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Original Articles

A Prospective Study of the Lymphedema and Fibrosis Continuum in Patients with Head and Neck Cancer

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Abstract

Background: The purpose of this study was to determine the prevalence and nature of internal, external, and combined lymphedema and fibrosis in patients with head and neck cancer (HNC).
Materials and Methods: We obtained consent from 100 patients newly diagnosed with having cancer of the head and neck for a 4-year, prospective, longitudinal descriptive study. Recruitment began in August 23, 2010, and the study was completed in April 24, 2014. Eighty-three were evaluated at regular intervals from pre-radiation therapy to 18 months post-treatment. Percentage developing external, internal, or both types of lymphedema and/or fibrosis and trajectories of the severity of external, internal, or both types of lymphedema and/or fibrosis were determined.
Results: Before treatment, lymphedema rates were the following: external: 62.7%, internal: 41.7%, or combined: 29.2%, and/or fibrosis: 42.2%. Ranges of lymphedema late-effect rates were even higher: external: 81.9%–90.1%, internal: 80.4%–89.4%, combined: 70.6%–80.9%, and fibrosis: 66.7%–77.4%. Approximately 75% had a late-effect trajectory characterized by moderate to severe external or internal lymphedema; ~47% had moderate to severe fibrosis.
Conclusion: Lymphatic and soft tissue complications of HNC occur not only post-treatment but also before treatment. They are ubiquitous throughout the first 18 months post-treatment, with greater than 90% of patients in our study experiencing some form of internal, external, or combined lymphedema, and over half of those patients developing fibrosis. Further research regarding these conditions is indicated.

Introduction

In the United States, ~45,000 individuals are diagnosed annually with having cancers of the oral cavity and pharynx.[1] Historically, head and neck cancer (HNC) has been associated with risk factors such as tobacco use and alcohol consumption.[2] More recently, human papillomavirus (HPV) has been causally linked with oropharyngeal cancer.[2] HPV-positive oropharyngeal squamous cell carcinoma rose from 16.3% pre-1990 to 72.7% for 2000–present.[3] The rise in HPV-associated cancers concurrent with improved treatment has contributed to an escalation in the number of HNC survivors to ~300,000 in the United States.[1,4] These survivors often experience significant acute and late effects of therapy.

The management of disease and treatment-related side effects is critical to ensure optimal function and quality of life in HNC survivors. Surgery and radiation (alone or in combination) serve as the primary curative treatment modalities for HNC, with chemotherapy used to enhance outcomes in patients with advanced disease.[5] Disruption or damage to soft tissue and lymphatic structures occurs as a result of these treatment modalities, placing patients at risk for both lymphedema and fibrosis.[6–8]

A previous cross-sectional study found that lymphedema may develop externally (e.g., face and neck) and/or internally (e.g., larynx and pharynx) in patients with HNC.[9] Data indicate that lymphedema correlates with the symptom burden and functional deficits that have plagued HNC survivors.[10] Despite the potential of lymphedema and fibrosis to negatively influence patients' outcomes, they remain underrecognized and undertreated by clinicians. In addition, little is known about their prevalence and trajectories over time in the post-treatment HNC population.[11]

The objective of this study was to describe the lymphedema and fibrosis continuum in patients with HNC through examination of rates and trajectories from baseline through the first

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18 months post-treatment. We had two primary hypotheses: H1: a minimum of 20% of HNC patients would experience lymphedema and/or fibrosis as a late effect of treatment and H2: we would be able to differentiate characteristic patterns of the development of late-effect lymphedema and/or fibrosis.

Materials and Methods

Design and participants

Permission for this 4-year, prospective, longitudinal descriptive study was obtained from the Vanderbilt University Institutional Review Board and the Vanderbilt-Ingram Cancer Center (VICC) Scientific Review Committee in Nashville, TN, USA. The focus of this study was the late effects of HNC treatment defined as manifestations beginning three or more months after end of treatment. The study was conducted within the ethical standards of the Helsinki Declaration and ran from July 1, 2010, to November 20, 2014.

A convenience sample of HNC patients was recruited at VICC from August 23, 2010, to August 27, 2012. Eligibility criteria included the following: (1) newly diagnosed histologically proven HNC; (2) disease Stage II or greater; (3) age 21 or over; (4) willingness to undergo baseline and follow-up assessments at the VICC facilities; and (5) the ability to speak English. Patients were excluded for one of three reasons: (1) medical record documentation indicating cognitive impairment that would preclude the ability to provide informed consent; (2) an unwillingness to undergo routine follow-up at VICC facilities; or (3) recurrent HNC.

Methods

Potential patients were screened for eligibility. Informed consent was obtained before enrollment in the study. Before commencing data collection, research team members were trained to conduct physical examinations by authors, Ridner and Murphy. Physicians conducting flexible fiber optic endoscopic evaluations of internal lymphedema were clinically active and had previously documented findings using the Patterson Scale.[9] Inter- and intrarater reliability evaluations were conducted on randomly selected examinations, representing 10% of the total of all examinations.

Data collection took place at baseline during diagnosis of cancer before radiation therapy, at end of treatment, at 6-week intervals after treatment through 48 weeks post-treatment, and at the 15- and 18-month intervals post-treatment for a total of 12 points of assessment.

Data collection instruments

Demographic and clinical. Demographic, tobacco, and alcohol use history variables were obtained through self-report. Clinical variables were obtained from participant medical records.

External lymphedema. External lymphedema was assessed through physical examination using the American Cancer Society (ACS) Lymphedema of the Head and Neck staging criteria,[12] which includes four stages ranging from Stage 0 (local swelling that does not affect regular function) to Stage 3 (severe swelling, ulcerations may be present on the skin or brain, and ability to eat is severely affected). Exact inter-rater agreement for grade assessed using the ACS was 89% with the discrepant assessments differing by only one grade (Kappa = 0.84).

Internal lymphedema. Internal lymphedema was visually assessed and documented using the validated Patterson Scale.[13] Eleven laryngopharyngeal structures and two spaces were graded for swelling: 0 (None) to 3 (Severe). The highest grade of swelling from the multiple assessed sites was used in this article as the single indicator of the presence and severity of internal lymphedema. Internal photographs were taken during each examination to document the presence of lymphedema/edema. Exact inter-rater agreement for grade across the 13 sites assessed using the Patterson Scale ranged from 41% to 82%. Agreement within ±1 grade ranged from 73% to 97% (Kappa: 0.12–0.84).

Fibrosis. Fibrosis was assessed through physical examination and documented using the Common Terminology Criteria for Adverse Events (CTCAE) Fibrosis Scale (version 3.0).[14] Assessment resulted in a grade ranging from 1 (minimal to moderate redundant soft tissue that was unresponsive to elevation or compression and that was also firm or spongy) to 3 (very marked density with a tether). Exact inter-rater agreement for grade was 84% with all but two (1.2%) discrepancies differing by only one grade (Kappa = 0.74, $p < 0.001$).

To reduce potential sources of bias, strict eligibility standards were adhered to and the primary investigators did not participate in the screening of potential participants, nor in data collection. Additionally, a comparison of characteristics between those patients lost to follow-up and those remaining in the study was planned before commencing the study.

Statistical analyses

The Wilson method was used to generate 95% confidence intervals (CIs) for the observed prevalence rates.[15] Group-based trajectory analysis[15] based on the zero-inflated Poisson (ZIP) distribution as implemented in SAS Proc Traj was used to detect longitudinal patterns of lymphedema and fibrosis severity (grades 0–3) beginning before treatment and up to 18 months post-treatment. Both Bayesian Information Criteria (BIC) and Akaike Information Criteria (AIC) were used to determine the best trajectory model fit to each of the three outcome datasets (external lymphedema, internal lymphedema, and fibrosis). Trajectory group membership was saved for subsequent plotting of the trajectory patterns using patient severity scores and for assessing associations of surgery before treatment with those trajectories. Logistic regressions were used to assess the extent to which prior surgery was associated with both the presence of lymphedema and/or fibrosis before treatment and the trajectory of those outcomes post-treatment. Sensitivity analyses of the findings were conducted using study cases with assessments after 12 months post-treatment ($N = 63$) compared with the reported findings from analyses from all study cases ($N = 83$) SAS (9.4), Stata (13), and SPSS (22) were used for statistical analyses. A maximum Type I error rate of 0.05 ($p < 0.05$) was used for determining statistical significance.[16–18]

Results

Demographics

Five hundred three patients were screened. Of the 149 patients who were approached by study staff to discuss

participation, 100 gave informed consent (Fig. 1). Reasons for nonparticipation included ineligible due to recurrent cancer ($n=316$), early stage cancer ($n=3$), under age 21 ($n=1$), unwilling to be in the study or unable to have treatment/follow-ups at Vanderbilt ($n=82$), and non-English speaking ($n=1$). Seventeen patients were lost to follow-up or withdrawn before the initial 3-month follow-up assessment for the following reasons: death ($n=2$, 15.4%), development of metastasis ($n=4$, 30.8%), local recurrence ($n=1$, 7.7%), transferred care ($n=4$, 30.8%), patient request ($n=1$, 7.7%), and poor compliance ($n=5$, 40.0%). Eighty-four were in the study 3 months post-treatment, 83 of which completed the first post-treatment follow-up and therefore comprised the study sample. Demographic and clinical characteristics of the patients in the study sample ($N=83$), as well as those lost to follow-up, are summarized in Table 1. Four of the 17 patients lost to follow-up did not complete baseline assessments; therefore, the comparison sample in Table 1 comprises 13

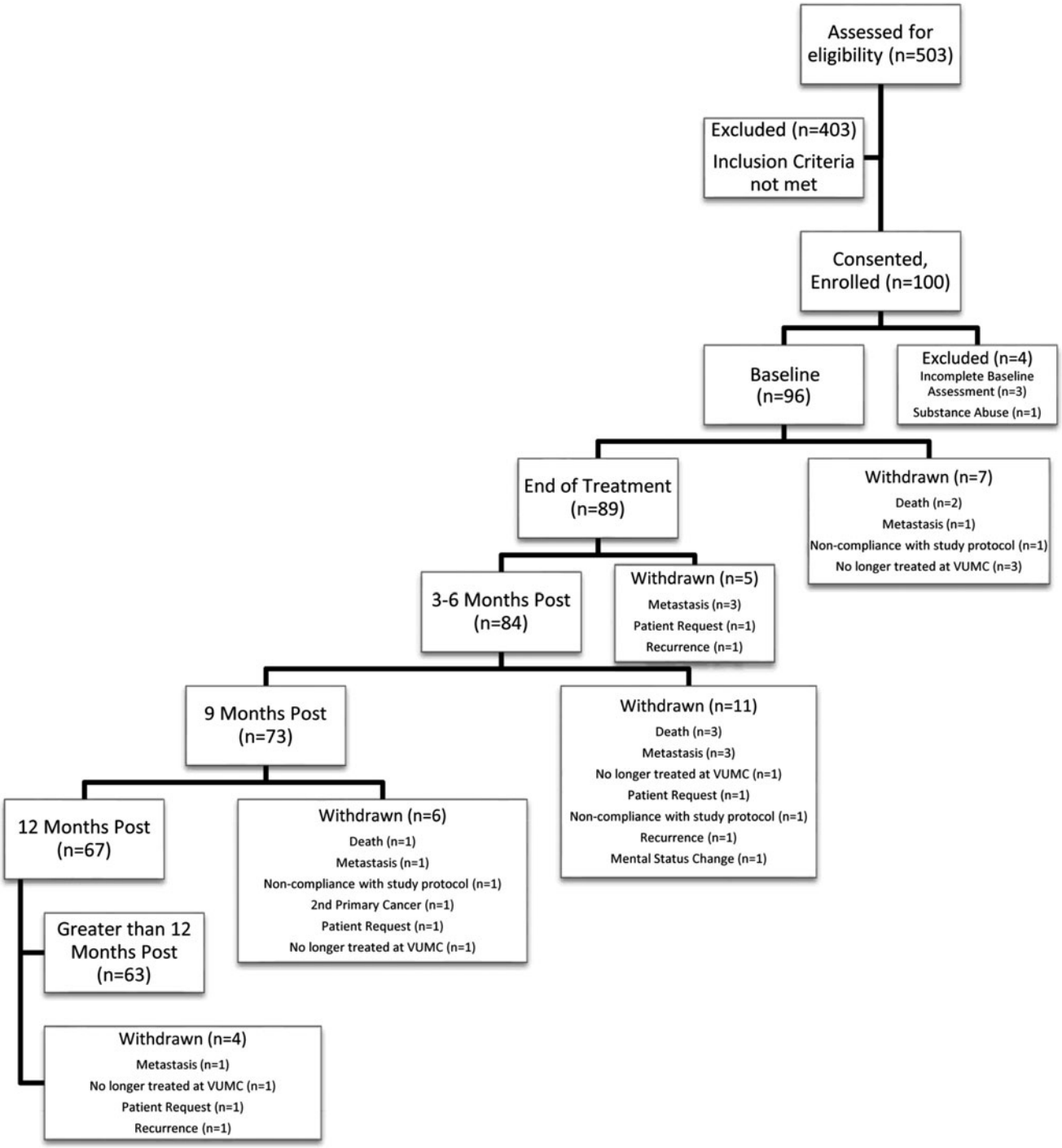

FIG. 1. Consort flow diagram documenting the number of patients screened, consented, and withdrawn during key study periods.

Table 1. Demographic and Clinical Characteristics of Cohorts in Study Analysis ($N=83$) and Those Lost to Follow-Up ($N=13$)

	In-study analysis		*Lost to follow-up*		
	N	*Mean (SD)*	N	*Mean (SD)*	p
Age	83	57.8 (11.3)	13	58.9 (11.5)	0.79
		Median [IQR]		Median [IQR]	
Education (years)	83	13.0 [12–15]	13	13.0 [12–16]	0.59
Gender	83	*N* (%)	13	*N* (%)	0.73
Female		23 (27.7)		3 (23.1)	
Male		60 (72.3)		10 (76.9)	
Race	83		13		0.59
White		75 (90.4)		11 (84.6)	
Black/African American		6 (7.2)		1 (7.7)	
Other		2 (2.4)		1 (7.7)	
Marriage	83		13		0.06
Married/partnered		65 (78.3)		7 (53.8)	
Single/widowed/other		18 (21.7)		6 (46.2)	
Employment	83		13		0.94
Employed		36 (43.4)		6 (46.2)	
Not employed		38 (45.8)		6 (46.2)	
Other		9 (10.8)		1 (7.7)	
Residence	83		13		0.18
City		34 (41.0)		8 (61.5)	
Country		42 (50.6)		3 (23.1)	
Other		7 (8.4)		2 (15.4)	
Income	83		13		0.97
Up to $30,000		24 (28.9)		4 (30.8)	
Over $30,000		44 (53.0)		7 (53.8)	
Do not care to respond		15 (18.1)		2 (15.4)	
Smoke (current@BL, past)	83	61 (73.5)	13	7 (53.8)	0.15
Drink alcohol (current@BL, past)	83	48 (57.8)	13	7 (53.8)	0.79
Insurance	83		13		0.35
Uninsured		11 (13.3)		3 (23.1)	
Insured		72 (86.7)		10 (76.9)	
Medical problems (current@BL, past)	83	60 (72.3)	13	11 (84.6)	0.35
Survival status at study endpoint	83		13		0.14
Alive		79 (95.2)		11 (84.6)	
Deceased		4 (4.8)		2 (15.4)	
Recurrence	83	8 (9.6)	13	1 (7.7)	0.82
Distant metastasis	83	7 (8.4)	13	4 (30.8)	0.02
2nd primary Ca after HNC	83	6 (7.2)	13	0 (0.0)	0.32
		Median [IQR]		Median [IQR]	
Known previous Ca (not HNC)	83	10 (12.0)	13	2 (15.4)	0.74
Months since diagnosis @BL	83	1.09 [0.6–2.0]	13	0.86 [0.6–1.4]	0.56
Cancer type	83	*N* (%)	13	*N* (%)	0.89
Squamous cell carcinoma		69 (83.1)		11 (84.6)	
Other type carcinoma		14 (16.9)		2 (15.4)	
Cancer location	83		13		0.64
Oropharynx		36 (43.4)		5 (38.5)	
Oral cavity		16 (19.3)		4 (30.8)	
Larynx		12 (14.5)		1 (7.7)	
Nasopharynx		6 (7.2)		2 (15.4)	
Other		13 (15.7)		1 (7.7)	
Stage	83		13		0.12
Stages I/II		4 (4.8)		1 (7.7)	
Stage III		21 (25.3)		0 (0.0)	
Stage IV		58 (69.9)		12 (92.3)	
T Stage	77		13		0.001
T1-3		62 (80.5)		5 (38.5)	
T4		15 (19.5)		8 (61.5)	
N Stage	83		13		0.69
N0		12 (14.5)		3 (23.1)	
N1-2		66 (79.5)		9 (69.2)	
N3		5 (6.0)		1 (7.7)	

(*continued*)

Table 1. (Continued)

	In-study analysis		*Lost to follow-up*		
	N	*Mean (SD)*	N	*Mean (SD)*	p
M Stage	83		13		0.08
M0		80 (96.4)		11 (84.6)	
MX/unknown		3 (3.6)		2 (15.4)	
Tracheostomy (any)	83	16 (19.3)	11	3 (27.3)	0.54
PEG tube (any)	83	41 (49.4)	11	8 (72.7)	0.15
Induction chemotherapy	83	43 (51.8)	13	11 (84.6)	0.03
Concurrent chemoradiation	83	81 (97.6)	11	11 (100.0)	0.60
Total treatment	82		11		0.41
Induction + ChemoXRT		35 (42.7)		7 (63.6)	
ChemoXRT		14 (17.1)		1 (9.1)	
Surgery + ChemoXRT		24 (29.3)		1 (9.1)	
Surgery + XRT		2 (2.4)		0 (0.0)	
Induction + surgery + ChemoXRT		7 (8.5)		2 (18.2)	

HNC, head and neck cancer; IQR, Interquartile range.

patients. Compared with the study sample, those lost to follow-up before the first post-treatment assessment had higher rates of distant metastasis (31% vs. 8%, $p=0.02$), American Joint Committee on Cancer (AJCC) stage T4 tumors (62% vs. 20%, $p=0.001$), and induction chemotherapy (85% vs. 52%, $p=0.03$). No other statistically significant differences were observed.

The final sample ($N=83$) consisted primarily of white males in their late fifties. More than half (59%) lived in nonurban areas, and almost one third (28.9%) had annual incomes of $30,000 or less. Squamous cell carcinoma was present in 83.1%. The oropharynx was the most common tumor location (43.4%), and 69.9% were diagnosed with having Stage IV disease. Nearly all participants (97.6%) received either primary or adjuvant concomitant chemoradiation (Table 1).

Prevalence rates

Before radiation treatment. At baseline assessment (before treatment), 62.7% (52/83) of the patients had some indication of external lymphedema with 20.5% (17/83) having moderate/severe findings (Table 2). Approximately 42% (30/72) had some indication of internal lymphedema with ~20% (14/72) moderate/severe. Of the 72 patients with both external and internal assessments completed in the requisite time frame, 29.2% (21/72) had both types of lymphedema. Finally, 42.2% (35/83) had indications of some grade of fibrosis, with 16.9% (14/83) having a grade of moderate or higher (Table 2). Ten of the 72 patients (13.9%) with all three assessments had indications of some grade of external and internal lymphedema, as well as fibrosis.

Approximately one third of the patients (32.5%, 27/83) had surgical treatment before baseline assessments. There were no statistically significant differences in the rates of external or internal lymphedema or in the groups with and without prior surgery (external: 66.7%, 18/27 surgery vs. 60.7%, 34/56 no surgery, OR: 1.29, Wald $\chi^2_{(df=1)}=0.28$, $p=0.60$, 95% CI: 0.49–3.39; internal: 30.4%, 7/23 surgery vs. 46.9%, 23/49 no surgery, OR: 0.50, Wald $\chi^2_{(df=1)}=1.73$, $p=0.19$, 95% CI: 0.17–1.41). Rates of fibrosis at baseline were higher, however, for the patients with prior surgery (59.3%, 16/27) than

Table 2. Prevalence of Any Grade of External and Internal Lymphedema and Fibrosis by Study Time Period

Type of phenomenon	*Baseline*	*3–6 Months post-treatment*	*9 Months post-treatment*	*12 Months post-treatment*	*>12 Months post-treatment*
External lymphedema					
Percentage (*n* of *N*)	62.7 (52 of 83)	90.1 (73 of 81)	81.9 (59 of 72)	85.5 (53 of 62)	82.3 (51 of 62)
95% CI	51.9–72.3	81.7–94.9	71.5–89.1	74.6–92.2	70.9–89.8
Internal lymphedema					
Percentage (*n* of *N*)	41.7 (30 of 72)	85.7 (60 of 70)	84.3 (43 of 51)	89.4 (42 of 47)	80.4 (41 of 51)
95% CI	30.9–53.2	75.6–92.1	71.9–91.8	77.4–95.4	67.5–89.0
Both external and internal lymphedema					
Percentage (*n* of *N*)	29.2 (21 of 72)	80.9 (55 of 68)	70.6 (36 of 51)	76.1 (35 of 46)	70.6 (36 of 51)
95% CI	19.9–40.5	69.9–88.5	57.0–81.3	62.0–86.1	57.0–81.3
Fibrosis					
Percentage (*n* of *N*)	42.2 (35 of 83)	74.1 (60 of 81)	66.7 (48 of 72)	69.4 (43 of 62)	77.4 (48 of 62)
95% CI	32.1–52.9	63.5–82.4	55.1–76.5	57.0–79.4	65.5–86.1

CI, confidence interval.

for those without prior surgery (33.9%, 19/56, OR: 2.83, Wald $\chi^2_{(df=1)}=4.65$, $p=0.03$, 95% CI: 1.10–7.30).

Prevalence of post-treatment lymphedema and fibrosis. Rates of any grade of lymphedema and fibrosis for specific post-treatment periods are summarized in Table 2. As noted, prevalence rates were substantially higher than hypothesized with lower bounds of each of the 95% CIs >55%. Of particular note were prevalence rates of late effects. Approximately 82% (51/62) of patients had some indication of external lymphedema more than 1 year post-treatment, with 46.8% (29/62) having a grade of moderate/severe. Similarly, 80.4% (41/51) had some degree of internal lymphedema more than 1 year post-treatment, with 43.2% (22/51) having a grade of moderate/severe. Finally, 77% (48/62) indicated some grade of fibrosis during the very late assessment periods, with 37.1% (23/62) having a grade of moderate or higher. Sensitivity analyses revealed essentially identical findings for the subset of patients with assessments beyond 12-months post-treatment ($N=63$ of 83).

Trajectory post-treatment. Since the vast majority of patients were found to have lymphedema and/or fibrosis, trajectories of the severity or grade of the conditions were modeled (Fig. 2(A): external lymphedema, (B): internal lymphedema, and (C): fibrosis). Two distinct trajectories for the patients were identified for each condition—the first characterized by none or a maximum of mild grade abnormality throughout the post-treatment study period (up to 18 months post); the second characterized by an escalation to moderate to severe grade abnormality between 6 and 12 months post-treatment with slight decline between 12 and 18 months. The trajectory for patients classified in the moderate to severe fibrosis pattern peaked slightly later (>12 months post; Fig. 2C).

Very similar rates of the two trajectories were found for external and internal lymphedema ($\sim$25% with no/mild trajectories, $\sim$75% with the moderate/severe trajectory; Fig. 2A, B). The two trajectories for fibrosis were represented approximately equally in the study patients (none/mild 53%, moderate/severe 47%; Fig. 2C). Sixty-one percent (44/72) of the patients had post-treatment trajectories characterized by moderate/severe grades of both internal and external lymphedema; 35% (25/72) had moderate/severe trajectories for all three types of lymphedema and fibrosis (not shown). Sensitivity analyses revealed essentially identical findings for the subset of patients with assessments beyond 12-months post-treatment ($N=63$ of 83).

Baseline/prior surgery and post-treatment lymphedema and fibrosis trajectories. There was no statistically significant increased likelihood of a moderate/severe trajectory of external lymphedema given the presence of external lymphedema before treatment (OR: 1.30, Wald $\chi^2_{(df=1)}=0.24$, $p=0.63$, 95% CI: 0.45–3.68), nor in the likelihood of a trajectory of moderate/severe fibrosis given the presence of fibrosis before treatment (OR: 2.04, Wald $\chi^2_{(df=1)}=2.48$, $p=0.12$, 95% CI: 0.84–4.93). The presence of internal lymphedema at baseline, however, did increase the likelihood of a moderate/severe post-treatment trajectory of internal lymphedema (OR: 6.12, Wald $\chi^2_{(df=1)}=6.99$, $p=0.01$, 95% CI: 1.59–23.43).

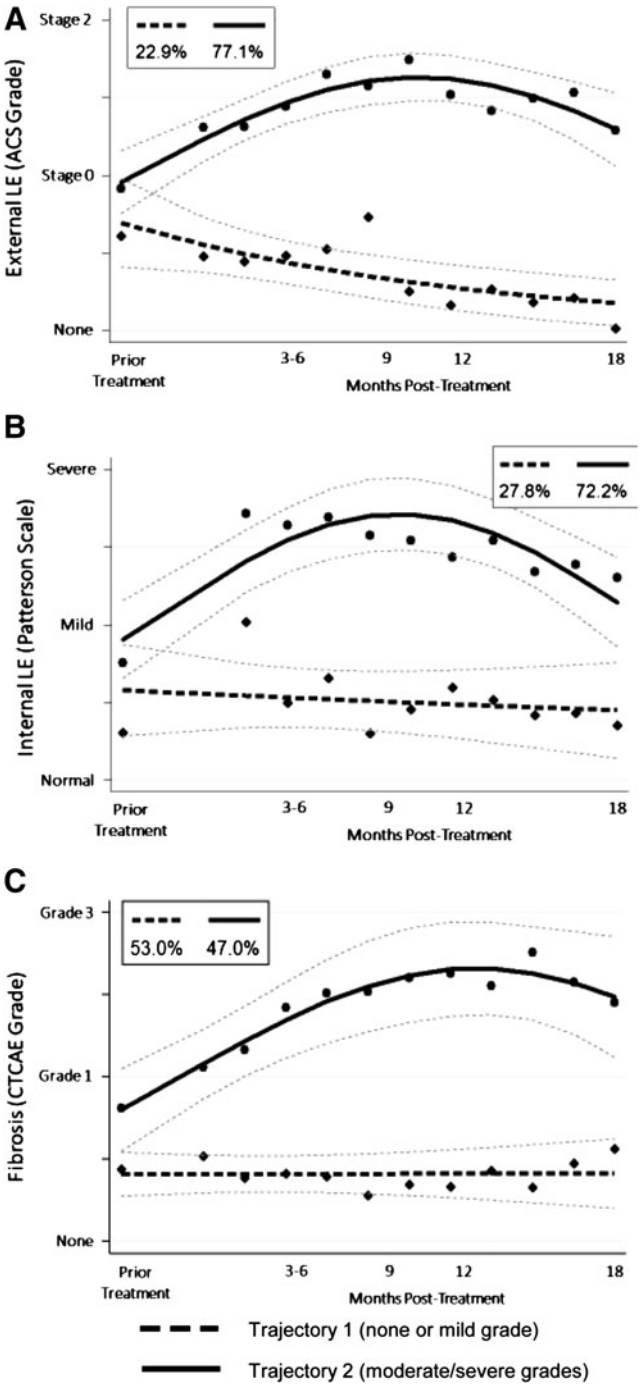

FIG. 2. Modeled trajectories of the severity or grade of lymphedema and fibrosis within the sample of patients beginning before treatment and ending 18 months post-treatment. Two distinct trajectory groups were observed for severity of external lymphedema (**A**, $N=83$), internal lymphedema (**B**, $N=72$), and fibrosis (**C**, $N=83$).

There was no statistically significant association of prior surgery with post-treatment external lymphedema trajectory patterns (OR: 0.44, Wald $\chi^2_{(df=1)}=2.41$, $p=0.12$, 95% CI: 0.15–1.25). There was a tendency for those with prior surgery to have a decreased likelihood of the moderate/severe internal lymphedema post-treatment trajectory pattern (OR: 0.33, Wald $\chi^2_{(df=1)}=3.99$, $p=0.05$, 95% CI: 0.11–0.98) and a statistically

significant increased likelihood of the moderate/severe fibrosis trajectory (OR: 3.33, Wald $\chi^2_{(df=1)}=5.97$, $p=0.02$, 95% CI: 1.26–8.76). Because all cases had baseline data, no sensitivity to missing data analyses were required for these analyses.

Discussion

Lymphedema and fibrosis were present in a subset of patients with HNC before any cancer treatment. This raises several questions. First, variability of internal and external lymphedema/swelling and fibrosis in the noncancer population is unknown, thus these findings could reflect normal variance. However, in many cases, external swelling was clearly pronounced near and downstream from the tumor in photographs taken at the same time of the physical examination. Given the late stage in which most HNC tumors are diagnosed, there could potentially be lymphatic transport inhibition related to the size and location of the tumor itself. Alternatively, it is possible that there is an underlying tumor-driven inflammatory mechanism that negatively impacts soft tissue and the lymphatics. We are currently analyzing a panel of cytokines drawn at each visit in this study in an attempt to evaluate this possibility. Regardless of baseline exam findings, the vast majority of patients experienced lymphedema and/or fibrosis as a late effect of cancer and its treatment. For most, the findings were in the moderate to severe range post HNC treatment. Manifestations of soft tissue and lymphatic damage were varied as patients experienced one or any combination of external or internal lymphedema and fibrosis. Postsurgical patients were more likely to develop moderate to severe fibrosis compared with patients treated only with primary radiation-based therapy.

The startlingly high prevalence rates and severity suggest a need to reconsider the current approach to assessing and managing lymphatic compromise and soft tissue toxicities in this patient population. Medical management of lymphedema and fibrosis-related symptoms and functional deficits has been largely reactive, not proactive, with treatment being initiated at the time they manifest, which is likely long after tissue damage has occurred. Lymphedema and fibrosis are not static processes.[19] Lymphedema is associated with ongoing inflammation resulting in progressive fibrosis and fatty tissue deposition.[20] Once fibrofatty tissue deposits develop, treatment with manual lymphatic drainage and compression garments may be less effective.

Research has indicated that aggressive therapy of early stage lymphedema in other cancer populations may result in reduced swelling with associated decreases in long-term morbidity.[20] Likewise, aggressive physical therapy may prevent progressive contracture and functional loss in patients with fibrosis. Thus, early assessment, identification, and treatment of lymphedema and fibrosis may diminish these late effects in the HNC population. As an example, aggressive preventative therapy may ameliorate the soft tissue toxicities in the arena of dysphagia as patients who maintain active swallow efforts throughout the course of radiation and into early recovery have improved swallowing outcomes.[21–23] Although the exact mechanism by which proactive swallow therapy enhances long-term outcomes is unknown, it may be postulated that swallowing exercises result in improved lymph flow with decreased acute edema and chronic lymphedema, prevention of constrictive fibrosis, and limiting muscular atrophy.

An even more proactive approach would be directed at preventing or minimizing soft tissue and lymphatic damage, for example, examination of intensity-modulated radiation therapy techniques and dose/volume strategies may be warranted. Additionally, pharmacologic agents, laser therapy, and cell-based therapy may need to be explored as tools to prevent and treat lymphedema and fibrosis.[24–27]

Our previous cross-sectional work supports the association between the severity of lymphedema and symptom severity.[10] Therefore, patients with moderate to severe lymphedema or fibrosis probably have significant symptom burden. Symptom presentation and functional deficits are commonly related to the site of involved tissue. For example, patients with pharyngeal lymphedema and/or fibrosis may be more prone to develop dysphagia. Similarly, patients with severe fibrosis involving the neck might develop impaired range of motion and musculoskeletal pain. Therefore, careful attention to lymphedema and fibrosis-related symptoms in clinical settings is indicated.

A limitation of our work is that as this is the first known study to longitudinally follow lymphedema and fibrosis in this patient population, we are unable to directly compare our findings with other published work. Variability was greatest in internal lymphedema scoring and less so for external lymphedema and fibrosis. The Patterson Scale used for internal swelling also did not capture swelling in areas such as the tongue. Although the prevalence and severity of internal lymphedema, external lymphedema, and fibrosis were carefully assessed using the best currently available tools, development of an improved battery of assessment tools is needed and development of such is currently being undertaken by our team.[27] Despite these limitations, the rates and severity of lymphedema and fibrosis found in this study are supported by its longitudinal nature, rigorous training, and ongoing evaluation of those conducting the assessments, with consistent findings across all measures. Generalizability should be limited to patients with HNC who had similar stage disease at time of diagnosis and underwent standard treatment for the condition as early stage disease is not well represented within this sample. However, as most HNC patients are not diagnosed at an early stage, we believe these findings apply to a majority of patients with HNC.

As a part of this study, we captured prospective data on biomarkers, symptoms, and functional outcomes. Careful assessments of the associations of severity of internal lymphedema, external lymphedema, and fibrosis with biomarkers and functional and symptom outcome measures are planned.

Conclusions

Soft tissue and lymphatic complications of HNC therapy are ubiquitous, with greater than 90% of patients experiencing both internal and external lymphedema and over half of patients developing fibrosis. Ongoing evaluation of internal and external swelling and of fibrosis by clinicians coupled with referral for physical and/or lymphedema therapy may be helpful to these patients. Further research of these conditions in this patient population is indicated.

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References

1. American Cancer Society. Cancer Facts & Figures 2015.
2. Adelstein DJ, Ridge JA, Gillison ML, et al. Head and neck squamous cell cancer and the human papillomavirus. Summary of a National Cancer Institute State of the Science Meeting, November 9–10, 2008, Washington, DC. Head Neck 2009; 31:1393–1422.
3. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011; 29:4294–5301.
4. National Cancer Institute. *SEER Cancer Statistics Factsheets. Oral Cavity and Pharynx Cancer*. Bethesda, MD. http://seer.cancer.gov/stastfacts/html/oralcav.html. Accessed May 1, 2015.
5. Koch WM. *Early Diagnosis and Treatment of Cancer. Head and Neck*. Philadelphia, PA: Elsevier, Inc.; 2010.
6. Deng J, Ridner SH, Dietrich MS, et al. Prevalence of secondary lymphedema in patients with head and neck cancer. J Pain Symptom Manage 2012; 43:244–252.
7. Rockson SG. The lymphatics and the inflammatory response. Lessons learned from human lymphedema. Lymphat Res Biol 2013; 11:117–120.
8. Baker A, Semple J, Moore S, Johnston M. Lymphatic function is impaired following irradiation of a single lymph node. Lymphat Res Biol 2014; 12:76–88.
9. Deng J, Ridner SH, Dietrich MS, et al. Factors associated with external and internal lymphedema in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2012; 84:e319–e328.
10. Deng J, Murphy BA, Dietrich MS, et al. Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. Head Neck 2013; 35:1026–1035.
11. Smith BG, Lewin JS. Lymphedema management in head and neck cancer. Curr Opin Otolaryngol Head Neck Surg 2010; 18:153–158.
12. American Cancer Society, Donaldson S. Lymphedema: *Understanding and Managing Lymphedema After Cancer Treatment*. Atlanta, GA: American Cancer Society; 2006.
13. Patterson JM, Hildreth A, Wilson JA. Measuring edema in irradiated head and neck cancer patients. Ann Otol Rhinol Laryngol 2007; 116:559–564.
14. National Cancer Institute. Common terminology criteria for adverse events v3.0 (CTCAE). In: *Cancer Therapy Evaluation Program*. Washington, DC: National Institutes for Health, 2006.
15. Agresti A, Coull BA. Approximate is better than ''exact'' for interval estimation of binomial proportions. Am Stat 1998; 52:119–126.
16. Nagin D. *Group-Based Modeling of Development*. Cambridge, MA: Harvard University Press; 2005.
17. Nagin DS. Analyzing developmental trajectories. A semiparametric, group-based approach. Psychol Methods 1999; 4:139–157.
18. Nagin DS, Land KC. Age, criminal careers, and population heterogeneity. Specification and estimation of a nonparametric, mixed poisson model. Criminology 1993; 31:327–362.
19. Földi M, Földi E. *Földi's Textbook of Lymphology for Physicians and Lymphedema Therapists* (3rd ed.). Munich: Elsevier GmbH, Elsevier Health Sciences; 2012.
20. Stout Gergich NL, Pfalzer LA, McGarvey C, et al. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer 2008; 112: 2809–2819.
21. Starmer HM. Dysphagia in head and neck cancer. Prevention and treatment. Curr Opin Otolaryngol Head Neck Surg 2014; 22:195–200.
22. Virani A, Kunduk M, Fink DS, et al. Effects of 2 different swallowing exercise regimens during organ-preservation therapies for head and neck cancers on swallowing function. Head Neck 2014; 37:162–170.
23. Hammerl B, Doller W. Secondary malignant lymphedema in head and neck tumors. Wien Med Wochenschr 2008; 158:695–701.
24. Micke O, Schomburg L, Buentzel J, et al. Selenium in oncology. From chemistry to clinics. Molecules 2009; 14:3975–3988.
25. Qi S, Pan J. Cell-based therapy for therapeutic lymphangiogenesis. Stem Cells Dev 2015; 24:271–283.
26. Smoot B, Chiavola-Larson L, Lee J, et al. Effect of low-level laser therapy on pain and swelling in women with breast cancer-related lymphedema. A systematic review and meta-analysis. J Cancer Surviv 2015; 9:287–304.
27. Deng J, Ridner SH, Aulino JM, et al. Assessment and measurement of head and neck lymphedema. State-of-the-science and future directions. Oral Oncol 2015; 51:431–437.

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