgical patients are equally likely to develop external and internal HNL in the first year following treatment as their surgical counterparts.

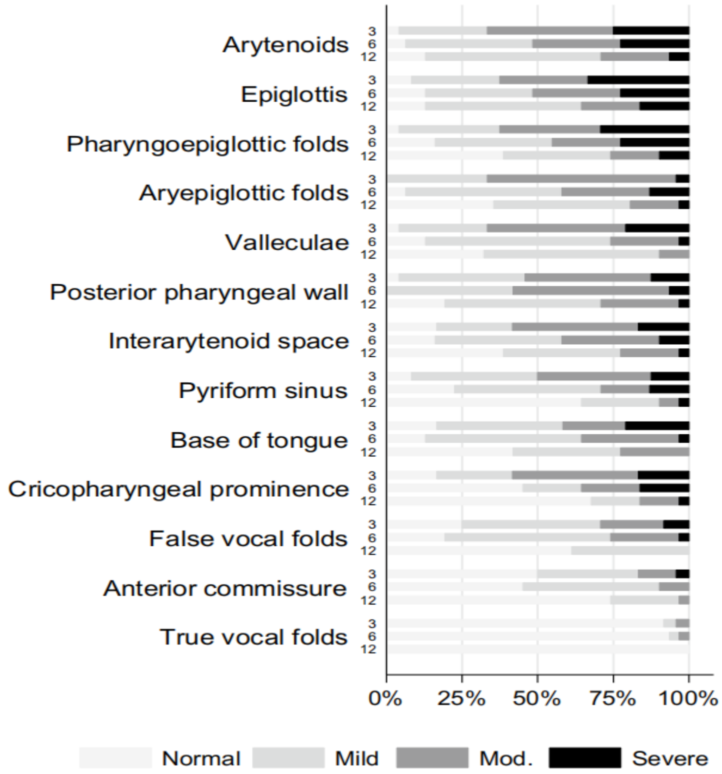

Fig. 2 : Location and severity of internal head and neck lymphoedema by time point.

However, there is one difference: in the current study, the peak severity of HNL occurred around 3 months, whereas it occurred In the longitudinal investigation by Ridner et al. [6], approximately 9 months. It whether this difference may be ascribed to them is unknown. Despite the population's diversity, there is a gap that calls for action additional investigation. Additionally, the current investigation has demonstrated that although internal HNL is still there a year after CRT, it presents differently each time. In contrast to other internal sites, like the epiglottis, which showed early improvement between 3 and 6 months before plateauing from 6 to 12 months, HNL that occurred at four of the 13 internal sites, including the aryepiglottic folds, valleculae, and pyriform sinus, consistently improved from 3 to 12 months. The arytenoids, on the other hand, showed only modest improvement from 3 to 6 months before significantly improving from 6 to 12 months. No other studies are currently available for comparison, but these results suggest that changes in HNL at individual internal sites are not uniform and that differences may exist in the lymphatic drainage of individual sites. Future studies that examine the trajectory of HNL at the individual internal sites, whilst also examining their lymphatic drainage patterns would be valuable.

Table 4 : Swallowing outcome measures by time point

Outcome measures	3 mths, n = 24, % (n)	6 mths, n = 31, % (n)	12 mths, n = 31, % (n)	p, 3 vs. 6 mths	p, 6 vs. 12 mths
PAS					
Level 1-2	67 (16)	65 (20)	87 (27)		
Levels 3-6	21 (5)	16 (5)	13 (4)		
Levels 7-8	13 (3)	19 (6)	0	0.317	0.077a
FOIS					
Level 1	4 (1)	3 (1)	0		
Levels 2-3	0	0	0		
Levels 4-6	83 (20)	74 (23)	68 (21)		
Level 7	13 (3)	23 (7)	32 (10)	**0.046**	0.180a
MASA-C					
Mean (SD)	177 (9.2)	178 (13.7)	186 (7.6)		
Range	154-187	120-192	174-198	0.450	**0.001b**
VHNSS sub-scale questions (Mean (SD))	*n = 20*	*n = 27*	*n = 27*		
Swallow general					
Longer to eat due to swallowing (q13)	5.2 (3.4)	5.1 (4.0)	3.9 (3.2)	0.264	0.423b
Swallowing takes great effort (q12)	3.0 (2.3)	2.9 (2.7)	2.2 (2.1)	0.627	0.418b
Swallow solids					
Trouble eating certain solid foods (q5)	6.2 (2.9)	5.3 (3.4)	4.1 (3.1)	0.083	0.204c
Food stuck in mouth (q7)	3.3 (2.4)	3.0 (2.5)	2.1 (1.5)	0.937	0.024c
Food stuck in throat (q8)	3.0 (2.5)	4.0 (3.0)	2.6 (2.1)	0.667	0.083c
Cough after swallow (q11)	2.4 (2.3)	2.3 (2.4)	1.7 (1.8)	0.097	0.259c
Choke or strangle on solid foods (q10)	1.8 (1.9)	2.6 (2.6)	1.4 (0.8)	1.000	0.136c
Swallow liquids					
Choke or strangle on liquids (q9)	1.7 (1.7)	1.7 (1.8)	1.1 (0.5)	0.054	0.188c
Trouble drinking thin liquids (q6)	1.6 (2.0)	2.3 (2.4)	1.0 (0.2)	0.370	**0.014c**
Nutrition					
Lost appetite (q2)	3.6 (2.3)	3.2 (3.3)	2.0 (2.2)	0.685	**0.004c**
Liquid supplements to maintain weight (q3)	3.6 (3.1)	2.3 (2.2)	1.6 (1.4)	0.064	0.343c
Trouble maintaining weight due swallow (q4)	3.1 (2.6)	2.0 (2.3)	1.3 (0.9)	0.108	0.219c
Losing weight (q1)	3.0 (2.9)	2.4 (2.1)	1.5 (1.1)	0.149	0.113c

Percentages may not total 100 due to rounding mths months, SD standard deviation, PAS penetration-aspiration scale, FOIS functional oral
intake scale, MASA-C mann assessment of swallowing ability—cancer, VHNSS vander bilt head and neck symptom survey, VHNSS scoring 1–3
mild, 4–6 moderate, 7–10 severe, p = p-value
a Wilcoxon signed-rank test
b Paired t-test
Additionally, whereas the general trend was towards improving both internal and exterior HNL, some participants' over the course of the 12-month research, HNL got worse. It was emphasized that the worst instances of both external and internal participants with severe dysphagia who were either tube-dependent or nil by mouth experienced HNL deterioration or limited to a specific type of food consistency. The fact that muscular contraction facilitates lymphatic flow through the lymphatic channels [34], hence it is possible to hypothesize that the swallows in those individuals were found to be weak and frequent, which specifically those participants who had severe dysphagia who depend on tubes could reduce the effectiveness even further used by the lymphatic system to remove clogged lymph. Speech pathologists may need to take into account the risk of no or limited oral intake for not

only increasing HNL but also disuse atrophy and fibrosis if this postulation is to be confirmed in a larger sample size. Despite being directed to a free hospital service, less than half of the participants in the current study who had external HNL at 3 months accessed therapy. These findings imply that some spontaneous recovery has taken place, as the external HNL of the majority of subjects was gone by 12 months. The fact that significant gains were not noticed until six months after the start of treatment may be a clue that many participants had to deal with the effects of their exogenous HNL for some time.

Therefore, prompt access to external HNL treatment is still necessary, even though there may be some hope for spontaneous recovery in HNC patients receiving CRT. The current study's findings confirm previous studies' findings that external and internal HNL are linked to more severe dysphagia [7, 13, 16, 18, 19], and that this association is present in the acute, sub-acute, and long-term post-HNC therapy phases as well. The lack of any descriptions of how external and internal HNL effect the physiological events that result in penetration-aspiration risk and problems with bolus flow and clearance represents a limitation of the current body of knowledge. It makes sense to patients with more severe and widespread internal conditions are anticipated. HNL would see modifications to their safety while swallowing and efficacy [16], as well as the findings of the present investigation would be consistent with this theory. However, in the future, research. It is necessary to incorporate a more thorough evaluation of swallowing function. Until then, speech pathologists and other oncological medical professionals must be aware of the internal and external HNL could have a negative influence on the ability of HNC patients after CRT to swallow. Laryngoscopy must be used to detect and assess internal HNL, as well as track its development and/or resolution over time.

The methods used to measure internal and exterior HNL are also called into doubt by the current investigation. The lack of a composite score in Patterson's Radiotherapy Oedema Rating Scale has prompted many authors [6, 9, 16, 18] to choose the highest severity value for internal HNL. The severity of internal HNL may vary over time, and this score may not reflect those variations. In this study, for instance, 64% of patients were classified as having moderate or severe internal HNL after 12 months, whereas only 2.2 of the 13 internal sites had this level of HNL on average. A more complete picture of how internal HNL changes over time might be provided by using a cumulative severity score or counting the number of internal sites affected, as was done in this study. The Revised Patterson Oedema Scale, formerly known as the Patterson's Radiotherapy Oedema Rating Scale, was recently updated [24], however there is still no guideline on composite grading. The MDACC Scale has limitations when used to evaluate external HNL. Due to the fact that it is solely a clinical evaluation, it lacks the sensitivity and psychometric testing of quantitative assessment tools like the ALOHA. As the ALOHA had not previously been utilised in a diagnostic capacity and had only been used to measure the reduction of external HNL over time, the MDACC Scale was used as the main assessment instrument in the current investigation [20, 21]. The analysis of the current study, however, also took into account normative TDC values for the head and neck region that were just published in 2021 [22]. The ability to use the ALOHA as a standalone evaluation tool has recently improved due to the availability of normative reference data.

Limitations:

There are a number of limitations to the current study, which is acknowledged. The first step was to establish a baseline or pre-treatment time point, but participation was lower than anticipated and there wasn't enough information to include in this study. The high levels of worry and distress related to diagnosis and therapy have been blamed for this. Similar to the 3-month time point, participation was low. Participants frequently declined this study session because they were still recovering from their previous treatments and had some anxiety about the findings of their post-treatment PET-CT scans. The generalizability of this study may be impacted by these elements as well as general attrition. Second, the internal validity of the existing research utilising Patterson's Radiotherapy Oedema Rating for HNL ratings also variable was scale. The present study utilised a set of educational materials to assist rating decisions that saw a higher degree of reliability than the authors' earlier work. However, more work in the field of clinician education is needed [10, 16] required. Additionally, the validity of the outside HNL ratings not examined in this research. The FEES process has a number of flaws, including no volumetric control with fluid trials, no meal trials, no way to measure pharyngeal residue, and more no explanation of bodily processes. additional negative effects. Xerostomia, secretions, and dysgeusia—conditions that are known to affect oral intake and swallowing after HNC treatment—were also not assessed.

Conclusion:

Following CRT, both external and internal HNL are common, and there are two distinct trajectory patterns in the 12 months after the last treatment. HNL from outside was most prominent at three months, started to become better at six months, and by 12 months had essentially been settled, whereas internal. HNL continued during the entire 12-month period, though with various modifications to the intensity and diffuseness. Patients who had more severe exterior or interior conditions HNL and those who additionally had internal HNL that was more diffuse felt dysphagia more severely. This research backs. Early detection, diagnosis, and post-treatment care for HNL are all important, but extra thought must be given to how internal HNL is managed and what function speech therapists play involvement in this management.

Declarations:

Conflict of interest:

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

References:

1. Sindhu SK, Bauman JE. Current concepts in chemotherapy for head and neck cancer. Oral Maxillofac Surg Clin North Am. 2019;31(1):145–54.

2. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist. 2010;15:994.

3. Barnhart MK, et al. Treatment toxicities and their impact on oral intake following non-surgical management for head and neck cancer: a 3-year longitudinal study. Support Care Cancer. 2018;26(7):2341–51.

4. Moroney LB, et al. Helical intensity-modulated radiotherapy with concurrent chemotherapy for oropharyngeal squamous cell carcinoma: a prospective investigation of acute swallowing and toxicity patterns. Head Neck. 2018;40(9):1955–66.

5. Miller MC, Shuman AG. Survivorship in head and neck cancer: a primer. JAMA Otolaryngol Head Neck Surg. 2016;142(10):1002–8.

6. Ridner SH, et al. A prospective study of the lymphedema and fibrosis continuum in patients with head and neck cancer. Lymphat Res Biol. 2016;14:198–205.

7. Murphy BA, Gilbert J, Ridner SH. Systemic and global toxicities of head and neck treatment. Exp Rev Anticancer Therapy.2007;7:1043–53.

8. Smith BG, Lewin JS. Lymphedema management in head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. 2010;18(3):153–8.

9. Deng J, et al. Prevalence of secondary lymphedema in patients with head and neck cancer. J Pain Symptom Manag. 2012;43:244–52.

10. Jeans C, et al. Comparing the prevalence, location, and severity of head and neck lymphedema after postoperative radiotherapy for oral cavity cancers and definitive chemoradiotherapy for oropharyngeal, laryngeal, and hypopharyngeal cancers. Head Neck. 2020;42(11):3364–74.

11. Deng J, et al. Factors associated with external and internal lymphedema in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012;84:e319-28.

12. Tribius S, et al. Prognostic factors for lymphedema in patients with locally advanced head and neck cancer after combined radio(chemo)therapy- results of a longitudinal study. Oral Oncol. 2020;109:104856.

13. Deng J, et al. Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. Head Neck. 2013;35:1026–35.

14. Deng J, et al. Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer. Support Care Cancer. 2012;20:1911–8.

15. Nixon JL, et al. A mixed methods examination of distress and person-centred experience of head and neck lymphoedema. Oral Oncol. 2018;83:18–24.

16. Jeans C, et al. Association between external and internal lymphedema and chronic dysphagia following head and neck cancer treatment. Head Neck. 2021;43(1):255–67.

17. Jeans C, et al. Patient perceptions of living with head and neck lymphoedema and the impacts to swallowing, voice and speech function. Eur J Cancer Care (Engl). 2019;28:e12894.

18. Jackson LK, et al. Internal lymphedema correlates with subjective and objective measures of dysphagia in head and neck cancer patients. J Palliat Med. 2016;19:949–56.

19. Queija DDS, et al. Cervicofacial and pharyngolaryngeal lymphedema and deglutition after head and neck cancer treatment. Dysphagia. 2020;35(3):479–91.

20. Nixon JL, et al. Pilot study of an assessment tool for measuring head and neck lymphoedema. Br J Community Nurs. 2014;19:S6.

21. Purcell A, et al. Measuring head and neck lymphedema: the “ALOHA” trial. Head Neck. 2014;38:79–84.

22. Mayrovitz HN, et al. An approach toward assessing head-and-neck lymphedema using tissue dielectric constant ratios: method and normal reference values. Lymphat Res Biol. 2021;19:562.

23. Patterson JM, Hildreth A, Wilson JA. Measuring edema in irradiated head and neck cancer patients. Ann Otol Rhinol Laryngol. 2007;116(8):559–64.

24. Starmer HM, et al. Development and reliability of the revised Patterson Edema scale. Clin Otolaryngol. 2021;46:752.

25. Carnaby GD, Crary MA. Development and validation of a cancer-specific swallowing assessment tool: MASA-C. Support Care Cancer. 2014;22(3):595–602.

26. Crary MA, Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil. 2005;86(8):1516–20.

27. Rosenbek JC, et al. A penetration-aspiration scale. Dysphagia. 1996;11(2):93–8.

28. Steele CM, Grace-Martin K. Refections on clinical and statistical use of the penetration-aspiration scale. Dysphagia. 2017;32(5):601–16.

29. Cooperstein E, et al. Vanderbilt head and neck symptom survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck. 2012;34(6):797–804.

30. StataCorp. Stata statistical software: release 15. College Station: StataCorp LLC; 2015.

31. Vanbelle S. A new interpretation of the weighted kappa coefficients Psychometrika. 2016;81(2):399–410.