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The Impact of Secondary Lymphedema after Head and Neck Cancer Treatment on Symptoms, Functional Status, and Quality Of Life

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Abstract

Background—Lymphedema may disrupt local function and affect quality of life (QOL) in patients with head and neck cancer. The study aim was to examine the associations among severity of internal and external lymphedema, symptoms, functional status, and QOL in patients with head and neck cancer.

Methods—The sample included 103 patients who were ≥3 months post head and neck cancer treatment. Variables assessed included severity of internal and external lymphedema, physical/psychological symptoms, functional status, and QOL.

Results—Severity of internal and external lymphedema was associated with physical symptoms and psychological symptoms. Patients with more severe external lymphedema were more likely to have a decrease in neck left/right rotation. The combined effects of external and internal lymphedema severity were associated with hearing impairment and decreased QOL.

Conclusions—Lymphedema severity correlates with symptom burden, functional status, and QOL in patients post head and neck cancer treatment.

Keywords

Head and neck cancer; Lymphedema; Symptom; Functional Status; Quality of life (QOL)

Introduction

Patients with locally advanced head and neck cancer are usually treated with aggressive multi-modality treatment regimens.[1] These regimens often lead to a damaged lymphatic system and leave patients at risk for developing secondary lymphedema (accumulation of

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lymph fluid in the interstitial space).[2,3] Lymphedema is associated with chronic inflammation; thus, lymphedema may result in a progressive, self-perpetuating process. Chronic inflammation may lead to fibrosis, the end stage of severe lymphedema.[2,3] The European literature reports that 12%–54% of patients developed secondary lymphedema as a late effect of head and neck cancer treatment.[4–7] The structures involved by lymphedema are related to the tissues damaged by surgery and/or radiation therapy.

Head and neck lymphedema may be categorized as involving external structures (e.g., skin and soft tissue of the face and neck), internal structures such as the mucosa and underlying soft tissue of upper aerodigestive tract (e.g., pharynx and larynx)[8–11], or a combination of both. It may be hypothesized that alterations in soft tissue architecture and pliability resulting from head and neck lymphedema and related fibrosis result in substantial symptom burden, functional loss, and decreased quality of life (QOL). For example, external lymphedema involving the face may lead to body image disturbance; internal lymphedema involving the pharynx may interrupt swallowing function. Studies are needed to directly and systematically examine the impact of lymphedema severity on QOL in patients following head and neck cancer treatment. Thus, the purpose of this study was to examine the associations of the severity of internal and external lymphedema with symptom burden, functional status, and QOL in patients with head and neck cancer.

Methods

Participants and Setting

Permission to conduct this descriptive, correlational study was obtained from the Institutional Review Board (IRB) at Vanderbilt University and the Scientific Review Committee at Vanderbilt-Ingram Cancer Center (VICC). Of the 114 patients with head and neck cancer who were approached, 103 (90.4%) patients consented and were recruited into the study. Eleven (9.6%) patients approached did not participate in the study. Reasons for not participating included: no time (n=4), feeling overwhelmed (n=4), and lack of interest (n=3). Participants were included if they were (1) ≥ 18 years of age, (2) ≥ 3 months post head and neck cancer treatment, (3) currently free of evidence of cancer, and (4) able to provide informed consent.

Written informed consent was obtained from all participants. Participants underwent a detailed physical examination assessing: 1) external lymphedema, 2) cervical range of motion, 3) jaw range of motion, and 4) hearing. The first author (RN) conducted all assessments using a standard procedure to ensure consistency. Participants then completed the self-report instruments regarding symptom burden and QOL. Participants subsequently underwent routine endoscopic evaluation to assess internal lymphedema.

Study Instruments

Demographic and medical information—Demographic information included gender, date of birth, race, educational level, marital status, employment status, residence area, income, and alcohol and tobacco use. Medical information was obtained from the

participants' electronic medical records, including date of diagnosis of head and neck cancer, site, histology, stage, and treatment type and dates.

Lymphedema

External lymphedema: External lymphedema was graded using Foldi's "Stages of Lymphedema" (*abbreviation*: Foldi's Stages) (see Appendix A). This scale was developed based on experience treating over 100,000 patients with lymphedema. Four stages are evaluated when using this scale, ranging from stage 0 to stage III.[2,12] A grade of Stage 0 indicates no evidence of external lymphedema. External lymphedema was considered to be present if participants had at least Stage I lymphedema.

Internal lymphedema: Internal lymphedema was ascertained via flexible fiberoptic endoscopic and graded using Patterson's scale (see Appendix B).[13] Patterson's scale includes eleven laryngopharyngeal structures and two spaces. The scale has good intra-rater reliability (weighted kappa, 0.84) and moderate inter-rater reliability (weighted kappa, 0.54).[13] Four grades are used to rate edema level, which include normal (no edema) to severe edema.[13] Internal lymphedema was considered present if one anatomical site on Patterson scale was edematous regardless of the severity of edema. The severity of internal lymphedema (possible range, 0–3) for each participant was the highest grade noted among all involved sites. A grade of '0' indicates that there was no evidence of internal lymphedema at any site. One of two study physicians conducted a routine endoscopic evaluation with assessment of internal lymphedema. The study physicians who conducted endoscopic examination and evaluated internal lymphedema were trained to grade the severity of internal lymphedema based on Patterson's scale. The first author was present at the endoscopic evaluation for the first 10% of participants each physician assessed to ensure there was no major deviation from the assessment process.

Symptoms

Physical symptoms: The 27-item Vanderbilt Head and Neck Symptom Survey (VHNSS) was used to assess physical symptom burden related to head and neck cancer and its treatment.[14,15] Studies have reported good internal consistency for the total VHNSS scale (alpha=0.94) and five subscales (i.e., swallow, nutrition, mucous/dry mouth, pain, voice) (alphas=0.77–0.93), and adequate convergent and divergent validity.[15] The VHNSS scale also includes two single items (i.e., dentition and hearing). Mean scores on each VHNSS subscale can range from 0 (none) to 10 (a lot). Higher scores reflect greater symptom burden.[14,15] The internal consistency coefficients (Cronbach's alphas) in this study was 0.94 for the overall scale and ranged from 0.69–0.92 for the five subscales.

Psychological symptoms: Two instruments were used to assess psychological symptoms. The 14-item Hospital Anxiety and Depression Scale (HADS) was used to measure symptoms of anxiety and depression among the non-psychiatric population.[16] Good internal consistency has been reported in physically ill patients with or without cancer (Cronbach's alphas for HADS-anxiety range from 0.68 to 0.93 and for HADS-depression from 0.67 to 0.90).[16] Construct validity of the HADS has been supported.[16] Higher scores indicate greater anxious and/or depressive symptom burden.[17–19] In the current study, the

Cronbach's alphas for HADS-anxiety and HADS-depression were 0.88 and 0.83, respectively.

The 10-item Body Image Scale (BIS) was used to examine participants' self-assessment of body image related to cancer and cancer treatment.[20] In previous research with a heterogeneous group of cancer patients, the BIS has demonstrated high reliability (alphas ranging from 0.86 to 0.91) and good discriminant validity.[21] Higher scores represent increasing symptom/distress of body image. The Cronbach's alpha for the BIS in this study was 0.92.

Functional status

Cervical range of motion: The Cervical Range of Motion (CROM) device, manufactured by Performance Attainment Associates (Lindstrom, MN, U.S.A.), was used to measure the degree of neck movement. [22,23]

Jaw range of motion: The Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) Trismus Grading Criteria was used to evaluate trismus.[24]

Hearing: The whispered voice test and the tuning fork test [25] were used to assess hearing impairment. Responses from these hearing tests were coded dichotomously as either intact (0) or abnormal (1). The whispered voice test has a sensitivity of 87%–96% and a specificity of 70%–90%.[26]

Quality of Life (QOL)—Functional Assessment Cancer Therapy-Head & Neck (FACT-H&N) was used to assess QOL.[27] The FACT-H&N (39-item) is a psychometrically validated scale to measure QOL related to head and neck cancer treatment. The five subscales in the FACT-H&N are Physical Well-being (PWB), Social/Family Well-being (SWB), Emotional Well-being (EWB), Functional Well-being (FWB), and Head and Neck Cancer subscale (HNCS). FACT-general (FACT-G) is scored by summing the four subscales scores, including the PWB, SWB, EWB, and FWB. FACT-H&N is scored by summing the FACT-G and HNCS scores. The internal consistency of most of the subscales has been shown to be adequate (alphas=0.59 – 0.79).[27] In the current study, the Cronbach's alphas for the five subscales were between 0.61 and 0.86.

Statistical Methods

Descriptive statistics were used to describe the sample and the distributions of the study variables. Frequency distributions were used to summarize the nominal and ordinal demographic and clinical data, including the severity of external and internal lymphedema. Most of the symptom, function, and QOL scores were, as expected, highly skewed; therefore, median and 25^{th} and 75^{th} interquartile ranges, representing the middle 50% of the distributions, were used to describe those values. Given this observation, all of these lymphedema severity, symptom, function, and QOL distributions were rank transformed prior to inclusion in linear regression analyses described below. Due to the limited sample size, the individual Foldi and Patterson scores (specific lymphedema severity grades) were not contrasted in the analyses. Linear regression analyses were used to assess the multiple

correlations of lymphedema severity with the continuous symptom, functional, and QOL dependent variables (e.g., VHNSS symptom scores, FACT-H&N scores); logistic regressions were used for the respective analyses of dichotomous functional measures (e.g., whispered voice test). Before conducting the main analyses, the associations of demographic and clinical characteristics with each of the dependent variables were examined to identify variables possibly contributing to the symptom, function, or QOL values. Statistically significant characteristics were entered into the initial step of each hierarchical regression analysis to control for those associations. Subsequently, the Foldi (external) and Patterson (internal) scores were simultaneously entered into each regression model to arrive at an adjusted multiple correlation of those combined severity indices on the symptom, function, or QOL measure of interest.

From the hierarchical multiple linear regressions, R square and standardized coefficients will be reported in the Results and tables to summarize the association of both external lymphedema severity (Foldi's Stages) and internal severity (Patterson's scale) with the continuous dependent variables of interest. Standardized coefficients (beta) summarize the respective unique adjusted associations of each of the external (Foldi's Stages) and internal (Patterson's scale) lymphedema severity scores. In similar multiple logistic models, Likelihood Chi-square statistics were used to test the statistical significance of the adjusted multiple and specific associations of lymphedema severity with dichotomous dependent measures. Analyses of multicollinearity of the variables in the multivariate models were conducted as were residuals from those models, and no problems were detected. Even though a large number of statistical tests were conducted in this study, given the exploratory and preliminary nature of this research an uncorrected alpha of 0.05 was used for evaluating statistical significance.

Results

Sample characteristics

From December 2009 through May 2010, 103 patients with head and neck cancer completed the study. Demographic, disease, and treatment characteristics of the sample are summarized in Tables 1 and 2. Eighty-one participants (78.6%) underwent endoscopy examination, while the remaining twenty-two participants (21.4%) did not have an endoscopic exam. Of those twenty-two participants, half of them (n=11) had no endoscopy appointments scheduled, while the other half (n=11) had an endoscopy exam scheduled beyond the study data collection period. The participants who had an endoscopy completed during the study period tended to have been diagnosed with head and neck cancer more recently (medians: 2.0 vs. 3.3 years, p=.030) and completed cancer treatment more recently (medians: 17.7 vs. 35.3 months, p=.034). No other demographic or clinical characteristics demonstrated statistically significant differences between the groups.

Lymphedema

Based on physical examination, 46.6% (n=48) of all participants had external lymphedema, with 20.4% (n=21) assessed at stage I and 26.2% (n=27) assessed at stage II. No participants were classified with stage III external lymphedema. The most common sites of external

lymphedema were the neck and submental area. Of the 81 participants who had endoscopies and were graded using Patterson's scale for internal lymphedema, mild lymphedema was present in 23.5% (n=19), moderate lymphedema in 30.9% (n=25), and severe lymphedema in 13.6% (n=11). Thirty-two percent (26 out of 81) had no evidence of internal lymphedema. In these same 81 patients, 38.3% (31 out of 81) had both (combined) internal and external lymphedema.

Symptoms

Physical symptoms (VHNSS)—The median score for individual items on the VHNSS subscale were in the range of 0.00 to 3.00 on a 10-point scale. This suggests that most of the participants were in the recovery stages after head and neck cancer treatment and had mild symptom burden. Among the demographic and clinical variables demonstrating statistically significant associations with symptom burden, it was found that an increasing number of cancer treatment modalities received was associated with more swallowing-related symptoms (p = .012), as well as with mucous/dry mouth-related symptoms (p = .003). Length of time with a head and neck cancer diagnosis was found to be positively associated with more dentition-related symptoms (p = .037). Age was inversely associated with self-reported pain (p = .004).

The associations of the lymphedema severity and symptom scores on the VHNSS after adjusting for above reported associated demographic and clinical phenomena are summarized in Table 3. As shown, there were statistically significant associations of increased lymphedema severity with increased swallowing difficulties, nutrition problems, mucous/dry mouth-related symptoms, and voice problems. The association with swallowing and nutrition problems appeared to be explained more by the severity of external than internal lymphedema (External: *beta*=0.32, p=.006 for both swallowing and nutrition; Internal: swallowing, *beta*=0.14, p=.216; nutrition, *beta*=0.08, p=.516). On the other hand, the severity of internal lymphedema appeared to be more associated with higher levels of self-reported voice-related problems (External: *beta*=0.01, p=.946; Internal: *beta*=0.30, p=.014). There appeared to be a pattern of both types of lymphedema severity contributing in a more balanced way to the multiple correlation found with mucous and dry mouth problems (External: *beta*=0.20, p=.074; Internal: *beta*=0.26, p=.020). No statistically significant associations of lymphedema severity with self-reported pain, dentition-related symptoms, and hearing-related problems were observed.

Psychological symptoms (BIS & HADS)—The BIS scores in this study ranged from 0 to 30 (mean=6.03, median=3.00). These results indicate most of the participants had mild body image issues. The values of two HADS subscales scores ranged from 0 to 16 (mean=3.94, median=3.00) for anxiety and 0 to 14 (mean=3.31, median=2.00) for depression. The results suggest that most of the participants had few or relatively minor anxiety and depressive symptoms.

Some statistically meaningful associations of the demographic and clinical variables with the psychological symptom measures were observed. Participants who were single or widowed and participants living in urban areas reported higher body image disturbance

scores than participants who were married or living with a partner ($p < .001$) and those living in rural communities ($p = .046$). The only other demographic or clinical variable found to be associated with these psychological symptoms was age ($p = .001$), which was inversely associated with reports of anxiety, that is, older participants tended to report less anxiety than younger participants. There was a statistically significant correlation of lymphedema severity with the BIS scores (R square change = 0.07, p=.049). Essentially, all of this association was explained by the severity of external lymphedema (*beta*=0.26, p=.024) and not internal lymphedema (*beta*=0.02, p=.866). No statistically significant associations of lymphedema severity with self-reports of anxiety and depression were observed.

Functional status

The median scores for six directions of neck movement were in the range of 31.3 to 53.3 degrees (normal range 45 to 80). This suggests that most of the participants had mildly to moderately decreased neck range of motion after head and neck cancer treatment. Thirty-two percent (33 out of 103) of all participants had trismus; 12.6% of the participants failed whispered voice tests, and 29.1% failed tuning fork tests. Scores on the functional status measures are summarized in Table 4. A number of statistically significant associations of the demographic and clinical variables with functional status were observed. Length of time with a head and neck cancer diagnosis and length of time post cancer treatment were inversely associated with several directions of the neck movement, including forward flexion (both $p = .014$), left lateral flexion ($p = .015$; $p = .028$ respectively), left lateral rotation (both p=.003), and right lateral rotation (both p=.032). Increasing age was also found to be associated less lateral flexion (right side, $p = .042$; left side, $p = .003$) and right lateral rotation ($p = .009$), and greater rates of failure on the whispered voice test ($p = .002$). An increasing number of cancer treatment modalities received was associated with greater rates of deafness based on the tuning fork test ($p = .002$). Finally, participants who reported a history of smoking or were currently smoking demonstrated lower degree of neck movement (extension, right flexion, and rotation) than those who never smoked ($p < .050$).

After adjusting for those statistically significant variables, only neck rotation demonstrated a statistically significant correlation with the severity of lymphedema (R square change = 0.07 for left rotation and 0.08 for right rotation) (see Table 5). In both of the directions, most of the inverse association with decreasing neck rotation was explained by increasing severity of external lymphedema and not internal. No statistically significant associations of the lymphedema severity with the severity of trismus were observed (data not displayed).

After controlling for the statistically meaningful demographic and clinical variable associations with hearing impairment, a statistically significant association was found between increasing severity of lymphedema and the presence of indicators of impairment (Logistic regression for tuning fork test: overall likelihood χ^2 (2, N=102) =6.02, p=0.049; external: O.R.= 1.77, p=0.083, 95% confidence interval: 0.93–3.38; internal: O.R.=1.43, p=0.205, 95% confidence interval: 0.82–2.49; Logistic regression for whispered voice test: overall likelihood χ^2 (2, N=102) =6.60, p=0.037; external: O.R.= 0.40, p=0.101, 95% confidence interval: 0.14–1.20; internal: O.R.=2.38, p=0.036, 95% confidence interval:

1.06–5.33). As noted by the odds ratios above, there were mixed results depending on the test used as to whether the association was due more to external or internal lymphedema severity.

Quality of Life (QOL)

In this study, the FACT-H&N subscale scores of participants' ranged from 2 to 28 for the Physical Well-being subscale (median=25.00), 7 to 28 for the Social/Family Well-being subscale (median=24.00), 1 to 24 for the Emotional Well-being subscale (median=22.00), 0 to 28 for the Functional Well-being subscale (median=22.00), and 6 to 59 for the Head and Neck Cancer subscale (median=44.50). These data indicate that most of the participants had a moderate to high degree of QOL. Age and marital status demonstrated the most commonly seen statistically significant associations of demographic or clinical variables with the FACT-H&N measures of QOL. Being single or widowed was associated with lower reports of social well-being (p = .003). Increasing age was associated with greater physical (p = .003), emotional (p = .001), and functional well-being (p = .027).

While statistically significant adjusted multiple correlations of lymphedema severity were observed between lymphedema severity and overall QOL (FACT-G and FACT-H&N total), the strongest specific multiple correlation appeared to be with Functional Well-being (FWB) and Head and Neck Cancer (HNCS) subscales (FWB: R square change = 0.13, p=.006; HNCS: R square change = 0.08, p=.037;) and likely explains most of the association with overall or total QOL. Most of the multiple correlation of lymphedema severity with FWB was explained by increased levels of external lymphedema severity and not internal lymphedema severity (External: *beta*= −0.31, p=.008; Internal: *beta*= −0.10, p=.374). However, the combination of the severity of both types, not either type alone, contributed to the association with HNCS score (see Table 6).

Discussion

This is the first study we are aware of to examine the associations between lymphedema severity with symptoms, functional status, and QOL in patients with head and neck cancer. The results clearly indicate that lymphedema is a frequent late effect of head and neck cancer. Forty-six percent (48/103) of participants had external lymphedema and sixty-eight percent (55/81) had internal lymphedema for those undergoing endoscopy. Internal lymphedema was rated as severe in 20% (11/55) of participants who were diagnosed with that condition. Furthermore, both types of lymphedema were associated with substantial symptom burden, functional deficits, and decreased QOL.

One of the most important findings was that external lymphedema severity was associated with self-reported swallowing difficulties. This finding is consistent with the reports from three previous studies with small sample sizes (*Ns*=11–26).[28–30] However, they only examined presence of lymphedema whereas our study clearly showed that increased lymphedema severity was associated with increased severity of swallowing difficulties. Swallowing is a complex process that requires precise anatomical coordination of numerous structures.[31,32] It may be hypothesized that lymphedema-associated swelling or fibrosis alters anatomical structures thereby affecting physiologic function.

The study also demonstrated that external lymphedema was associated with self-reported nutrition-related symptoms (e.g., losing weight). Lymphedema may contribute to nutrition-related symptoms through two possible mechanisms. First, impaired swallowing results in decreased oral intake, leading to decreased caloric intake and weight loss. Second, lymphedema is associated with chronic inflammation.[3] In a number of disease processes, acute and chronic inflammation have been associated with systemic effects, including cachexia.[33,34] It may, therefore, be hypothesized that lymphedema-associated chronic inflammation results in metabolic alterations that lead to weight loss. Further research evaluating the systemic manifestations of lymphedema is needed.

One of the notable findings in this study is that lymphedema severity was associated with mucous/dry mouth-related symptoms. There are two potential reasons for this association. First, dry mouth may be a marker of an increased dose or an extended field of radiation. If that is the case, increased radiation doses or a more extended field of radiation may result in an increased risk of late tissue damage as manifested by lymphedema and fibrosis. Second, dry mouth may result in ongoing mucosal irritation and injury. This may lead to increased susceptibility to the development of lymphedema and fibrosis.

The study identified that internal lymphedema was associated with self-reported voice-related symptoms. Previous studies have demonstrated that patients who receive radiation therapy for vocal cord lesions experience alterations in voice characteristics and quality.[35] Although tissue edema and fibrosis are commonly ascribed mechanisms for alterations in vocal function, few prior reports have correlated lymphedema and voice-related symptoms. One study reported 16 patients with head and neck cancer who had voice dysfunction related to internal pharyngeal edema.[29]

This is the first study we are aware of to examine the association between lymphedema severity and body image in patients with head and neck cancer. Lymphedema may cause facial disfiguration and distress in patients with head and neck cancer;[36–38] thus, the finding of a significant relationship between external lymphedema and body image disturbance was not surprising. These results are similar to those reported in the breast cancer population where secondary lymphedema has been associated with body image issues.[39–42]

The lack of a statistically significant correlation between lymphedema severity and anxiety was unexpected. Although no studies are available for comparison regarding these relationships in patients with head and neck cancer, studies conducted in patients with breast cancer found that patients with more severe lymphedema had more anxiety.[43–45] Another interesting finding in this study is that participants with more severe lymphedema did not report more depressive symptoms. This finding was consistent with at least one study conducted in patients with breast cancer and secondary arm lymphedema, which reported that arm lymphedema severity was not correlated to depressive symptoms.[41] Nevertheless, small sample size may have contributed to the negative findings in the current study and further research is warranted.

Lymphedema severity was associated with decreased cervical range of motion. Specifically, participants with more severe external lymphedema had poorer left lateral and right lateral

rotation. This finding is similar to studies in patients with breast cancer and arm lymphedema.[40] These patients frequently reported decreased arm range of motion. We hypothesized that lymphedema may contribute to trismus in patients with head and neck cancer if lymphedema-related fibrosis affects the muscles of mastication; however, study finding did not support this hypothesis. One possible explanation for this finding is that only eight participants with facial lymphedema (swelling or fibrosis) were identified in this study, so the relationship between lymphedema and trismus could not be assessed with confidence. There is a need to recruit more participants with facial lymphedema and further examine the relationship between facial lymphedema/fibrosis and trismus.

Radiation therapy may cause Eustachian tube dysfunction and otitis media secondary to edema and tissue damage with associated secondary hearing loss.[46–48] In this study, the combined effects of external and internal lymphedema severity were related to decreased hearing as measured by tuning fork test and whispered voice test. Although this correlation was expected, further testing of this correlation with more sensitive hearing measures (such as formal audiological testing) is warranted to clearly identify whether external and/or internal lymphedema contributes to hearing impairments in patients post head and neck cancer treatment.

Finally, this study demonstrated that lymphedema severity was associated with overall QOL. This finding is similar to the outcomes from two previous studies.[10,11] When evaluating QOL subscales, data suggest that external lymphedema severity tended to correlate most strongly with the Functional and Head and Neck Subscales. This is rational because the content of these two subscales is reflective of the expected deficits associated with lymphedema.

The study has some limitations that need to be acknowledged. Because of the race distribution and the heterogeneity of the sample with respect to disease site, treatment modality, time since head and neck cancer diagnosis, time since completed treatment, and tumor stage, the study findings may not be generalizable to ethnic groups not represented in the study sample or to those with less severe disease, single modality of treatment, or shorter duration since completed cancer treatment. The majority of the participants (65%) in the current study had stage IV disease. It would be helpful for future studies to assess patients at uniform points in time, after head and neck cancer diagnosis and receiving particular types of cancer treatment. This study was cross-sectional in design; thus, causal relationships cannot be determined nor could the trajectory of lymphedema and prognostic factors for lymphedema development be delineated. Given the exploratory and preliminary nature of this study, an uncorrected alpha of 0.05 was used for evaluating statistical significance even though a large number of statistical tests were conducted. Care was taken to interpret the strongest and most apparent clinically meaning associations; however, the likehood of the false positive results is elevated in this study due to the large number of statistical tests conducted. Clearly future replication of the findings from this study will be helpful.

Moreover, multiple studies conducted in patients with breast cancer and arm lymphedema have demonstrated that patients with lymphedema may have altered sensation-related symptoms, such as numbness in the affected skin area.[41,49] These sensation-related

symptoms, however, were not captured in this study because valid instruments assessing lymphedema specific symptoms were not available for the head and neck cancer population. Development of a lymphedema-specific symptom instrument for patients with head and neck cancer is currently underway. In this study, endoscopic evaluation was done as part of routine follow-up. It is possible that patients who undergo endoscopy for evaluation of symptoms may have a higher likelihood of lymphedema. However, we wanted an unselected patient sample to ensure generalizability to the overall population of patients with head and neck cancer (not restricted to those with overt symptoms). The endoscopic evaluation was conducted outside of the time limit specified by the study in 21.4% of participants. This limits our ability to capture the entire picture of internal lymphedema status in the sample. Moreover, there might be other unmeasured differences between those who did versus did not undergo endoscopy examination in the study. In addition, due to physician scheduling difficulties, we were unable to directly examine inter-rater reliability of the internal lymphedema ratings for the entire sample. However, prior to data collection, the two physicians involved in the internal lymphedema data collection were trained regarding how to grade the severity of internal lymphedema. Moreover, the first author was present during the first 10% of the endoscopic examinations and did not find any significant differences for grading internal lymphedema between the two physicians. Thus, discrepancies between the two physicians who were grading severity of internal lymphedema appeared to be minimized.

Despite these limitations, some clinical implications are noteworthy. Healthcare professionals need to conduct physical examinations to detect external lymphedema (e.g., soft tissue and skin examination of the face and neck to identify any swelling and/or fibrosis) and internal lymphedema (e.g., endoscopic examinations). If lymphedema is identified, patients should be queried about associated symptoms. Referrals to lymphedema therapists, speech-language pathologists, and physical therapists should be made when appropriate.

Conclusions

Lymphedema is a frequent late effect of combined modality therapy for locally advanced head and neck cancer, and it is associated with substantial symptom burden and functional deficits. As expected, lymphedema was associated with poor body image and decreased QOL. Although data regarding the efficacy of therapeutic interventions are lacking, referral to appropriate specialty services is recommended for patients with head and neck cancer who also have symptomatic lymphedema. Studies exploring the temporal presentations of lymphedema and symptoms are needed to clearly elucidate the relationship between lymphedema, symptoms, and QOL. Interventional studies are needed to explore strategies regarding treatment of lymphedema, symptomatology, and improving QOL in patients with lymphedema after head and neck cancer treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic Characteristics

Characteristic	Frequency (%) (N=103)
Gender	
Male	71 (68.9)
Female	32 (31.1)
Race	
White	92 (89.3)
Black	11 (10.7)
Education Level	
<12th grade	11 (10.7)
≥12th grade	92 (89.3)
Marital Status	
Single/Widowed/Other	37 (35.9)
Married/Living with a partner	66 (64.1)
Employment Status	
Employed	52 (50.5)
Unemployed/Other	51 (49.5)
Residence Area	
Metropolitan	65 (63.1)
Rural	38 (36.9)
Insurance Coverage	
Medicare/ Medicaid/TennCare/TriCare	58 (56.3)
Private Insurance /HMO	37 (35.9)
None/other	8 (7.8)
Yearly Household Income	
≥ $20,000	19 (18.4)
$20,001 to $50,000	15 (14.6)
Over $50, 000	36 (35.0)
Do not care to respond	33 (32.0)
Smoking (any current or past use)	
Yes	68 (66.0)
No	35 (34.0)
Drinking Alcohol (any current or past use)	
Yes	42 (40.8)
No	61 (59.2)
Age (Mean, Median, IQR25–75, Min, Max)	59.8, 60.2, 51.9/66.6, 33.1, 86.7

Table 2

Head and Neck Cancer Disease and Treatment Characteristics

Characteristic	**Frequency (%) (N=103)**
Location	
Paranasal sinuses	5 (4.9)
Oral cavity	15 (14.6)
Nasopharynx	3 (2.9)
Oropharynx	49 (47.6)
Hypopharynx	4 (3.9)
Larynx	18 (17.5)
Salivary gland/Other	9 (8.7)
Tumor TNM Stage at Diagnosis	
Stage I	6 (5.8)
Stage II	9 (8.7)
Stage III	16 (15.5)
Stage IVa	59 (57.3)
Stage IVb	8 (7.8)
Could not be staged	5 (4.9)
Type of Tumor	
Squamous cell carcinoma (SCC)	96 (93.2)
Non-SCC	7 (6.8)
Complete Treatment Received	
Surgery alone	8 (7.8)
Radiation alone	2 (1.9)
Concurrent Chemo-radiation (CCR)	13 (12.6)
Surgery and radiation	10 (9.7)
Surgery and CCR	30 (29.1)
Chemo-induction and CCR	30 (29.1)
Surgery, chemo-induction, and CCR	10 (9.7)

Characteristic	Mean	Median	IQR (25, 75)	Min	Max

Characteristic	Frequency (%) (N=103)					
Head and Neck Cancer Duration (years)	2.8	2.1	1.0	3.9	0.5	14.6
Time Since Treatment Ended (months)	27.4	19.9	6.0	39.3	3.1	156.4

Table 3

Standardized Betas from Hierarchal Multiple Regression Analyses Predicting Symptom Scores from Lymphedema Severity (n=79)

	VHNSS													
	Swallow		Nutrition		Mucous /Dry mouth		Pain		Voice		Dentition		Hearing	
	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change
Final step: lymphedema severity		0.13**		0.12**		0.13**		0.05		0.09*		0.01		0.01
External (Foldi's Stages)	0.32**		0.32*		0.20		−0.04		0.01		0.04		−.0.10	
Internal (Patterson's scale)	0.14		0.08		0.26*		0.23*		0.30*		0.08		0.06	
R^2 (Full model)		0.28**		0.12**		0.24**		0.16		0.09*		0.04		0.01

Note:

(1) VHNSS= Vanderbilt Head and Neck Symptom Survey

(2) "β" is the standardized coefficient that reflects the specific adjusted association of external and internal lymphedema with each of the measures after controlling for all covariates.

(3) "R^2 change" is the amount of variance accounted for by including both types of lymphedema severity after any covariates have been controlled for.

(3) "R^2 (Full model)" is the amount of variance accounted for by the whole model which includes covariates as well as lymphedema severity scores.

(4) * p<0.05, ** p<0.01

Table 4

Functional Status Data

Characteristic	**Mean**	**Median**	**IQR (25, 75)**	**Min**	**Max**	**(Degree)(n=100)**
Cervical Range of Motion						
Forward flexion	43.5	42.7	33.3	50.3	19.3	70.0
Extension	49.2	48.0	38.3	60.8	15.3	88.7
Left lateral flexion	32.8	32.0	23.3	41.0	13.3	58.7
Right lateral flexion	31.3	31.3	22.5	39.3	11.0	58.0
Left lateral rotation	54.6	53.3	45.0	62.7	29.3	80.7
Right lateral rotation	53.8	52.0	44.7	64.0	26.0	80.0

Characteristic	Frequency (%) (N=103)
Trismus	
None	70 (68.0)
Grade 1	16 (15.5)
Grade 2	14 (13.6)
Grade 3	3 (2.9)
Whispered Voice Test	
Pass	89 (86.4)
Fail	13 (12.6)
Not applicable	1 (1.0)
Tuning Fork Test	
Normal	73 (70.9)
Conduction deafness (left ear)	3 (2.9)
Conduction deafness (right ear)	2 (1.9)
Nerve deafness (left ear)	13 (12.6)
Nerve deafness (right ear)	11 (10.7)
Not applicable	1 (1.0)

Table 5

Standardized Betas from Hierarchal Multiple Regression Analyses Predicting Cervical Range of Motion (CROM) Scores from Lymphedema Severity (n=80)

	Forward		Extension		Left Lateral		Right Lateral		Left Rotation		Right Rotation	
	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change
Final step: lymphedema severity		0.06		0.02		0.02		0.06		0.07*		0.08*
External (Foldi's Stages)	−0.19		−0.14		−0.16		−0.25*		−0.28*		−0.27*	
Internal (Patterson's scale)	−0.13		0.06		0.02		0.09		0.07		−0.06	
R^2 (Full model)		0.15		0.07		0.11		0.17		0.26*		0.23*

Note:

(1)"β" is the standardized coefficient that reflects the specific adjusted association of external and internal lymphedema with each of the measures after controlling for all covariates.

(2)"R^2 change" is the amount of variance accounted for by including both types of lymphedema severity after any covariates have been controlled for.

(3)"R^2 (Full model)" is the amount of variance accounted for by the whole model which includes covariates as well as lymphedema severity scores.

(4)* p<0.05, ** p<0.01

Table 6

Standardized Betas from Hierarchal Multiple Regression Analyses Predicting Quality of Life Scores from Lymphedema Severity (n=79)

	FACT-H&N													
	PWB		SWB		EWB		FWB		HNCS		FACT-G		FACT-H&N Total	
	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change	β	R^2 change
Final step: lymphedema severity		0.03		0.02		0.01		0.13**		0.08*		0.09*		0.12**
External (Foldi's Stages)	−0.16		0.04		−0.10		−0.31**		−0.21		−0.22		−0.30*	
Internal (Patterson's scale)	−0.05		−0.13		−0.04		−0.10		−0.14		−0.15		−0.10	
R^2 (Full model)		0.15		0.11		0.11		0.16**		0.14*		0.13*		0.17**

Note:

(1)FACT-H&N= Functional Assessment Cancer Therapy – Head & Neck

(2)PWB=Physical Well-being, SWB=Social/Family Well-being, EWB=Emotional Well-being, FWB=Functional Well-being, HNCS=Head & Neck Cancer Subscale, FACT-G=PWB+SWB+EWB+FWB, FACT-H&N Total=FACT-G and HNCS

(3)"β" is the standardized coefficient that reflects the specific adjusted association of external and internal lymphedema with each of the measures after controlling for all covariates.

(4)"R^2 change" is the amount of variance accounted for by including both types of lymphedema severity after any covariates have been controlled for.

(5)"R^2 (Full model)" is the amount of variance accounted for by the whole model which includes covariates as well as lymphedema severity scores.

(6)* p<0.05, ** p<0.01