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A prospective observational cohort study examining the development of head and neck lymphedema from the time of diagnosis

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Abstract

Introduction: Head and neck lymphedema can occur in the internal or external structures of the head and neck region. Little is known about the development of this condition over the course of treatment for head and neck cancer. This study aimed to observe the development of internal and external lymphedema from diagnosis to 12 weeks postacute treatment.

Methods: A single center, prospective observational cohort study assessed participants for external lymphedema, internal lymphedema, quality of life, and symptom burden. Assessments were conducted prior to starting radiotherapy (RT), at the end of RT, 6 and 12 weeks after RT.

Results: Forty-six participants were recruited. External lymphedema as measured by percentage water content, increased from 41.9 at baseline (95% CI: 39.3–44.4) to 50.4 (95% CI: 46.0–54.8) at 12 weeks following RT (p-value < .001). After adjusting for changes in weight and participant age at baseline, a general increase in tape measurements was observed over time with significant increases from baseline to 12 weeks post-RT for all measurement points. By 12 weeks post-RT, all participants had lymphedema present in eight of 13 internal sites assessed.

Conclusions: Internal and external head and neck lymphedema was observed to increase from baseline to 12 weeks after completion of RT without abatement. People with head and neck cancer should be educated about the potentially extended duration of this treatment side effect. Further research is required to determine the point at which swelling symptoms recede.

KEYWORDS
chemotherapy, head and neck neoplasms, lymphedema, quality of life, radiotherapy

1 | INTRODUCTION

Head and neck lymphedema can occur in either the internal or external structures of the head and neck. External lymphedema is visible to the clinician, whereas, internal lymphedema affects the mucosal surface of the body including the oral cavity, larynx, or pharynx.[1] The combined presentation of internal and external lymphedema appears to be more common in the postacute treatment phase,[1,2] whereas internal lymphedema alone seems more common in the longer term.[3] The development of head and neck lymphedema is precipitated by radiotherapy (RT) and surgical lymph node dissection.[4,5] RT and surgery alter the function of the lymphatic vessels leading to fluid accumulation, which may develop into lymphedema.[6,7] Other proposed correlates of head and neck lymphedema include older age, higher BMI, extent of disease and treatment,[8] although research into these correlates is not conclusive.

The impact of head and neck lymphedema is troublesome, and the incidence of chronic head and neck lymphedema is high. People with head and neck lymphedema experience more frequent and intense distress from higher symptom burden and functional deficits than similar patient cohorts without head and neck lymphedema.[9] Symptoms associated with head and neck lymphedema include swelling, tightness, heaviness, difficulty swallowing, difficulty moving the head or neck, hardness, taste changes, vocal difficulty, and pain.[2,10,11] Beyond these functional symptoms, head and neck lymphedema impacts psychosocial aspects including distress and changes in emotional wellbeing, body image, and socialisation.[11,12] Recent studies have identified head and neck lymphedema in 75.3% of (n = 81) participants 3 months post diagnosis[13]; 97.8% of (n = 46) participants 18 months post-treatment[2]; and, up to 99% of (n = 79) participants 1–3 years post-treatment.[14] Despite awareness of chronic lymphedema, there is very little research into acute head and neck lymphedema in the time after diagnosis and during RT and surgical treatment, which may delay the onset of head and neck lymphedema therapy.

Research into the efficacy of head and neck lymphedema therapy is limited by a paucity of large randomized controlled trials.[15] Smaller studies have associated head and neck lymphedema therapy with reductions in water content,[16] size measurements,[16–18] improvements in lymphatic flow,[19] and reductions in distress.[12] Therapy for head and neck lymphedema occurs on an ad hoc basis in contrast to conditions like breast cancer where a prospective monitoring and early intervention has been shown to reduce symptom burden and longevity of the condition.[20,21] Improved understanding of the development of head and neck lymphedema, particularly in the acute phase is required to identify suitable intervention schedules for potentially beneficial therapy. Therefore, the primary aim of this study was to observe the development of internal and external lymphedema from head and neck cancer diagnosis to 12 weeks post-RT. The secondary aim was to measure distress and quality of life associated with head and neck lymphedema.

2 | METHODS

2.1 | Design

This single center study was a prospective observational cohort study conducted at a quaternary hospital, the Princess Alexandra Hospital, Brisbane Australia. Ethics approval was received from the hospital (HREC/2019/QMS/47451) and university (2019000653/HREC/2019/QMS/47451) ethics boards. All participants provided informed written consent prior to commencing participation. Recruitment occurred from May 2019 to March 2020 in line with study resourcing. All assessors underwent a training program to enhance consistency and an initial period of observation by the lead investigator (AP).

2.2 | Participants

Participants attended the multidisciplinary head and neck clinic at the study site and were offered inclusion if they were over 18 years of age; had a diagnosis of oral cavity, nasopharyngeal, oropharyngeal, laryngeal, or hypopharyngeal cancer treated with chemoradiation, postoperative RT or definitive RT with curative intent; had a life expectancy of greater than 12 months; and were able to provide informed written consent. Participants were excluded if they had cancer recurrence; previous RT and/or surgery to the neck; co-morbidity factors that may have precipitated head and neck lymphedema, or impacted their swallowing and voice function; were unable to attend follow-up appointments; or had facial hair precluding completion of external head and neck lymphedema assessment.

2.3 | Procedure

Patients were referred by their treating medical team, screened for suitability, and contacted either face-to-face or via telephone to provide information about the study. Consenting participants were assessed at four time points: prior to starting RT, at the end of RT, 6 weeks after RT, and 3 months after RT.

2.4 | Outcome measures

Clinician-rated external lymphedema was measured using three assessments. The ALOHA tape measurement system[22] was used to measure the size of neck region. A standardized setup position was used with measurements taken at three defined anatomical landmarks (lower neck circumference, upper neck circumference, length from ear to ear). Percentage Water Content was measured to assess the content of free and bound local tissue water using a LymphScanner (Delfin Technologies Ltd). The LymphScanner generates an

electromagnetic wave, which reflects the water content of measured tissue to measure tissue dielectric constant to estimate the percentage water content (0%–99%). A higher value shows a higher water content (more lymphedema). A probe was placed on the skin at a defined point of the submental region, and a reading was taken with the average of three measurements recorded. These assessments have been previously investigated, with findings supporting their reliability and validity in a head and neck lymphedema population.[22] Finally, the MD Anderson Cancer Centre Head and Neck Lymphedema Rating Scale (MDACC Rating Scale)[23] was used to record observations of external lymphedema. This is a four-point ordinal scale where scores range from zero (no visible edema but patient reports heaviness) to three (irreversible tissue changes).

Clinician-rated internal lymphedema was assessed with one researcher (BB) examining and rating observations of nasendoscope images (still or dynamic) using the original Patterson's Radiotherapy Oedema Rating Scale.[24] This is a reliable and valid scale that rates edema in 11 laryngopharyngeal structures and two spaces as normal, mild, moderate, or severe. Internal lymphedema was not measured at assessment three (end of RT) due to expected participant discomfort from RT side effects. For reliability purposes, 20% of images were assessed by a second rater (CJ) who was blind to the first rating.

Quality of life was measured using the EQ-5D-5L.[25] questionnaire comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The scale also includes the EQ-VAS to record self-rated health on a vertical visual analogue scale anchored by "best imaginable" (100) and "worst imaginable" (0) health states. Symptom burden was recorded using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30)[26] supplemented by the EORTC QLQ Head and Neck 43 (QLQ-HN43)[27] to more specifically focus on head and neck symptoms. The QLQ-30 generates six functional scales (physical, role, emotional, social, cognitive, and global quality of life), three symptom scales (fatigue, pain, and nausea/vomiting), and six single items (dyspnoea, sleep disturbance, appetite, diarrhoea, constipation, and financial difficulties). The QLQ-HN43[27] generates seven multiple item scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality) and 11 single item scales including neck swelling. Participants were asked to report the presence of a symptom either: on a four-point Likert type scale where 1 = not present at all and 4 = very much present; using a categorical yes/no scale; or report overall health and quality of life on a seven-point visual analogue scale. Points from each scale are combined and transformed to assign a single or subscale score ranging from 0% indicating the least symptoms to 100% indicating the most symptoms.

A modified Distress Thermometer[28] was used to record self-perceived distress. This is a visual analogue scale ranging from 0 (no distress) to 10 (extreme distress) where participants rate their level of distress in relation to head and neck lymphedema over the past week.[12]

Demographic details were extracted from the participant's medical chart.

2.5 | Data analysis

Exploratory analysis comprised descriptive statistics to summarize baseline characteristics in the study cohort. Descriptive statistics were reported as frequencies with percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. For comparison, characteristics were summarized separately for participants who completed all four assessments.

Subsequent analyses investigated expected changes in external lymphedema, internal lymphedema, and psychosocial outcomes over time, using participant-level data on all completed assessments.

Trends in external lymphedema (tape measurements and Percentage Water Content) were estimated using linear mixed effects modeling. Models applied to each outcome included a categorical fixed effect for assessment number, with baseline assessment defined as the reference level. Continuous fixed effects for participant age (years) and body weight (kg) recorded at each assessment were included to adjust for possible confounding. Random effects were defined per participant to account for sources of within-subject variation. Expected outcomes were reported as parameter estimates with 95% confidence intervals, adjusted for average age and body weight within the full cohort.

To determine the clinical relevance of external lymphedema, comparison of percentage water content measurements was made with published tissue dielectric constant normative values.[29] Using the formula: tissue dielectric constant = (77.5/100) × "percentage water content" +1.[30]

Longitudinal changes in internal lymphedema were summarized graphically, based on severity (normal, mild, moderate, severe) for individual sites assessed by Patterson's scale. Maximum severity was assessed using the maximum rating for any one site at each assessment point. Follow-up analysis focussed on inter-rater reliability of Patterson's ratings for the same assessment number. Inter-rater reliability was assessed for each site using quadratic weighted kappa statistics, to account for partial matches in ordinal scores.

Subjective symptom measures recorded by QLQ-HN43 were summarized graphically to identify temporal trends across instrument subscales. Psychosocial measures (EQ-5D, Distress Thermometer) were summarised by timepoint as observed means with 95% confidence intervals. Across EQ-5D domains, the percentage of participants who reported some problems was also calculated.

All statistical analyses were completed using available packages in R version 4.0.3 or higher.

3 | RESULTS

Forty-six participants were recruited between May 2019 and March 2020. Baseline characteristics for all participants (n = 46) and the subgroup of participants who completed all four assessments (n = 15) are summarized in Table 1. Overall, descriptive statistics were similar between groups. The median age of participants at entry was 63 years, and 85% were male. All participants were diagnosed with squamous cell carcinoma, and 72% were p16 positive.

TABLE 1 Baseline characteristics

Characteristic	Full study cohort ($n = 46$)	Completed all assessments ($n = 15$)
Male: *n* (%)	39 (85)	13 (87)
Age in years: Median (IQR)	63 (58 to 67)	67 (63 to 71)
Identified as having social support: *n* (%)	44 (96)	15 (100)
Cancer type: *n* (%) SCC	46 (100)	15 (100)
Tumour site: *n* (%) p16 Positive Oropharynx	33 (72)	11 (73)
Larynx	5 (11)	2 (13)
Oral cavity	3 (7)	0 (0)
p16 negative oropharynx	2 (4)	1 (7)
Nasopharynx	2 (4)	0 (0)
Lymph nodes/unknown primary	1 (2)	1 (7)
Cancer Stage: *n* (%) I	14 (30)	5 (33)
II	14 (30)	3 (20)
III	11 (24)	4 (27)
IV	7 (16)	3 (20)
Received chemotherapy: *n* (%)	38 (84)	14 (93)
Received radiotherapy: *n* (%)	46 (100)	15 (100)
Underwent neck dissection surgery: *n* (%)	3 (7)	1 (7)

Eighty-four percent of participants underwent chemotherapy in addition to RT.

External lymphedema as assessed by tissue water content steadily increased over the study period from 41.9% at baseline (95% CI: 39.3–44.4) to 50.4% (95% CI: 46.0–54.8) at 12 weeks following RT (p-value < .001). To examine the clinical relevance of the baseline percentage water content, these results were compared to normative values for the related parameter of tissue dielectric constant.[29] Study participants had a baseline tissue dielectric constant of 33.5 (95% CI: 31.46–35.1) in comparison to normative values for the submental region of 35.9 +/− 7.7[29] indicating that participants did not have external lymphedema at baseline. External lymphedema assessment with tape measurements were affected by participant weight which decreased from a median of 84 kg (IQR: 73–100 kg) to 72 kg (IQR: 60–86 kg) from baseline to 12 weeks after RT (Table 2). After adjusting for changes in weight and participant age at baseline, a general increase in tape measurements over time with significant increases from baseline to 12 weeks post-RT for all measurement points was found. Changes in tape measurements varied between a 4.8% relative increase for ear to ear (baseline: 27.1 cm [95% CI: 26.6–27.6 cm]; 12 weeks: 28.4 cm [95% CI: 27.6–29.2 cm]; $p < .001$) and a 6.1% relative increase in the upper neck (baseline: 44.2 cm [95% CI: 43.2–45.2 cm]; 12 weeks: 46.9 cm [95% CI: 45.6–48.3 cm]). Clinical observation of external lymphedema showed 41 participants (89%) had a MDACC rating score of 0 at baseline indicating no visible oedema, compared with 32% (9/28) at the end of RT and 50% (7/14) at 12 weeks post-RT.

Extent of internal lymphedema showed a general trend toward having a greater number of sites involved over time (Figure 1). By 12 weeks post-RT, all participants had lymphedema present in a minimum of eight sites (base of tongue, posterior pharyngeal wall, epiglottis, pharyngoepiglottic folds, arytenoids, false vocal folds, valleculae, and piriform sinus). Maximum severity of internal lymphedema also increased over time from being most frequently mild/moderate at baseline (number of participants with no oedema = 4 [9%], mild = 16 [36%], moderate = 17 [39%], severe = 7 [16%]); to moderate/severe at 6 weeks post-RT (no oedema = 0, mild = 3 [14%], moderate = 8 [38%], severe = 10 [48%]); and 12 weeks post-RT (normal = 0, mild = 1 [8%], moderate = 8 [62%], severe = 4 [31%]). Due to the subjective nature of the Patterson's scale, inter-rater reliability was assessed and noted to vary between sites (Table S1). Of note, not all sites could be visualized on each assessment, and only those visualized are reported. Estimated inter-rater reliability found moderate levels of agreement for epiglottis ($n = 16$, kappa = .79) and interarytenoid spaces ($n = 16$, kappa = .80). In contrast, low inter-rater reliability was found for pharyngoepiglottic folds ($n = 14$, kappa = −.02) and valleculae ($n = 16$, kappa = .19).

Patterns of self-reported symptom burden assessed on the QLQ-HN43 showed increased average scores between baseline and the end of RT, followed by a steady decline back to baseline levels by the final assessment point (Figure S1). An exception was the subscale "dry mouth and sticky saliva," which showed similar average scores across the end of RT and post-therapy periods. Results for fear of progression showed an initial decrease in average score at the end of RT (Mean = 29.31[95%CI: 19.2–39.4]), before increasing toward baseline levels at 12 weeks post-RT (mean = 36.90 [95% CI: 28.4–45.4]). Subjective reports of head and neck lymphedema were assessed via a single item question on the QLQ-HN43, which asked participants if they had

TABLE 2 External lymphedema identified by tape measure and LymphScanner

Timepoint	Baseline ($n = 46$)	End of radiotherapy ($n = 29$)	6 weeks postradiotherapy ($n = 18$)	12 weeks postradiotherapy ($n = 14$)
Weight, kg Median (IQR)	84.1 (72.7–100.5)	77.9 (70.8–95.0)	74.1 (66.4–87.8)	72.1 (60.4–86.1)
Ear to ear length, cm Adjusted mean (95% CI) *p*-value	27.1 (26.6–27.6) –	26.4 (25.8–27.0) .031	27.2 (26.5–27.9) .677	28.4 (27.6–29.2) .002
Lower neck, cm Adjusted mean (95% CI) *p*-value	42.1 (41.2–42.9) –	41.8 (40.8–42.7) .498	42.3 (41.2–43.4) .695	44.6 (43.4–45.8)<.001
Upper neck, cm Adjusted mean (95% CI) *p*-value	44.2 (43.2–45.2) –	44.1 (43.0–45.2) .746	45.2 (44.0–46.4) .073	46.9 (45.6–48.3)<.001
Percentage water content				
Adjusted mean (95% CI) *p*-value	41.9 (39.3–44.4) –	43.7(40.6–46.9) .308	44.8(41–48.7) .181	50.4 (46–54.8) .001

Note: Linear mixed model output for external lymphedema, adjusted for average participant age at baseline (63 years), and weight by assessment timepoint. Hypothesis testing applied to differences in measurements at each assessment point relative to baseline.

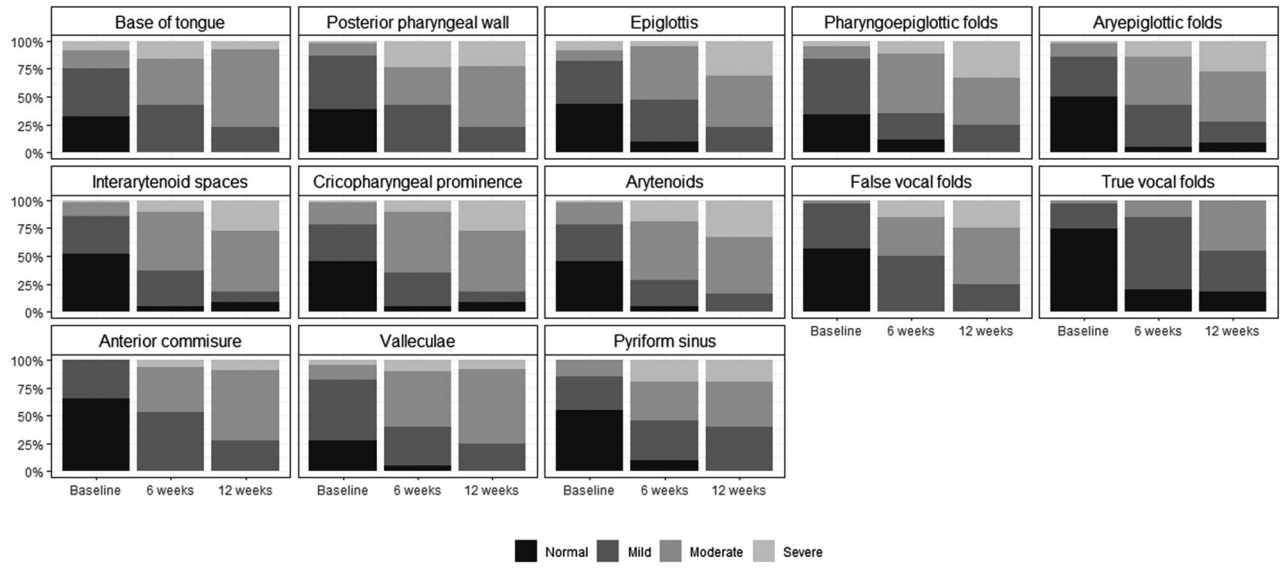

FIGURE 1 Internal lymphedema by anatomical site using Patterson's Radiotherapy Oedema Rating Scale

swelling in the neck in the previous week. Participants reported reducing swelling across the study period with most reporting having "a little" swelling at baseline and "not at all" 6 weeks after RT (Figure 2). Participant distress about lymphedema (Table 3) similarly increased from baseline to end of RT. Lowest levels of distress were reported 6 weeks post-RT but increased again at 12 weeks post-RT.

Quality of life as assessed by EQ-VAS remained constant throughout the study with a small reduction at the end of RT (Table 3). EQ-5D domain scores showed trends in the pain/discomfort and usual activities domains, with the largest differences observed between baseline and end of RT assessments. For unadjusted scores on pain/discomfort, the percentage of participants who reported some problems increased from 75% at baseline to 97% and the end of RT; and at 12 weeks post-RT, this had decreased to 64%. Similarly, the percentage of participants reporting some problems with usual activities increased from 30% at baseline to 79% at the end of RT. Few participants reported some problems with personal care over the follow-up period.

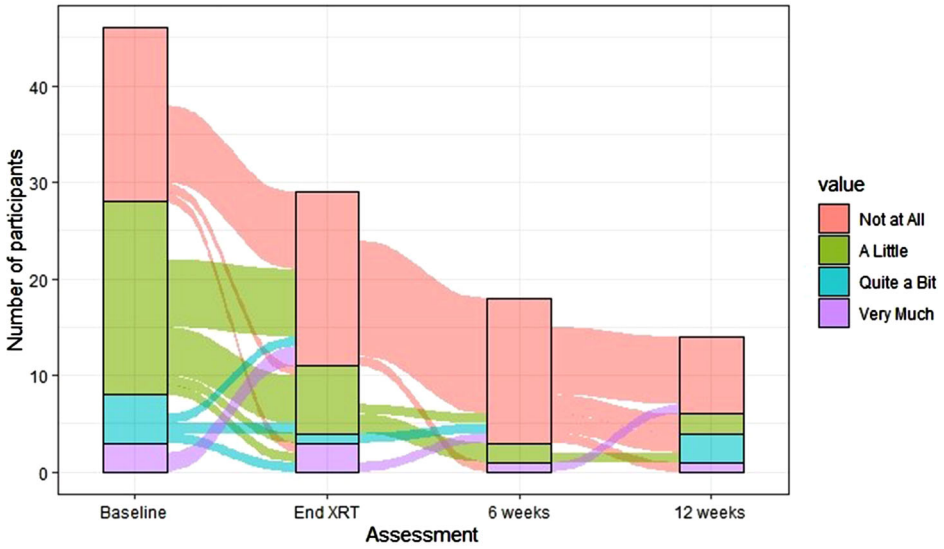

FIGURE 2 Self-reported presence of neck swelling by assessment time (EORTC QLQ-HN43) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Descriptive data for psychosocial measures across timepoints

	Timepoint			
Psychosocial measure	**Baseline**	**End of radiotherapy (RT)**	**6 weeks post RT**	**12 weeks post-RT**
Distress thermometer: Mean (95% CI)	3.54 (2.80–4.29)	3.97 (2.88–5.05)	1.61 (.97–2.25)	3.13 (1.70–4.56)
EQ-VAS: Mean (95% CI)	75.5 (71.1–80.0)	66.3 (60.7–72.0)	76.3 (71.2–81.3)	76.8 (69.5–84.0)
EQ-5D domain scores: Reported some problems[†]: *n* (%)	26 (57)8 (17)	17 (59)5 (17)	4 (22)5 (28)	6 (43)3 (21)
Anxiety depression	34 (74)	28 (97)	14 (78)	9 (64)
Mobility	1 (2)	2 (7)	0 (0)	0 (0)
Pain discomfort	14 (30)	23 (79)	11 (61)	6 (43)
Personal care				
Usual activities				

[†]EQ-5D "Reported some problems" was defined by an ED-5D score greater than 1.

4 | DISCUSSION

The primary aim of this study was to observe the development of internal and external lymphedema from head and neck cancer diagnosis to 12 weeks post-RT. External lymphedema measurements (percentage water content and tape measurements) showed steady increases from baseline to the end of RT with significant increases from the end of RT to 12 weeks post-RT. Weight loss over the duration of the study impacted the interpretation of tape measurement raw scores as they decreased in line with weight. The importance of recording weight has not been previously highlighted in head and neck lymphedema; however the findings from this study highlight its importance for accurate data interpretation. The clinical significance of the increases in percentage water content and tape measurements is supported by a change in the most frequent MDACC rating scale from 0 (no visible swelling) at baseline to 1a (soft visible edema; no pitting, reversible) at the end of RT and 12 weeks post-RT. The absence of swelling at baseline is also supported by the percentage water content falling within the normative range at that time. The increasing presence of external lymphedema 12 weeks after RT completion is an important finding given the usual expectation is that the early side effects of head and neck RT should decrease within weeks to a few months following completion of RT.[31,32]

Internal lymphedema occurred frequently over the duration of this study with a general trend toward greater severity over time. All study participants had internal lymphedema of at least one site by 12 weeks post-RT. This is a much higher prevalence than that found by Deng and colleagues[13] who reported only 68% of their sample (n = 81) had internal lymphedema in any one site at the same timepoint. While other studies have investigated the presence of internal and external lymphedema after treatment,[13,33] this study presents important information about the lymphedema experience from diagnosis, during and acutely after head and neck cancer treatment. This information can be used to guide expectations and plan supportive care for people undergoing head and neck cancer treatment.

Self-reported symptom burden showed a trend to increase between baseline and the end of RT, followed by a steady decline back to baseline levels by the final assessment point (for problems with body image, mouth pain, senses, teeth, sexuality, skin, social eating, speech, swallowing) as would be expected with recovery from RT. Fear of cancer progression increased at 12 weeks post-RT, a time of repeat staging scans. This pattern was also reflected in participant self-ratings of distress indicating that fear of cancer progression was related to timing of surveillance scans, as has been found by others.[34] Of note, 28 (61%) participants already reported swelling at baseline prior to treatment, and this number reduced across the study in contrast to the objective measurements of internal and external lymphedema. The authors hypothesize several possible reasons for this trend. This may represent the subjective experience of cancer creating a feeling of fullness at diagnosis, which changes after cancer treatment. It may also reflect adjustment to the presence of head and neck lymphedema as has been found for other subjective side effects such as dry mouth, swallowing, taste where these side effects continue to be present, but they are reported at lower rates over time.[35]

Quality of life was relatively high throughout the study with a small reduction at the end of RT when participants usual activities were most disrupted (participant EQVAS range 66–77/100). Quality of life was similar to previous studies of head and neck cancer patients before and after RT. A study of head and neck cancer patients ($N = 2065$) at diagnosis point reported a median baseline EQ-VAS of 75/100.[36] In our study, EQ-5D domain scores reflected the experience of participants' symptom burden showing a decrease in functional performance between baseline and the end of RT, followed by a gradual increase back to baseline levels. These trends were similar when age was added as a covariate, which was in contrast to previous studies, which found different domain patterns for different age groups. A study of ($n = 357$) head and neck cancer participants undergoing RT found older participants scored significantly better for emotional and social functioning than participants <65 years but worse for physical functioning.[37] A previous systematic review of the head and neck cancer cohort supported the return to baseline levels of quality of life, finding that although global quality of life returned at 12 months post active treatment, ongoing challenges with symptom burden (physical functioning, fatigue, xerostomia and sticky saliva) continued to contribute to distress.[38] This may indicate an ongoing need for psychosocial support for this patient group.

The strengths of this study include that its design was longitudinal and prospective with symptom monitoring including objective internal and external lymphedema measures, subjective swelling assessment, and quality of life domains to represent the complete and complex experience of head and neck cancer. In the absence of a "gold standard" measure for external head and neck lymphedema, it was assessed using three outcome measures, which all followed a consistent trend. The reliability of the internal lymphedema ratings were low for some structures (e.g., pharyngoepiglottic folds and valleculae). This should be considered within the context of the small sample size and the high prevalence of responses in single category responses. As kappa is known to be sensitive to prevalence rates, this may have affected the result.[39] Recently the Patterson's scale has been revised[40] to improve reliability across discipline and experience levels and in future studies should be used in place of the original scale. Participants in this study were most frequently male with SCC of the oropharynx and had received chemotherapy and RT reflecting expectations for this patient group.[41] The study sample was small in size with high attrition due to limitations imposed by the response to the COVID19 pandemic. Despite this, participants in full study cohorts had similar characteristics to those who completed all assessments. Further research is recommended to continue symptom monitoring beyond the 12 week follow-up assessment point to determine whether there is a symptom resolution point for head and neck lymphedema and to explore the potential benefits of early intervention.

5 | CONCLUSION

The combined presentation of internal and external lymphedema develops across the duration of acute head and neck cancer treatment and remains prevalent 12 weeks after the completion of acute treatment without decline. People undergoing head and neck cancer treatment require symptom support from the start of treatment through to 12 weeks follow-up at minimum, with the potential for psychosocial support being required beyond this time frame.

AUTHOR CONTRIBUTIONS

AP, JN, BB, and SP designed the study. AP, BB, CJ, SP, HL, and BP participated and/or supported data collection. NW completed data analysis with oversight from AP, SM, JN, and BB. AP and NW drafted the final manuscript with final review and approval from all authors. All authors agree to be accountable for all aspects of the work and answer questions as required.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author

ETHICS STATEMENT

Ethics approval was received from the hospital (HREC/2019/QMS/47451) and university (2019000653/HREC/2019/QMS/47451) ethics boards. All participants provided informed consent prior to commencing participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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