Lymphedema and Fibrosis in Head and Neck Cancer Survivors: Manifestations and Assessment

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Educational Goals

• To describe **clinical manifestations** of lymphedema and fibrosis in head and neck cancer survivors

• To discuss **clinical assessment** of lymphedema and fibrosis in head and neck cancer survivors
Untreated or Under-treated Lymphedema

- Lymphedema results in - Disfigurement – Pain – Disability
Head and Neck Cancer Statistics

• **65,410** new cases in the U.S.A. in 2019

• Epidemic of **HPV-associated** cancer
  – 70-80% of oropharyngeal cancer

• Over **half a million** survivors in the U.S.A.

• The **sixth** most common type of cancer worldwide
Physiology

- Head and neck requires massive lymph drainage to maintain vital functions
- 300 lymph nodes
- 1/3 of the total amount in the human body
Treatment Related Effects on Lymph Flow

- **Surgery**
  - Removal of lymph nodes
  - Transection of lymph channels
  - Decreased muscular contraction

- **Radiation therapy**
  - Fibrosis of lymph nodes
  - Scaring of lymph channels
  - Decreased muscular contraction

- **A goal of therapy is to eliminate nodal disease**
Research Projects

- Descriptive Studies (scope and impact)
- Measurement Projects (tools)
- Interventional Trials (treatment/self-care)
Study 1 (Quantitative) –
Impact of Lymphedema in Patients with Head and Neck Cancer

Funded by Oncology Nursing Society Foundation in United States
External Lymphedema

patient permission obtained
Internal Lymphedema

Epiglottis  No Lymphedema

Epiglottis  Severe Lymphedema
Epiglottis Function

https://www.youtube.com/watch?v=t17JeebmBPM
Prevalence

Type of Lymphedema

- None 25%
- External 7%
- Internal 30%
- Both 38%
- None 25%

## Physical Symptom Burden

### Associations between Lymphedema Severity and VHNSS Scores

<table>
<thead>
<tr>
<th>Lymphedema Severity</th>
<th>Sample size (n)</th>
<th>Swallowing</th>
<th>Nutrition</th>
<th>Mucous/Dry mouth</th>
<th>Pain</th>
<th>Voice</th>
<th>Dentition</th>
<th>Hearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>External lymphedema</td>
<td>100</td>
<td>0.32 (.001)</td>
<td>0.27 (.007)</td>
<td>0.29 (.004)</td>
<td>0.03 (.790)</td>
<td>0.12 (.226)</td>
<td>0.17 (.084)</td>
<td>-0.05 (.600)</td>
</tr>
<tr>
<td>Internal Lymphedema</td>
<td>78</td>
<td>0.23 (.042)</td>
<td>0.18 (.113)</td>
<td>0.27 (.016)</td>
<td>0.22 (.047)</td>
<td>0.30 (.008)</td>
<td>0.07 (.548)</td>
<td>0.02 (.833)</td>
</tr>
<tr>
<td>Combined lymphedema</td>
<td>79</td>
<td>0.13 (.003)</td>
<td>0.12 (.008)</td>
<td>0.13 (.004)</td>
<td>0.05 (.134)</td>
<td>0.09 (.030)</td>
<td>0.01 (.669)</td>
<td>0.01 (.700)</td>
</tr>
</tbody>
</table>

**Note:** (1) Beta or R-square Change is highlighted if p < 0.05.
Psychological Symptom Burden

- Altered appearance
- Body image disturbance
- Anxiety
Function Impact – Neck Range of Motion

![Box plots showing neck range of motion across different stages and Foldi's Scale with p-values: P = .018, P = .020, P = .021.](image)
Quality of Life Impact (FACT-H&N)

Foldi's Scale

P = .005

Summary

- Lymphedema in patients with HNC
  - Frequent
  - Substantial symptom burden
  - Decreased functional status
  - Decreased overall quality of life
Study 2 (Qualitative) –
Symptom Experience in Head and Neck Cancer Patients with Lymphedema

Funded by Vanderbilt Office of Clinical and Translational Scientist Development
Symptoms

- Symptoms are the most common reason people seek health care.
- Symptoms are felt or noticed by a patient.
- Symptoms may not be captured by anyone else.
- Symptoms are important for early identification of a disease.
• Can you tell me about when you first noticed lymphedema/swelling?

• What symptoms did you have with the lymphedema/swelling?
Temporal Onset

- 70% of participants: first noticed facial or neck swelling/lymphedema **within three months** following either surgery or radiation therapy
- 20% of participants: identified by oncologists
- 10% of participants: noticed before HNC therapy
Situational Factors
Symptoms/Complaints

- Tightness
- Discomfort
- Tenderness
- Numbness
- Tingling
- Spasm
- Pressure
- Throbbing

*Altered Sensations*
Symptoms/Complaints

- Impaired speech
- Impaired eating
- Difficulty swallowing
- Breathing difficulties
- Blurred vision
- Problems opening mouth

Altered Functions
Symptoms/Complaints

- Pain
- Stiffness
- Limited neck/shoulder ROM
- Limited driving
- Limited swimming

Neck-Shoulder Musculoskeletal Impairments
Symptoms/Complaints

- Skin texture change
- Loose skin
- Skin color change (hyper- or hypo-pigmentation)
Symptoms/Complaints

- Altered appearance
- Negative self-image
- Fear
- Anxiety
- Acceptance
  (swelling as part of life)

Psychosocial Symptoms
Study 3 –
Internal Lymphedema: Correlation with Dysphagia

• Hypothesis:
  – Dysphagia is in part due to soft tissue swelling of pharyngeal and laryngeal structures secondary to lymphedema

• Is this distinction important?
  – Yes....
    • Mechanism
    • Prevention
    • Treatment
Internal Lymphedema: Correlation with Dysphagia

• 81 HNC patients
  – VHNSS v 2.0: including -13 swallowing/nutrition-related questions grouped in 3 clusters: swallow solids, swallow liquids, nutrition
  – External lymphedema: Foldi’s scale (physical exam)
  – Internal lymphedema: Patterson scale (endoscopic exam)
  – Modified-barium swallow study (MBSS) rated by:
    o Dysphagia Outcome and Severity Scale (DOSS)
    o In combination with swallow evaluation, by National Outcomes Measurement System (NOMS)

• Examinations performed at varied time points to assess the lymphedema spectrum, from baseline to 18 months post-therapy

Correlation of VHNSS Subscales with Internal Lymphedema by Patterson Scale

<table>
<thead>
<tr>
<th>Patterson Scale Site</th>
<th>VHNSS Swallow solids</th>
<th>VHNSS Swallow liquids</th>
<th>VHNSS Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiglottis</td>
<td>.39, p = .004</td>
<td>.36, p = .009</td>
<td>.36, p = .007</td>
</tr>
<tr>
<td>Pharyngoepiglottic folds</td>
<td>.41, p = .003</td>
<td>.35, p = .12</td>
<td>.41, p = .002</td>
</tr>
<tr>
<td>Aryepiglottic folds</td>
<td>.53, p &lt; .001</td>
<td>.44, p = .001</td>
<td>.41, p = .003</td>
</tr>
<tr>
<td>Arytenoids</td>
<td>.39, p = .004</td>
<td>.31, p = .023</td>
<td>.35, p = .009</td>
</tr>
<tr>
<td>False vocal cords</td>
<td>.41, p = .003</td>
<td>.24, p = .081</td>
<td>.24, p = .084</td>
</tr>
<tr>
<td>Pyriform sinus</td>
<td>.46, p &lt; .001</td>
<td>.37, p = .005</td>
<td>.49, p = .002</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>.22, p = .107</td>
<td>.34, p = .010</td>
<td>.42, p = .001</td>
</tr>
</tbody>
</table>

No correlations exist between VHNSS and external lymphedema (p>0.20)
Correlation of Internal Lymphedema by Patterson Scale with Objective Swallow Evaluation

<table>
<thead>
<tr>
<th>Patterson scale site</th>
<th>NOMS</th>
<th>DOSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiglottis</td>
<td>.44, p = .002</td>
<td>.30, p = .029</td>
</tr>
<tr>
<td>Pharyngoepiglottic folds</td>
<td>.50, p = .001</td>
<td>.33, p = .015</td>
</tr>
<tr>
<td>Aryepiglottic folds</td>
<td>.47, p = .001</td>
<td>.32, p = .018</td>
</tr>
<tr>
<td>Arytenoids</td>
<td>.44, p = .002</td>
<td>.36, p = .006</td>
</tr>
<tr>
<td>False vocal cords</td>
<td>.42, p = .004</td>
<td>.34, p = .011</td>
</tr>
<tr>
<td>Pyriform sinus</td>
<td>.44, p = .002</td>
<td>.35, p = .009</td>
</tr>
</tbody>
</table>

NOMS/DOSS ratings correlated with external lymphedema (p<0.01)
Clinical Implications

• HNC patients with lymphedema experience *multiple symptoms*

• Some of symptoms may be *unique indicators* of this pathophysiological condition

• Potential *situational factors* and possible risk reduction strategies for head and neck lymphedema
Clinical Implications

- Clinicians should educate HNC patients about symptoms associated with lymphedema.
- Clinicians should inquire HNC patients about lymphedema-related symptoms and provide adequate supportive care to diminish symptom burden.
Measurement Issues: Lessons Learned

- No “Gold Standard” available
- Multiple methods explored
- Limitations to all measurement tools

Measurement Projects

- Patient-Reported Outcome Measure (PRO)
- Clinician-Reported Outcome Measure (CRO)
- Imaging Techniques
**Lymphedema Symptom Intensity and Distress Survey-Head & Neck (sample)**

Instructions: Please read each of the symptoms and circle **yes** or **no** to indicate whether you have had this symptom **over the past week**. If you circle **yes**, please indicate the **severity** of this symptom and the **bother** of this symptom.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes/No</th>
<th>Severity</th>
<th>Bother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling uncomfortable in your head or neck</td>
<td>Yes No</td>
<td>Slight</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td>Heaviness</td>
<td>Yes No</td>
<td>Slight</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td>Tightness</td>
<td>Yes No</td>
<td>Slight</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td>Firmness or hardness of your skin</td>
<td>Yes No</td>
<td>Slight</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td>Stiffness</td>
<td>Yes No</td>
<td>Slight</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight</td>
<td></td>
</tr>
</tbody>
</table>
Manifestations – Symptom Assessment Tool
Most Common Complaints

- Feeling uncomfortable in head and neck
- Tightness
- Firm or hard skin
- Stiffness
- Tenderness
- Limited movement
- Problems swallowing
- Voice changes
- Feel like something stuck in throat
- Feeling tired
- Feel like people are staring at me

Table 1 Symptom Prevalence Differences ($p < 0.05$)

<table>
<thead>
<tr>
<th>Frequency of Symptoms</th>
<th>LE (%) (N=23)</th>
<th>No LE (%) (N=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altered sensation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness of the face/neck skin</td>
<td>34.8</td>
<td>8.7</td>
<td>0.032</td>
</tr>
<tr>
<td>Heaviness of the face/neck skin</td>
<td>21.7</td>
<td>0.0</td>
<td>0.018</td>
</tr>
<tr>
<td>Warmth of the face/neck skin</td>
<td>17.4</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Pain without head/neck movement</td>
<td>17.4</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Neck – Shoulder musculoskeletal/skin symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling in face</td>
<td>17.4</td>
<td>0.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Swelling in neck</td>
<td>21.7</td>
<td>0.0</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Head and neck-specific functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems swallowing mashed food</td>
<td>39.1</td>
<td>9.1</td>
<td>0.019</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>26.1</td>
<td>0.0</td>
<td>0.009</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>21.7</td>
<td>0.0</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Systemic symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel worse when flying in air plane</td>
<td>25.0</td>
<td>0.0</td>
<td>0.017</td>
</tr>
</tbody>
</table>
Clinician-Reported Outcome Measures

- Four scales available
  - Two for head and neck lymphedema
    - CTCAE Lymphedema Scale –H&N (v3.0)
    - ACS Lymphedema Scale –H&N
  - Two for general lymphedema
    - Foldi’s Scale
    - CTCAE Fibrosis Scale (v3.0)

Development Project

- Head and Neck External Lymphedema-Fibrosis Assessment Criteria (HN-LEF)

- Method: Two-phase Study
  - Development phase (15 expert participants)
  - Preliminary test phase (30 patient participants)

- Findings
  - Head and Neck Lymphedema Scale
    - Good content/face validity
    - Acceptable inter-rater reliability
    - (83% exact agreement, 100% within 1 grade,
      \( \kappa = 0.752, p < .001 \))
  - Further studies for psychometric testing justified

<table>
<thead>
<tr>
<th>Type</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>No visible tissue swelling; palpable thickening and/or tightness of dermis</td>
</tr>
</tbody>
</table>
| Type B | Visible soft tissue swelling; involved tissues are soft to touch; tissue swelling is reducible and fluctuates in severity  
**Grade:**  
Mild – visible soft tissue swelling on close inspection  
Moderate – easily visible swelling that significantly alters normal tissue contours  
Severe – extreme or massive tissue swelling |
| Type C | Visible soft tissue swelling; involved tissues are firm to touch; tissue swelling is non-reducible and persistent  
**Grade:**  
Mild – visible soft tissue swelling on close inspection  
Moderate – easily visible swelling that significantly alters normal tissue contours  
Severe – extreme or massive tissue swelling |
| Type D | Firm tissues with increased density and decreased compliance in the absence of swelling  
**Grade:**  
Mild – palpable firmness of soft tissues  
Moderate – soft tissues are extreme hard and have a woody texture  
Severe – fibrosis associated with contracture |

**Type:**  
Description of some *physical characteristics* of the soft tissue abnormalities observed by physical exam

**Grade:**  
Description of the *severity* of the soft tissue abnormalities
Clinical Use of HN-LEF - Protocol Development

- Clinical training: Working with HNC medical oncologists
- Procedures: Patient interview and physical examination
- Documentations: Table and figures
Have you experienced any swelling or firmness in your head or neck area as a result of your tumor or treatment?

Does swelling change or fluctuate throughout the day?

Please tell me if anything (e.g., specific activities) aggravates the swelling.
Protocol Development
- Physical Examination (sample)

- Wash hands or clean hands using antiseptic hand wash
- Ask patient for permission to palpate face and neck
- Make sure patient is sitting comfortably, facing the examiner, and have patient remove glasses or necklace if needed
- Visual inspection
- Palpation
- Then use HN-LEF Grading Criteria to determine the types and grades of LEF
- Wash hands or clean hands using antiseptic hand wash
Head and Neck External Lymphedema and Fibrosis Documentation Sheet

Start time: _____

History:
1. Since being diagnosed head and neck cancer (HNC) or end of HNC treatment, have you experienced any swelling in your head and neck area (using the same order listed in the Documentation Sheet, e.g., around eyes, cheek)? Please document patient-reported swelling sites: ____________________________

2. Does swelling change or fluctuate throughout the day? (also, check if swelling increases or decreases and at what time of day)
   ____No; ____Yes, please specify: ____________________________

<table>
<thead>
<tr>
<th>Sites of Tissue Swelling/Fibrosis</th>
<th>Type</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Peri-orbital Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Peri-orbital Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Cheek</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Cheek</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submental Region</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Imaging Techniques
- CT Scan

• Goal: To develop a measurement tool to quantify CT changes after HNC treatment
  – Reliable assessment sites
  – Easy to use
  – Standardized criteria
Epiglottis Thickness

Baseline

4 Mon Post-CCR
Prevertebral Soft Tissue Thickness

Baseline

4 Mon Post-CCR

[Images showing prevertebral soft tissue thickness measurements]
Imaging Techniques
- Ultrasound Measure
- Anatomical Sites and Measurement Distances

Ultrasound Elastography

Notes:

1. The box (region of interest) within each image shows how measurement of shear wave velocity on each anatomical site was made. The calculated shear wave velocity (mean ± standard deviation) is shown within each image.

2. SCM: Sternocleidomastoid Muscle.
Establishing Lymphedema and Fibrosis Measures in Oral Cancer Patients

(NIH/NIDCR R01, PI Deng)

- **Goal:** To assess and compare patient-reported, clinician-reported, and imaging measures of LEF across the trajectory of treatment, recovery, and survival.
- **Design:** Prospective, longitudinal.
- **Population:** Patients with locally advanced oral cavity or oropharyngeal cancer.
Feasibility and Preliminary Efficacy of Yoga in Head and Neck Cancer Survivors

• NIH/NCI R21
• Design: Wait-list control RCT, >3 months post-treatment
• Intervention: 8-week hatha yoga
• Assessment: baseline, 4-week, and 8-week
• Major findings (n=40):
  – Feasibility: recruitment/retention rate, satisfaction and no AEs
  – Efficacy: shoulder ROM (p<.05), pain (p<.005), and anxiety (p=.015)
Lymphedema Management Project
(American Cancer Society Research Scholar Grant, PI Deng)

• Challenges for lymphedema management
  – Lymphedema: incurable, chronic, progressive
  – Intensive lymphedema therapy
  – Long-term self-care
Patient Barriers – Lymphedema Self-Care

- Lack of Guidelines
- Lack of Monitoring
- Limited Knowledge
- Lack of Training on Skills for Self-Care
- Lack of Motivation
- Low Self-Efficacy
- Difficult in Integrating into Daily Routine

March is Lymphedema Awareness Month