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Clinical Investigation: Head and Neck Cancer

Factors Associated With External and Internal Lymphedema in Patients With Head-and-Neck Cancer

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Summary

The sample included 81 participants ≥3 months after head-and-neck cancer treatment. The study focused on examination of factors associated with the presence of external and/or internal lymphedema. Select tumor and treatment parameters are associated with the presence of lymphedema in the sample.

Purpose: The purpose of this study was to examine factors associated with the presence of secondary external and internal lymphedema in patients with head-and-neck cancer (HNC).

Methods and Materials: The sample included 81 patients ≥3 months after HNC treatment. Physical and endoscopic examinations were conducted to determine if participants had external, internal, and/or combined head-and-neck lymphedema. Logistic regression analysis was used to examine the factors associated with the presence of lymphedema.

Results: The following factors were statistically significantly associated with presence of lymphedema: (*1*) location of tumor associated with presence of external ($P = .009$) and combined lymphedema ($P = .032$); (*2*) time since end of HNC treatment associated with presence of external ($P = .004$) and combined lymphedema ($P = .005$); (*3*) total dosage of radiation therapy ($P = .010$) and days of radiation ($P = .017$) associated with the presence of combined lymphedema; (*4*) radiation status of surgical bed was associated with the presence of internal lymphedema, including surgery with postoperative radiation ($P = .030$) and (salvage) surgery in the irradiated field ($P = .008$); and (*5*) number of treatment modalities associated with external ($P = .002$), internal ($P = .039$), and combined lymphedema ($P = .004$). No demographic, health behavior-related, or comorbidity factors were associated with the presence of lymphedema in the sample.

Conclusions: Select tumor and treatment parameters are associated with increased occurrence of lymphedema in patients with HNC. Larger and longitudinal studies are needed to identify adjusted effects and causative risk factors contributing to the development of lymphedema in patients with HNC. © 2012 Elsevier Inc.

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Introduction

There are over one-half million head-and-neck cancer (HNC) survivors in the United States (1). Although aggressive use of multimodality therapy has contributed to improvement in overall survival rates, it has also left many patients with HNC at risk for experiencing secondary complications from their cancer and cancer treatment. Lymphedema is one of the under-reported but common side effects of HNC therapy (2, 3). Treatment for HNC may disrupt lymphatic structures and damage surrounding soft tissues, leading to increased accumulation of lymphatic fluid in interstitial spaces. The retention of lymphatic fluid activates inflammatory and immune responses and results in skin and subcutaneous soft tissue fibrosis and adipose deposition (4), which further impair lymphatic function.

Head-and-neck lymphedema may involve external structures (eg, soft tissue of the face and neck) (5), as well as internal anatomical sites (eg, mucous membranes and underlying soft tissues of the upper aerodigestive tract) (6). Thus, the potential clinical impact of head-and-neck lymphedema is profound. For instance, in patients with external lymphedema, swelling and fibrosis in the neck can cause decreased neck range of motion (2, 3); in patients with internal lymphedema, tissue swelling in the upper aerodigestive tract can affect articulation, cause airway obstruction, and result in swallowing difficulties (2, 3). Hence, it is particularly important to identify risk factors contributing to secondary lymphedema in patients with HNC in order to identify reversible or preventable causes. Currently, a limited number of studies are available in this area. The purpose of this study was to examine factors associated with external and internal lymphedema in patients with HNC.

Methods and Materials

Samples and setting

A cross-sectional, correlational design was used. A convenience sample of 103 participants was enrolled between December 2009 and May 2010 at a comprehensive cancer center. However, 81 participants (78.6%) underwent both physical and endoscopic examination, while the remaining 22 participants (21.4%) did not have an endoscopic examination available during the study data collection period. Half of those 22 participants (n = 11) had no endoscopy appointments scheduled, while the other half (n = 11) had an endoscopy examination scheduled beyond the study data collection period. Eligibility for participation included age ≥18 years, ≥3 months after completion of HNC treatment, no current evidence of cancer, and ability to provide informed consent. The study was approved by the institutional review board at the study site. Written informed consent was obtained from the participants.

Assessment of lymphedema

External lymphedema was identified on physical examination. All assessments were performed by the first author using a standard procedure to ensure consistency. External lymphedema was graded using Foldi's stages of lymphedema, which range from stage 0 (latency) to stage III (elephantiasis) (7, 8). Foldi's scale was chosen because it is the only tool that captures the continuum of soft tissue abnormalities ranging from reducible pitting edema to brawny, hard edema that does not recede with elevation. The psychometric properties of this tool have not been reported; however, Foldi et al (7) developed this scale based on treating more than 100,000 patients with lymphedema, thus, content validity of the scale can be assumed. In our study, external lymphedema was considered to be present if participants had at least stage I lymphedema. Also, based on the characteristics of head-and-neck lymphedema, we recruited patients with visible but nonpitting edema which was graded as stage I as a modification of the traditional Foldi's scale (7). In addition, intraoral lymphedema was included in the external lymphedema group.

Internal lymphedema was identified by flexible fiber optic endoscopic or mirror examination and graded by 1 of 2 trained study physicians, based on Patterson's scale (8, 9). Patterson's scale grades edema involving 11 structures and 2 spaces. The scale has good intrarater reliability (weighted kappa, 0.84) and moderate interrater reliability (weighted kappa, 0.54) (9). Internal lymphedema was considered to be present if 1 anatomical site was edematous regardless of lymphedema severity.

The combined lymphedema category included participants meeting both external and internal lymphedema criteria simultaneously.

Assessment of factors associated with lymphedema

Participants completed a Demographic and Background Information form. Medical information was collected from chart review by the first author. Radiation was delivered using intensity modulated radiation therapy (IMRT). In the majority (78%) of participants, the prescribed dose to the gross tumor volume and involved lymph node levels was between 2.0 Gy and 2.1 Gy/fraction to 60 Gy-69.3 Gy; prophylactic level doses to nodes was either 1.7 Gy/fraction to 56.1 Gy or 2.1 Gy/fraction to 50.4 Gy. Treatment was given once per day for 5 consecutive days each week. The IMRT technique, organs at risk, and doses used in treating study participants have been described previously (10).

In this study, 5 categories of variables were examined to see whether they were associated with the presence of lymphedema: (*1*) demographics (age, gender, race, education, marital status, employment status, residence area); (*2*) health-related behaviors (smoking consumption [yes/no], alcohol use [yes/no]); (*3*) comorbidity status (hypertension [yes/no], diabetes mellitus [yes/no], tracheotomy [yes/no], body mass index [BMI]); (*4*) tumor characteristics (location, histological type of tumor, stage of tumor); and (*5*) HNC treatment-related characteristics (start and end dates of HNC treatment, total dosage of radiation, days of radiation, primary site of surgery, characteristics of neck dissection, type of neck dissection, radiation status of surgical bed, and number of treatment modalities).

Location of HNC was coded as larynx, pharynx, oral cavity, or other. The pharynx category included participants with nasopharynx, oropharynx, and hypopharynx involvement. The other category included participants with paranasal sinuses, salivary gland tumors, and unknown primaries. Histology was coded as squamous cell carcinoma (SCC) and non-SCC. The non-SCC category included acinic cell carcinoma, clear cell mucoepidermoid, embryonal rhabdomyosarcoma, hemangiopericytoma, and small cell carcinoma. Primary site of surgery was coded as no primary tumor excision, oral cavity, pharynx, larynx, or other.

Characteristic of neck dissection was coded as no neck dissection, neck dissection with preservation of jugular vein, and neck dissection with sacrifice of jugular vein. Type of neck dissection was coded as no neck dissection, unilateral neck dissection, and bilateral neck dissection. Radiation status of surgical bed was coded as surgery only, surgery with postoperative radiation, and (salvage) surgery in the irradiated field. Number of treatment modalities used was coded as (*1*) single treatment modality (ie, surgery only or radiation only), (*2*) surgery with radiation or concurrent chemotherapy and radiation therapy, (*3*) surgery and concurrent chemotherapy and radiation therapy or chemo-induction therapy followed by concurrent chemotherapy and radiation therapy, or (*4*) chemo-induction followed by concurrent chemotherapy and radiation therapy, then surgery.

Data analysis

Categorical and ordinal data were summarized using frequency distributions. Ordinal data summaries also included the median value. Due to non-normal distributions, continuous data were described using median values and 25th-75th interquartile ranges (IQRs). For consistency of analysis, associations with the presence of lymphedema were tested by using the likelihood chi-square statistic generated using logistic regression analysis for each type of variable (nominal, ordinal, continuous). For this preliminary investigation, the critical alpha value for determining statistical significance was not adjusted for multiple tests; rather, a maximum alpha of $P<.05$ was used for each test.

Results

Sample characteristics

Most participants were male (71.6%) and white (88.9%). Median age was 59.7 years. Sixty-eight percent of participants reported a smoking history, and 40.7% of participants reported drinking alcohol. The oropharynx was the most common (42.0%) primary tumor site. Advanced stage disease (III-IV) was present in 80.2% of all participants. The histological type of most participants' tumors was SCC (95.1%). Most participants (87.6%) received at least 2 modalities of HNC treatment. The time since the end of HNC treatment ranged from 3.1 to 156.4 months (median, 17.7 months).

Lymphedema data

Lymphedema findings from both physical and endoscopic/mirror examinations are summarized in Table 1. The external sites most frequently involved were the submental region and the neck. Some participants had lymphedema around their eyes, cheeks, tongues, and upper shoulders.

Table 1 Lymphedema data

Type of lymphedema	Frequency (%) (n=81)
No lymphedema	20 (24.7)
Lymphedema	61 (75.3)
Total	81 (100.0)
Distribution of lymphedema type	Frequency (%) (n=61)
External lymphedema only	6 (9.8)
Internal lymphedema only	24 (39.4)
Combined lymphedema	31 (50.8)
Subtotal	61 (100.0)

All participants completed both endoscopic and external examinations.

Factors associated with lymphedema

Demographics

There were no statistically significant associations between the presence of any type of lymphedema (external, internal, or combined) and age, gender, race, education, marital status, employment status, and residence area (Tables 2, 3, and 4).

Health-related behaviors

No statistically significant associations were identified between the presence of any type of lymphedema and smoking or alcohol use (Tables 2, 3, and 4).

Comorbidities

There were no statistically significant associations identified between the presence of any type of lymphedema and hypertension, diabetes mellitus, tracheotomy, or obesity (BMI $\geq$30) (Tables 2, 3, and 4).

Tumor-related factors

Tumors in the pharynx were more commonly associated with external ($P=.009$) and combined lymphedema ($P=.032$) than tumors in other sites (Tables 2 and 4). No statistically significant associations were found between other tumor-related factors (ie, histological type of tumor or stage of tumor) and lymphedema (Tables 2, 3, 4).

Cancer treatment-related factors

The number of treatment modalities was associated with an increased likelihood of all types of lymphedema ($P<.05$) (Tables 2, 3, and 4). Total dosage of radiation ($P=.010$) and number of days of radiation ($P=.017$) were associated with an increased likelihood of combined lymphedema (Table 4). Radiation status of the surgical bed was associated with an increased likelihood of internal lymphedema ($P=.001$) (Table 3). Finally, months since the end of HNC treatment was associated with an increased likelihood of external ($P=.004$) and combined lymphedema ($P=.005$) (Tables 2 and 4). There were no statistically significant associations between the remaining cancer treatment-related factors and any type of head-and-neck lymphedema ($P>.05$).

In summary, the study identified 6 factors that were statistically significantly associated with the presence of head-and-neck lymphedema in the sample, including location of tumor, months since the end of HNC treatment, total dosage of radiation therapy, days of radiation, radiation status of the surgical bed, and number of treatment modalities.

Discussion

This is the first study we are aware of that systematically examined associations between demographic characteristics, health-related behaviors, comorbidity status, tumor characteristics, and treatment parameters and the presence of lymphedema after HNC treatment. We focused on secondary lymphedema rather than acute edema;

Table 2 Logistic regression of factors on external lymphedema

Characteristic	Sample size (n)	External lymphedema Yes, n (%)	External lymphedema No, n (%)	*P* value
Gender				
Female	81	9 (24.3)	14 (31.8)	.457
Male		28 (75.7)	30 (68.2)	
Race				
White	81	31 (83.8)	40 (90.9)	.337
Black		6 (16.2)	4 (9.1)	
Marital status				
Married/living with partner	81	25 (67.6)	25 (56.8)	.323
Single/widowed/other		12 (32.4)	19 (43.2)	
Employment status				
Employed	81	20 (54.1)	23 (52.3)	.873
Retired/disabled/unemployed		17 (45.9)	21 (47.7)	
Residence area				
Metropolitan	81	25 (67.6)	24 (54.5)	.234
Rural		12 (32.4)	20 (45.5)	
Smoking				
Yes	81	25 (67.6)	30 (68.2)	.953
No		12 (32.4)	14 (31.8)	
Drinking alcohol				
Yes	81	15 (40.5)	18 (40.9)	.973
No		22 (59.5)	26 (59.1)	
Hypertension				
Yes	81	13 (35.1)	21 (47.7)	.254
No		24 (64.9)	23 (52.3)	
Diabetes mellitus				
Yes	81	6 (16.2)	2 (4.5)	.099
No		31 (83.8)	42 (95.5)	
Tracheotomy				
Yes	81	2 (5.4)	7 (15.9)	.152
No		35 (94.6)	37 (84.1)	
Location of HNC (*P* = .010)				
Other*	81	0 (0.0)	10 (22.7)	
Oral cavity		3 (8.1)	9 (20.5)	.333
Pharynx		28 (75.7)	16 (36.3)	.009
Larynx		6 (16.2)	9 (20.5)	.106
Histological type of HNC				
SCC	81	37 (100.0)	40 (90.9)	.999
Non-SCC		0 (0.0)	4 (9.1)	
Primary site of surgery (*P* = .658)				
No primary tumor excision*	48	6 (30.0)	4 (14.3)	
Oral cavity		5 (25.0)	9 (32.1)	.244
Pharynx		4 (20.0)	5 (17.9)	.500
Larynx		3 (15.0)	4 (14.3)	.488
Other		2 (10.0)	6 (21.4)	.148
Characteristic of neck dissection (ND) (*P* = .446)				
No ND*	48	1 (5.0)	5 (17.9)	
ND with preservation of jugular vein		16 (80.0)	20 (71.4)	.226
ND with sacrifice of jugular vein		3 (15.0)	3 (10.7)	.239
Type of ND (*P* = .418)				
No ND*	48	1 (5.0)	5 (17.9)	
Unilateral ND		12 (60.0)	13 (46.4)	.190
Bilateral ND		7 (35.0)	10 (35.7)	.297

(*continued on next page*)

Table 2 (*continued*)

Characteristic	Sample size (n)	External lymphedema Yes, n (%)	External lymphedema No, n (%)	*P* value
Radiation status of surgical bed (*P*=.246)				
Surgery only*	48	1 (5.0)	7 (25.0)	
Surgery with postoperative radiation		11 (55.0)	13 (46.4)	.120
(Salvage) Surgery in irradiated field		8 (40.0)	8 (28.6)	.099

	Sample size (n)	External lymphedema Yes, n (median, IQR 25th-75th)	External lymphedema No, n (median, IQR 25th-75th)	*P* value
Age	81	37 (58.7, 49.8-64.2)	44 (60.3, 53.5-70.0)	.114
Education	81	37 (14.0, 12.0-16.0)	44 (12.0, 12.0-14.8)	.196
BMI	71	34 (27.0, 22.8-31.5)	37 (26.0, 22.0-28.5)	.275
Stage of tumor	77	36 (4.0, 4.0-4.0)	41 (4.0, 3.0-4.0)	.070
Months since end of HNC treatment	81	37 (6.8, 4.0-24.3)	44 (24.5, 8.3-41.4)	.004
Total dosage of radiation	59	31 (6930.0, 6600.0-6930.0)	28 (6600.0, 6000.0-6930.0)	.071
Days of radiation	67	36 (46.0, 44.0-51.0)	31(44.0, 39.0-49.0)	.085
Number of treatment modalities	81	37 (3.0, 3.0-3.0)	44 (3.0, 2.0-3.0)	.002

Abbreviations: BMI = body mass index; HNC = head-and-neck cancer; IQR = interquartile range; ND = neck dissection; SCC = squamous cell carcinoma.

* The referent category used during logistic regression analysis.

thus, we recruited patients with HNC who had completed their cancer treatment ≥3 months prior to study entry. Acute treatment-related swelling should have resolved prior to study enrollment. The most common primary tumor site was the oropharynx; most participants had a locally advanced stage of tumors at the time of diagnosis of HNC; the histological type of most participants' tumors was SCC; and most participants received at least 2 modalities of cancer treatment. The primary treatment and cancer-related characteristics for patients enrolled in this study are similar to those reported in the literature (11). Thus, we believe our study sample is representative of HNC survivor populations.

Surprisingly, we did not find that any of the demographic factors, health-related behaviors, or comorbidities was associated with lymphedema in our sample. These findings are different from those of reports in breast cancer survivors. Several studies of breast cancer treatment-related lymphedema found that age (12), hypertension (13), diabetes mellitus (13), and BMI (13, 14) were significantly related to arm lymphedema development, although the underlying causes of the relationships between occurrence of arm lymphedema and these demographic/comorbidity factors are unknown. We postulate 2 possible explanations for this distinction. First, lymphatic structures in the head-and-neck region and the chest and arm area differ anatomically. There is a rich lymphatic system in the head-and-neck region including approximately 300 lymph nodes, which comprise 30% of the total 800 lymph nodes in the human body (15). This might lead to different manifestations and expression of lymphedema in the HNC population compared to that in the breast cancer population. Second, tumor and treatment-related factors may play a more profound role in HNC sequelae, overshadowing or negating any potential effect of demographic or comorbidity factors. Given the cross-sectional nature of this study and the modest sample size, longitudinal studies of these factors with larger sample sizes are indicated to confirm our findings.

Regarding tumor parameters, an interesting finding is the association between location of HNC and presence of lymphedema. That is, individuals with pharyngeal carcinoma were more likely to experience lymphedema than individuals with tumors in other sites. Currently, no studies are available for comparison. However, pharyngeal carcinoma is one of the most frequent tumors in HNC populations (11), indicating that a substantial number of patients are at risk for post-treatment lymphedema. It is not surprising that histological type was not correlated with the presence of lymphedema in this sample, because treatment was similar across histologic subtypes. The finding that stage did not correlate with lymphedema was unexpected. Tumor stage may be considered a surrogate for (*1*) intensity of treatment sequelae for cure and (*2*) the extent of normal tissue damage secondary to treatment; thus, we expected that increasing stage would be associated with increased incidence of lymphedema. Furthermore, in the breast cancer population, stage of tumor was significantly related to lymphedema development (13). The lack of correlation between stage and lymphedema in the head-and-neck population may be explained by (*1*) predominance of advanced stage diseases in this cohort analysis or (*2*) a lack of correlation between stage and the severity of treatment induced normal tissue damage.

Our study found that specific treatment parameters were significantly related to the presence of head-and-neck lymphedema. An important finding is the inverse association between the presence of head-and-neck lymphedema and time since the end of HNC treatment; that is, increased time since completion of therapy was less likely to be associated with lymphedema. Although no studies have examined this phenomenon over time, it confirms our clinical experience that head-and-neck lymphedema develops 2-6 months after cancer treatment and subsides spontaneously over time in some patients. Spontaneous resolution of lymphedema may be partial or complete. In addition to spontaneous regression, patients were routinely referred for lymphedema therapy. Although well-conducted trials confirming the efficacy of lymphedema therapy in patients with HNC are lacking, it is clear that lymphedema therapy can result in marked regression of lymphedema and associated symptoms.

A number of radiation treatment parameters correlated with lymphedema. Individuals with higher dosages of radiation were

Table 3 Logistic regression of factors on internal lymphedema

Characteristic	Sample size (n)	Internal lymphedema		*P* value
		Yes, n (%)	No, n (%)	
Gender				
Female	81	13 (23.6)	10 (38.5)	.171
Male		42 (76.4)	16 (61.5)	
Race				
White	81	47 (85.5)	24 (92.3)	.389
Black		8 (14.5)	2 (7.7)	
Marital status				
Married/living with partner	81	32 (58.2)	18 (69.2)	.185
Single/widowed/other		23 (41.8)	8 (30.8)	
Employment status				
Employed	81	28 (50.9)	15 (57.7)	.568
Retired/disabled/unemployed		27 (49.1)	11 (42.3)	
Residence area				
Metropolitan	81	36 (65.5)	13 (50.0)	.266
Rural		19 (34.5)	13 (50.0)	
Smoking				
Yes	81	40 (72.7)	15 (57.7)	.179
No		15 (27.3)	11 (42.3)	
Drinking alcohol				
Yes	81	23 (41.8)	10 (38.5)	.774
No		32 (58.2)	16 (61.5)	
Hypertension				
Yes	81	22 (40.0)	12 (46.2)	.601
No		33 (60.0)	14 (53.8)	
Diabetes mellitus				
Yes	81	5 (9.1)	3 (11.5)	.731
No		50 (90.9)	23 (88.5)	
Tracheotomy				
Yes	81	5 (9.1)	4 (15.4)	.405
No		50 (90.9)	22 (84.6)	
Location of HNC (*P* = .464)				
Other*	81	5 (9.1)	5 (19.2)	
Oral cavity		7 (12.7)	5 (19.2)	.696
Pharynx		32 (58.2)	12 (46.2)	.172
Larynx		11 (20.0)	4 (15.4)	.240
Histological type of HNC				
SCC	81	53 (96.4)	24 (92.3)	.442
Non-SCC		2 (3.6)	2 (7.7)	
Primary site of surgery (*P* = .613)				
No primary tumor excision*	48	8 (28.6)	2 (10.0)	
Oral cavity		8 (28.6)	6 (30.0)	.251
Pharynx		4 (14.3)	5 (25.0)	.121
Larynx		4 (14.3)	3 (15.0)	.318
Other		4 (14.3)	4 (20.0)	.191
Characteristic of ND (*P* = .361)				
No ND*	48	2 (7.2)	4 (20.0)	
ND with preservation of jugular vein		23 (82.1)	13 (65.0)	.176
ND with sacrifice of jugular vein		3 (10.7)	3 (15.0)	.560
Type of ND (*P* = .278)				
No ND*	48	2 (7.2)	4 (20.0)	
Unilateral ND		17 (60.7)	8 (40.0)	.134
Bilateral ND		9 (32.1)	8 (40.0)	.414

(*continued on next page*)

Table 3 (*continued*)

Characteristic	Sample size (n)	Internal lymphedema Yes, n (%)	Internal lymphedema No, n (%)	*P* value
Radiation status of surgical bed (*P*=.001)				
Surgery only*	48	0 (0.0)	8 (40.0)	
Surgery with postoperative radiation		15 (53.6)	9 (45.0)	.030
Salvage surgery in irradiated field		13 (46.4)	3 (15.0)	.008

	Sample size (n)	Internal lymphedema Yes, n (median, IQR 25th-75th)	Internal lymphedema No, n (median, IQR 25th-75th)	*P* value
Age	81	55 (59.7, 51.2-65.8)	26 (60.5, 51.0-70.6)	.491
Education	81	55 (12.0, 12.0-15.0)	26 (13.5, 12.0-16.0)	.371
BMI	71	50 (27.0, 22.0-30.3)	21 (26.0, 22.0-28.0)	.281
Stage of tumor	77	54 (4.0, 3.0-4.0)	23 (4.0, 2.0-4.0)	.196
Months since end of HNC treatment	81	55 (16.7, 5.4-33.7)	26 (20.8, 6.7-35.6)	.619
Total dosage of radiation	59	45 (6930.0, 6600.0-6930.0)	14 (6360.0, 5985.0-6930.0)	.209
Days of radiation	67	51 (46.0, 43.0-51.0)	16 (43.5, 39.8-46.0)	.062
Number of treatment modalities	81	55 (3.0, 2.0-3.0)	26 (3.0, 1.0-3.0)	.039

Abbreviations: BMI = body mass index; HNC = head-and-neck cancer; IQR = interquartile range; ND = neck dissection; SCC = squamous cell carcinoma.

* The referent category used during logistic regression analysis.

more likely to have head-and-neck combined lymphedema. This finding was similar to the result from 1 study which reported that laryngeal lymphedema was significantly correlated with select dosimetric parameters including mean laryngeal dosage (16). Based on their findings, those authors suggested that the mean laryngeal radiation dose should be kept as low as possible to minimize the risk of edema. It should be noted that radiation therapy was identified as a significant risk factor for the development of arm lymphedema in breast cancer patients (12). We also found that individuals with surgery followed by postoperative radiation or salvage surgery in an irradiated field were more likely to have internal lymphedema than patients with surgery treatment only. These findings suggest that radiation may play a critical role in soft tissue damage in patients with HNC.

Contemporary models depict lymphedema as 1 end of a continuum with fibrosis at the other end. Additionally, fibrosis has been depicted as the end-stage manifestation of lymphedema. This phenomenon may be explained by data obtained from studies conducted in animal models which demonstrate that radiation damage to lymph nodes and lymph vessels leads to abnormal lymphatic flow and stimulates inflammatory response (17). Furthermore, in a mouse tail model, investigators found that radiation caused tissue edema that resolved in 12-24 weeks (18). Despite resolution of acute edema, irradiated tissue displayed continuing lymphatic dysfunction due to depletion of lymphatic vessels, lymphatic endothelial cells, and soft tissue fibrosis. This experimental phenomenon mirrors observed clinical manifestations of radiation therapy: acute edema leading to chronic lymphedema and fibrosis. Of note, many of the late effects of HNC therapy, including dysphagia and decreased range of motion in the neck and shoulders, have been attributed solely to fibrosis. It is likely that most patients who have completed HNC therapy first develop a component of lymphedema that later transforms to fibrosis. In addition, some patients may develop severe fibrosis without evidence of lymphedema.

Although we did not find that other surgical factors (including primary site of surgery, characteristic of neck dissection, and type of neck dissection) were statistically related to the presence of head-and-neck lymphedema, there was a trend toward more lymphedema cases in the neck dissection groups (19 of 42 participants [45.2%]) than in the no neck dissection group (1 of 6 participants [16.7%]) in the study. This finding was consistent with the data from another study (19). Those authors found that 17% (4 of 24) of sentinel node biopsy patients with HNC had mild lymphedema, whereas 36% (9 of 25) of patients treated with selective neck dissection developed mild and moderate lymphedema (19). However, that difference was not statistically significant (19). Nevertheless, many studies conducted in breast cancer-related lymphedema have found that surgery, especially more extensive surgical treatment, increases risk of development of lymphedema (12). Small sample size may contribute to the negative findings in this study. Thus, more studies with larger sample sizes, using longitudinal designs are needed to examine the association between head-and-neck lymphedema and these surgical factors.

Another important finding is that the number of treatment modalities exposed was significantly associated with the presence of lymphedema. It may be hypothesized that the more extensive or aggressive the therapy, the more likely there will be acute and long-term tissue damage. This finding would add to the argument that treatment plans must balance efficacy with acute and late toxicity. This argument is most powerful in non smokers with human papillomavirus (HPV)-associated oral cavity cancers. It has been demonstrated that this subgroup of patients has an excellent long-term prognosis (20). Studies are currently under way to determine whether therapeutic intensity and, therefore, acute and late toxicities may be decreased in this subgroup of patients without adversely impacting survival rates.

The main strengths of our study are that it was the first attempt to systematically examine factors related to the presence of lymphedema after HNC treatment and that participants underwent both external and internal examinations. The study also has some limitations that need to be acknowledged. We used a convenience sampling method rather than randomly selecting participants. Thus, the findings from this study may not be generalizable. Based

Table 4 Logistic regression for factors of combined lymphedema

Characteristic	Sample size (n)	Combined lymphedema		*P* value
		Yes, n (%)	No, n (%)	
Gender				
Female	81	8 (25.8)	15 (30.0)	.684
Male		23 (74.2)	35 (70.0)	
Race				
White	81	27 (87.1)	44 (88.0)	.904
Black		4 (12.9)	6 (12.0)	
Marital status				
Married/living with partner	81	20 (64.5)	30 (60.0)	.951
Single/widowed/other		11 (35.5)	20 (40.0)	
Employment status				
Employed	81	17 (54.8)	26 (52.0)	.804
Retired/disabled/unemployed		14 (45.2)	24 (48.0)	
Residence area				
Metropolitan	81	20 (64.5)	29 (58.0)	.700
Rural		11 (35.5)	21 (42.0)	
Smoking				
Yes	81	22 (71.0)	33 (66.0)	.642
No		9 (29.0)	17 (34.0)	
Drinking alcohol				
Yes	81	12 (38.7)	21 (42.0)	.770
No		19 (61.3)	29 (58.0)	
Hypertension				
Yes	81	11 (35.5)	23 (46.0)	.353
No		20 (64.5)	27 (54.0)	
Diabetes mellitus				
Yes	81	4 (12.9)	4 (8.0)	.476
No		27 (87.1)	46 (92.0)	
Tracheotomy				
Yes	81	0 (0.0)	9 (18.0)	.999
No		31 (100.0)	41 (82.0)	
Location of HNC (*P* = .030)				
Other*	81	0 (0.0)	10 (20.0)	
Oral cavity		3 (9.7)	9 (18.0)	.234
Pharynx		24 (77.4)	20 (40.0)	.032
Larynx		4 (12.9)	11 (22.0)	.204
Histological type of HNC				
SCC	81	31 (100.0)	46 (92.0)	.999
Non-SCC		0 (0.0)	4 (8.0)	
Primary site of surgery (*P* = .323)				
No primary tumor excision*	48	6 (37.5)	4 (12.5)	
Oral cavity		5 (31.2)	9 (28.1)	.244
Pharynx		2 (12.5)	7 (21.8)	.107
Larynx		1 (6.3)	6 (18.8)	.081
Other		2 (12.5)	6 (18.8)	.148
Characteristic of ND (*P* = .664)				
No ND*	48	1 (6.2)	5 (15.6)	
ND with preservation of jugular vein		13 (81.3)	23 (71.9)	.366
ND with sacrifice of jugular vein		2 (12.5)	4 (12.5)	.512
Type of ND (*P* = .521)				
No ND*	48	1 (6.2)	5(15.6)	
Unilateral ND		10 (62.5)	15 (46.9)	.303
Bilateral ND		5 (31.3)	12 (37.5)	.547

(*continued on next page*)

Table 4 (*continued*)

Characteristic	Sample size (n)	Combined lymphedema Yes, n (%)	No, n (%)	*P* value
Radiation status of surgery bed (*P*=.059)				
Surgery only*	48	0 (0.0)	8 (25.0)	
Surgery with postoperative radiation		8 (50.0)	16 (50.0)	.171
(Salvage) Surgery in irradiated field		8 (50.0)	8 (25.0)	.072

	Sample Size (n)	Combined lymphedema Yes, n (median, IQR 25th-75th)	No, n (median, IQR 25th-75th)	*P* value
Age	81	31 (58.7, 50.5-64.9)	50 (60.3, 52.5-68.6)	.185
Education	81	31 (14.0, 12.0-16.0)	50 (13.0, 12.0-15.3)	.711
BMI	71	28 (27.0, 22.0-32.5)	43 (26.0, 22.0-29.0)	.428
Stage of tumor	77	30 (4.0, 4.0-4.0)	47 (4.0, 3.0-4.0)	.123
Months since end of HNC treatment	81	31 (6.3, 3.9-20.5)	50 (23.1, 7.8-40.9)	.005
Total dosage of radiation	59	26 (6930.0, 6720.0-6930.0)	33 (6600.0, 6000.0-6930.0)	.010
Days of radiation	67	31 (46.0, 44.0-52.0)	36 (44.0, 39.5-46.8)	.017
Number of treatment modalities	81	31 (3.0, 3.0-3.0)	50 (3.0, 2.0-3.0)	.004

Abbreviations: BMI = body mass index; HNC = head-and-neck cancer; IQR = interquartile range; ND = neck dissection; SCC = squamous cell carcinoma.

* The referent category used during logistic regression analysis.

on a cross-sectional design without a true time dimension, the study investigated only factors associated with the presence of secondary lymphedema. Statements about relationships with the development or causes of lymphedema cannot be made with confidence. The sample size was too small for multivariate analyses. Given the complexity of disease processes, it is highly likely that multivariate associations will be more informative. In addition, Foldi's scale (7) is not specific for head-and-neck lymphedema. Thus, validation and modification of this scale may be needed in future studies. The Patterson scale is excellent for assessing internal edema of the base of tongue, larynx, and pharynx but offers no way to assess tissue firmness and pitting edema.

Conclusions

Despite these limitations, the study findings can be used to inform patient care and future research. Healthcare professionals need to be aware that patients with HNC are at high risk of developing lymphedema following cancer treatment. Second, healthcare professionals need to conduct lymphedema assessment as a component of routine clinical examination, especially for individuals at high risk (eg, multimodality treatment involvement). Third, if internal or external lymphedema is identified, referral to a certified lymphedema specialist should be considered. Larger, prospective, and longitudinal studies are needed to evaluate possible underlying multivariate, causative factors leading to the development of HNC-related lymphedema.

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