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Lymphedema in Patients With Head and Neck Cancer

Jie Deng, PhD, RN, OCN®, Sheila H. Ridner, PhD, RN, FAAN, and Barbara A. Murphy, MD

An estimated 49,260 Americans developed head and neck cancer (HNC) and 11,480 died from oral cavity, pharynx, and larynx cancer in 2010 (American Cancer Society [ACS], 2010). The overall incidence of HNC in the United States has decreased slightly since the 1990s; however, the incidence of tongue and tonsillar cancer has increased because of a rise in the incidence of human papilloma virus (HPV)-associated cancers (Mouth Cancer Foundation, 2008; National Cancer Institute [NCI], 2008). This trend is critical to note because patients with HPV-associated tumors tend to be younger, nonsmokers, and nondrinkers (ACS, 2008; Argiris, Karamouzis, Raben, & Ferris, 2008).

Early detection and multimodality therapy have led to improvement in overall survival rates, leaving many patients with HNC at risk for experiencing secondary complications from their cancer treatment (Bentzen et al., 2003; Oncology Nursing Society, 2007). More than half a million HNC survivors are living in the United States (Jemal et al., 2007; NCI, 2008; Oishi, 2007). Because of the increase in the number of HNC survivors, healthcare providers are spending more time and effort identifying and managing the late effects of cancer therapy.

One of the common but overlooked late effects of HNC therapy is secondary lymphedema. Lymphedema results from an inability of the lymphatic system to transport the lymph fluid volume delivered to tissues (NCI, 2007). Cancer, surgery, radiation, or chemotherapy may disrupt lymphatic structures; therefore, HNC survivors are at risk for developing this potentially debilitating late effect (Dennert & Horneber, 2007; Lymphoedema Framework, 2006; Murphy, Gilbert, & Ridner, 2007; Ridner, 2008). Lymphedema may involve external (Hammond, 2007; Zimmermann et al., 2005) and internal (Bruns et al., 2004; Micke et al., 2003) structures. Involvement of external sites may lead to decreased range of motion in the neck and shoulders. In addition, the face, neck, and shoulders are highly visible structures that are integral to a person's sense of self. External lymphedema, when severe, may lead to issues with body image (Micke et al., 2003), isolation, and social avoidance. Internal structures,

Purpose/Objectives: To describe the current state of the science on secondary lymphedema in patients with head and neck cancer.

Data Sources: Published journal articles and books and data from the National Cancer Institute, the American Cancer Society, and other healthcare-related professional association Web sites.

Data Synthesis: Survivors of head and neck cancer may develop secondary lymphedema as a result of the cancer or its treatment. Secondary lymphedema may involve external (e.g., submental area) and internal (e.g., laryngeal, pharyngeal, oral cavity) structures. Although lymphedema affects highly visible anatomic sites (e.g., face, neck), and profoundly influences critical physical functions (e.g., speech, breathing, swallowing, cervical range of motion), research regarding this issue is lacking. Studies are needed to address a variety of vital questions, including incidence and prevalence, optimal measurement techniques, associated symptom burden, functional loss, and psychosocial impact.

Conclusions: Secondary lymphedema in patients with head and neck cancer is a significant but understudied issue.

Implications for Nursing: A need exists to systematically examine secondary lymphedema related to treatment for head and neck cancer and address gaps in the current literature, such as symptom burden, effects on body functions, and influences on quality of life. Oncology nurses and other healthcare professionals should have empirical evidence to help them manage lymphedema after head and neck cancer treatment.

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such as the tongue, larynx, and pharynx, play a critical role in speech, swallowing, and breathing. When internal sites are affected, the symptom burden and functional impact of lymphedema may be profound.

This literature review will examine critical issues related to secondary lymphedema in patients with HNC: incidence and prevalence, mechanisms, risk factors, measurement issues, symptoms burden and functional issues, management, cost to patients and society, and influences on quality of life. These major issues were determined based on the reviewed literature. These vital components will enhance comprehension of the significance and complexity of secondary lymphedema related to HNC treatment and will help identify gaps in research and clinical guidelines in this area.

The authors conducted a comprehensive literature review based on CINAHL® and PubMed from 1989–2009. Primary search terms included *head and/or neck cancer, incidence, prevalence, lymphedema, edema, symptom, function, quality of life, risk factor, sign or measurement, management, and treatment*. The search yielded 32 citations that were relevant to the topic and provided the basis for this review. Among the 32 citations, three studies had *edema* as a key word. Those articles examined impairment of the lymphatic system and, therefore, were synthesized into this review. Studies that examined edema without lymphatic system components were excluded from this review. The authors also reviewed data and information from NCI, ACS, and other related healthcare professional association Web sites.

Incidence and Prevalence of Secondary Lymphedema

No reports are available on the incidence and prevalence of secondary lymphedema related to HNC treatment in the United States. Four European studies reported different incidence rates of secondary lymphedema after HNC treatment. The first study, Buntzel, Glatzel, Mucke, Micke, and Bruns (2007), examined late toxicities related to multimodal therapy of advanced HNC in a total of 851 patients from 1998–2001 using the Radiation Therapy Oncology Group Common Toxicity Criteria. During the follow-up period (a median of 643 days), 412 (48%) patients developed lymphedema. The second study, Dietz et al. (1998), investigated late toxicities in 68 patients after radiotherapy or radiochemotherapy for advanced head and neck tumors from 1992–1995. Based on the Late Effects Normal Tissues–Subjective Objective Management Analytic (LENT-SOMA) system, 37 (54%) patients developed laryngeal lymphedema during the follow-up period (the median time was 250 days). The third study, Schiefke et al. (2009), examined patients with HNC and their postoperative lymphedema as two groups: a sentinel node biopsy (SNB) group ($n = 24$) and a selective neck dissection (SND) group ($n = 25$). Based on the modified Miller Score for head

and neck edema, four (17%) patients who underwent SNB had mild lymphedema, whereas nine (36%) patients who underwent SND developed mild and moderate lymphedema during the follow-up period (the median follow-up was 26.8 months \pm 17.3 months). Wolff et al. (2009) evaluated toxicity of daily low-dose cisplatin in radiochemotherapy for locally advanced HNC ($N = 50$). Based on the LENT-SOMA scoring system for chronic toxicity, six (12%) patients developed lymphedema or fibrosis during the median follow-up of 24.2 months. Therefore, the literature suggests that the incidence of secondary lymphedema after HNC treatment varies from 12%–54%. The variation in incidence of secondary lymphedema in patients with HNC may reflect differences in grading criteria, variations in the structures assessed for manifestations of lymphedema (e.g., internal versus external), differences in the duration of follow-up (Bruns, Micke, & Bremer, 2003), and different cancer treatment regimens among the studies.

Mechanisms

No study of the mechanisms for lymphedema development in patients with HNC was identified during this review; therefore, an additional review of relevant anatomy, physiology, and pathophysiology was conducted. The head and neck are anatomically rich with lymph channels and nodes (Foldi, Foldi, Strobenreuther, & Kubik, 2006), and tumor invasion of soft tissue or surgical treatment may cause destruction or obstruction of lymph channels. Radiation therapy causes DNA and non-DNA damage to structures within the radiation port (Su, Meador, Geard, & Balajee, 2010). Following radiation, the damaged tissue begins to heal; however, tissue damage may be of such severity that lymphedema or fibrosis develop. Data indicate that chronic inflammation might have a critical role in the pathogenesis of lymphedema (Tabibiazar et al., 2006). The accumulation of lymph fluid in the interstitial tissue activates an inflammatory response. That response leads to a massive infiltration of inflammatory cells (e.g., neutrophils, macrophages) and, because of the lymphatic dysfunction, cytokines and chemokines, which generally are cleared from the interstitium, remain in the tissue and recruit inflammatory cells from the circulation system, resulting in an ongoing inflammatory response in the tissue. Accumulation of protein-rich lymph fluid also incites lipogenesis and fat deposition. The chronic inflammatory responses later result in increased fibrocyte activation and connective tissue overgrowth. In this way, patients develop progressively firmer subcutaneous fibrosis tissue that may compromise the lymphatic system even more (Angeli & Randolph, 2006; Tabibiazar et al., 2006; Warren, Brorson, Borud, & Slavin, 2007).

Risk Factors

Two studies reported potential risk factors for secondary lymphedema in patients with HNC. Sanguineti et al. (2007) examined the correlation of laryngeal lymphedema and dosimetric parameters through a retrospective study of 66 patients and found that the only independent predictors for laryngeal lymphedema were mean laryngeal radiation dose and positive lymph nodes. Sanguineti et al. (2007) suggested the laryngeal radiation dose should be kept as low as therapeutically possible to minimize the risk of edema. Warren and Slavin (2007) reported on 11 patients with lymphedema at the site of a scar from a trauma or a surgical procedure. The swelling was attributed to damaged lymphatic channels causing lymphatic dysfunction and trapping lymphatic fluid. These studies suggest that tumor stage, radiation dose, and surgical disruption of lymphatics might be related to the development of secondary lymphedema in patients with HNC.

Based on this information, that tumor- or treatment-related factors that damage tissue or contribute to ongoing inflammation may increase the risk for developing lymphedema is a valid hypothesis. In addition, genetic polymorphisms of key inflammatory and fibrosis mediators may predict clinically evident lymphedema and fibrosis, but these avenues currently are unexplored. Also, risk factors such as comorbid conditions, behavior (e.g., smoking), and situational factors (e.g., vocation) related to secondary lymphedema have yet to be explored.

Measurement

The measurement of head and neck lymphedema is challenging. Methods that have been used include (a) standardized toxicity criteria, (b) endoscopic evaluation for documentation of mucosal edema of the oropharynx and larynx, (c) tape measurement, (d) sonography, and (e) external photographs.

Standardized Toxicity Criteria: External Lymphedema

The NCI's *Common Toxicity Criteria for Adverse Events*, version 3.0, is a comprehensive, multimodality grading system for reporting the acute and late effects of cancer treatment (NCI, 2006; Trotti et al., 2003) that provides a grading scale (from 1–5) to describe head and neck lymphedema. The ACS also provides a method of evaluating lymphedema of the head and neck from stages 0–III (ACS, 2006; Chevillat et al., 2003). These two scales are interchangeable (e.g., grade 1 = stage 0, grade 2 = stage I) (see Table 1). The weaknesses of these scales are the failure to address clinical manifestations such as skin changes or fibrosis and the lack of guidance on how the scales should be used to grade lymphedema involving mucosal surfaces.

Pathology-based systems, such as the Clinical Classification of Lymphedema (CCL) (Keeley, 2000) and the Stages of Lymphedema Scale (Foldi et al., 2006), provide alternative options for grading head and neck lymphedema or fibrosis. The CCL scale was developed by the International Society of Lymphology and evaluates limb lymphedema through three elements: edema, skin changes (including fibrosis and elephantine changes), and impact of elevation on edema. The Stages of Lymphedema Scale was developed based on the clinical experience of treating more than 100,000 patients with lymphedema. The Stages of Lymphedema Scale has three components: pathologic characteristics, clinical presentation (signs and symptoms), and diagnostic method. Consequently, the scale captures information on clinical manifestations of lymphedema and underscores the relationship of lymphedema and fibrosis (Foldi et al., 2006). Although neither of these scales is specific for head and neck lymphedema, they provide a framework from which to work.

Each of the four scales has advantages and disadvantages, and comparing them to identify the overlaps (similarity) and differences is important. Clearly, a need exists for an evidence-based measurement scale of secondary lymphedema for patients with HNC.

Standardized Criteria: Internal Lymphedema

The Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer (RTOG/EORTC) system and the LENT-SOMA system (Budach, Zurlo, & Horiot, 2002; Denis et al., 2003; Trotti et al., 2003) have been used to examine internal lymphedema in the three studies. In one study (Rudat et al., 1999) (N = 29), the RTOG/EORTC was used to diagnose the grade of laryngeal lymphedema. In two studies (Bruns et al., 2004; Micke et al., 2003) (N = 36, each), interstitial endolaryngeal edema was clinically graded using the LENT-SOMA system. The RTOG/EORTC and LENT-SOMA scoring systems grade only lymphedema occurring at the larynx and do not take into account other anatomic sites that may develop lymphedema, such as the pharynx and oral cavity.

Endoscopy

One rating scale (Patterson, Hildreth, & Wilson, 2007) has been developed to measure edema in the larynx and pharynx for patients treated with radiation. The development of edema in the larynx and pharynx was attributed to fibrotic changes during irradiation along with disruption of lymphatic channels resulting in a common complication of head and neck radiotherapy. Eleven structures and two spaces were identified as areas sensitive to the development of edema (see Figure 1). The scale had good intrarater reliability (weighted kappa = 0.84) and content and face validity.

Table 1. Comparison of the Four Staging or Grading Criteria Across Scales

Stage/Grade	CTCAE	ACS Lymphedema of the Head and Neck ^a	CCL ^b	Stages of Lymphedema ^c
0/1	Localized to dependent areas; no disability or functional impairment	Swelling is local and does not affect regular functioning.	No or minimal fibrosis (i.e., edema pits on pressure and reduces with limb elevation)	Pathology: latency—focal fibrosclerotic tissue alterations Signs and symptoms: none Diagnosis: functional isotope lymphography
I/2	Localized facial or neck edema with functional impairment	Swelling is local and affects regular functioning.	Substantial fibrosis clinically (i.e., edema does not pit and does not reduce with limb elevation)	Pathology: reversible—high protein edema; focal fibrosclerotic tissue alterations Signs and symptoms: pitting edema; elevation reduces the swelling and possibly “pain of congestion.” Diagnosis: basic diagnostic procedures
II/3	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	General swelling in the face or neck affects regular functioning (e.g., it may make it more difficult for a person to turn his or her head or open and close his or her mouth).	Grade 2 plus elephantine (trophic) changes	Pathology: spontaneously irreversible—extensive fibrosclerosis, proliferation of adipose tissue Signs and symptoms: brawny, hard swelling that does not recede with elevation Diagnosis: basic diagnostic procedures
III/4	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Swelling is severe and may accompany ulcers on the skin or brain swelling; the ability to eat is severely affected.	–	Pathology: elephantiasis—extensive fibrosclerosis, proliferation of adipose tissue Signs and symptoms: like stage II; invalidism Diagnosis: basic diagnostic procedures
5	Death	–	–	–

^a Reprinted with permission from the American Cancer Society. *Lymphedema: Understanding and Managing Lymphedema After Cancer Treatment*. Atlanta, GA: American Cancer Society, 2006, p. 60, cancer.org/bookstore.

^b From “Clinical Features of Lymphoedema” (p. 45), by V. Keeley in R. Twycross, K. Jenks, and J. Todd (Eds.), *Lymphoedema*, 2000, Oxford, United Kingdom: Radcliffe Medical Press Ltd. Copyright 2000 by Radcliffe Publishing. Reprinted with permission.

^c From *Foldi’s Textbook of Lymphology* (2nd ed., p. 245), by M.E. Foldi, E. Foldi, R.H.K. Stroebenreuther, and S. Kubik, 2006, Munchen, Germany: Elsevier, Urban, and Fischer Verlag. Copyright 2006 by Elsevier. Reprinted with permission.

ACS—American Cancer Society; CCL—Clinical Classification of Lymphedema; CTCAE—Common Toxicity Criteria for Adverse Events, version 3.0

Note. CTCAE and CCL terminology used “grade”; all others used “stage.”

Note. Based on information from National Cancer Institute, 2006.

Tape Measurement

Lymphedema traditionally has been assessed by tape measure using well-defined anatomic sites as reference points. The use of a tape measure is fraught with difficulty in patients with HNC because of issues in establishing reference points that enable constant and reproducible results. Two studies reported some success in grading external head and neck lymphedema using measuring tape; however, Zimmermann et al. (2005) (N = 20) used four anatomic sites (tragus, nostrils, corner of the mouth, and tip of the chin) as reference points and Piso et al. (2001) (N = 11) used seven anatomic marks (tragus, mental protuberance, mouth angle, mandibular angle, nasal wing, internal eye corner, and external

eye corner) as the reference points. Although tape measurements of external head and neck lymphedema have been investigated, they cannot be considered evidence-based clinical assessment methods because of the small sample sizes of the studies and inconsistency of the measurement reference points.

Sonographic Assessment

Sonographic assessment of soft tissue width at the face and neck has been used to measure external lymphedema (Piso et al., 2001), helpful in patients with massive swelling and difficult to detect anatomic marks. Two studies used the sonographic method to measure soft tissue width of the head and neck (Piso, Eckardt,

Liebermann, & Gehrke, 2002; Piso et al., 2001) and reported acceptable results.

External Photographs

Digital photography has been proposed as an effective way to document and evaluate changes of external lymphedema. The photos should be taken in the same positions so they can accurately be compared over time (LymphNotes.com, 2009). Digital photos, particularly three-dimensional digital images, may provide a promising method to measure external lymphedema in patients with HNC. The digital image technology may offer the ability to accurately and dynamically record, save, demonstrate, and compute the degree of external lymphedema by digital data information. Such data would be helpful to clinicians.

Symptom Burden and Functional Loss

Six studies (Bruns et al., 2004; Eisbruch et al., 2004; Machtay et al., 2004; Micke et al., 2003; Piso et al., 2001; Rudat et al., 1999) discussed lymphedema-induced symptoms and function loss in patients with HNC; two studies reported coexisting fibrosis. Review of the pooled data (N = 193) from these studies indicated that lymphedema caused unpleasant symptoms such as tension and pain in the facial region and functional impairments such as dysphagia, dyspnea, and altered speech (see Table 2). No studies directly evaluated these symptoms based on a psychometrically validated symptom-assessment instrument. This lack of symptom assessment using standardized methods or instruments is a critical issue.

The alterations in tissue architecture and pliability that result from head and neck lymphedema and related fibrosis may result in substantial physical symptom burden and functional loss. The incidence, severity, and trajectory of HNC treatment-related lymphedema or fibrosis are unknown. This is primarily because late effects of HNC therapy are not characterized by the underlying mechanism of tissue damage but rather they are characterized by the specific symptom manifestation or the specific function lost. For example, late-effect dysphasia is a well-recognized and common issue in patients with HNC post-treatment as it may be related to a combination of lymphedema and fibrosis of the pharyngeal structures. Although considerable data exist regarding the

frequency and severity of dysphasia, the degree to which either lymphedema or fibrosis contributes to this issue has not been clarified and requires additional study.

A true understanding of the symptomatic impact of lymphedema and fibrosis on survivors of HNC will require a shift in the paradigm used to study late effects. Investigators must emphasize the mechanism of late-effect damage instead of looking solely at the primary manifestations.

Two relatively early studies reported that HNC survivors appear to be particularly vulnerable to depression or experience depressive symptoms (Derogatis et al., 1983; Morton, Davies, Baker, Baker, & Stell, 1984). The data are supported by studies that also report depression and emotional distress in HNC survivors receiving all combinations of surgery, chemotherapy, and radiation (Chen et al., 2009; Verdonck-de Leeuw et al., 2009). Dissatisfaction with appearance and body image impairment after HNC treatment is well documented (Gamba et al., 1992; Liu, 2008). However, no studies were identified to evaluate secondary lymphedema as a possible contributing factor to these psychological issues. External head and neck lymphedema is highly

Structures	Rating of Edema			
	Normal	Mild	Moderate	Severe
Base of tongue				
Posterior pharyngeal wall				
Epiglottis				
Pharyngoepiglottic folds				
Aryepiglottic folds				
Interarytenoid space				
Cricopharyngeal prominence				
Arytenoids				
False vocal folds				
True vocal folds				
Anterior commissure				

Spaces	Rating of Edema			
	Normal	Mildly Reduced	Moderately Reduced	Severely Reduced
Valleculae				
Pyriform sinus				

Figure 1. Patterson's Scale for Edema in Larynx and Pharynx

Note. From "Measuring Edema in Irradiated Head and Neck Cancer Patients," by J.M. Patterson, A. Hildreth, and J.A. Wilson, 2007, *Annals of Otolaryngology, Rhinology, and Laryngology*, 116, p. 560. Copyright 2007 by Annals Publishing Company. Adapted with permission.

visible and may lead to body image issues (Micke et al., 2003), social isolation, and psychological disturbances. In addition, experts agree that the psychosocial effects of secondary lymphedema in patients with HNC may be substantial (Dennert & Horneber, 2007; Murphy et al., 2007).

Management

Management of head and neck lymphedema is challenging. In general, patients undergo extensive education regarding (a) postural techniques to minimize fluid accumulation, (b) importance of skin care, (c) the signs and

Table 2. Symptom and Functional Impairment Studies

Study	Description	Cancer Treatment Modality and Follow-Up Period	Symptom, Functional Status Assessment Methods, and Instruments	Results, Symptoms, and Functional Impairments
Bruns et al., 2004	To investigate the impact of selenium in the treatment of lymphedema of the head and neck region after cancer treatment (N = 36)	Radiation alone or in combination with surgery The median interval was four months after the end of head and neck cancer treatment (range = 2–12 months).	A scoring system modified after the LENT-SOMA criteria for endolaryngeal lymphedema (i.e., subjective parameters assessing breathing from grades 0–4)	Interstitial endolaryngeal lymphedema associated with stridor and dyspnea symptoms
Eisbruch et al., 2004	To identify the anatomic structures whose damage or malfunction caused late dysphagia and aspiration after intensive chemotherapy and RT for head and neck cancer (N = 26)	Chemotherapy and RT Early (1–3 months) and late (6–12 months) after cancer therapy completion	Evaluation of swallowing with videofluoroscopy and direct endoscopy	Coexisting fibrosis with impaired aspiration and swallowing Stiffness of laryngeal and epiglottic walls from lymphedema and fibrosis Mucosal and submucosal fibrosis at base of tongue or at its attachment to pharyngeal musculature
Machtay et al., 2004	To determine the feasibility, toxicity, and preliminary efficacy of a regimen of postoperative reirradiation, chemotherapy, and the radioprotector amifostine after salvage head and neck surgery (N = 16)	Multimodality cancer treatment The median follow-up was 35 months (range = 12–52 months).	RTOG/EORTC late effects criteria (i.e., subjective domain evaluating pharynx and dysphagia)	Coexisting fibrosis with swallowing and voice dysfunction
Micke et al., 2003	To investigate the influence of selenium in the treatment of lymphedema of the head and neck region after cancer treatment (N = 36)	Radiation alone or by irradiation after surgery The median interval was four months after the end of cancer treatment (range = 2–12 months).	A scoring system modified after the LENT-SOMA criteria (i.e., subjective domain evaluating breathing from grades 0–4)	Laryngeal lymphedema associated with stridor and dyspnea
Piso et al., 2001	To evaluate manual lymphatic drainage and compression garments for postoperative head and neck lymphedema after curative surgery for orofacial tumors (N = 11)	Surgery alone As many as 30 days after surgery	Self-reported intensity of tension and pain caused by the swelling (VAS of 0–10) and difficulties with swallowing and speaking (0–6) Impaired swallowing and speaking were quantified from 0 (no difficulties) to 3 (severe difficulties).	Feeling of tension in the face and neck, pain in the submandibular region Impaired swallowing and speaking
Rudat et al., 1999	To detect the associations of acute and late radiation effects, tumor control, and in vitro radiosensitivity of primary normal tissue fibroblasts (N = 68)	Simultaneous concomitant boost radiochemotherapy with carboplatin The median follow-up was 21 months (range = 2.5–81 months).	A tracheotomy had to be performed in 5 of 68 patients (7%) because of the radiation-induced chronic larynx lymphedema.	Impaired breathing function

LENT-SOMA—Late Effects Normal Tissues–Subjective Objective Management Analytic; RT—radiation therapy; RTOG/EORTC—Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer; VAS—visual analog scale

symptoms of infection, (d) head and neck exercises, and (e) access to appropriate treatment methods and management strategies. The hallmark interventions for external lymphedema are compression devices and manual lymphatic drainage (MLD) (Piso et al., 2001). Because of the contour and location of head and neck lymphedema, compression bandages are not feasible or appropriate for all patients (Coopee, 2008). Medical contraindications include issues such as hypersensitive carotid sinus or cardiac dysrhythmias (Foldi et al., 2006).

Patients may have difficulty tolerating compression garments for any significant length of time, leading to decreased effectiveness. In addition, customized compression garments may be required. Only one study, Piso et al. (2001) (N = 11), examined the effectiveness of compression garments. The authors found that two (18%) patients did not complete the compression garment treatment, but reasons why were not reported. Piso et al. (2001) suggested that larger studies are necessary to validate the efficacy and tolerability of compression garments. Four studies (Piso et al., 2001; Preisler, Hagen, & Hoppe, 1998; Reiss & Reiss, 2003; Ruger, 1993) reported efficacy of MLD for treatment of head and neck lymphedema and found that MLD did not increase the rate of local cancer recurrence (Preisler et al., 1998). In addition, MLD decreased patients' symptom burdens and improved their quality of life (Piso et al., 2001; Preisler et al., 1998; Reiss & Reiss, 2003).

Pharmaceutical agents (e.g., benzopyrones, diuretics, corticoids) often are used to treat lymphedema related to conditions such as congestive heart failure. However, these agents are not usually recommended for treatment of secondary lymphedema because they may cause severe long-term side effects (i.e., benzopyrones cause hepatotoxicity; diuretics and corticoids worsen protein accumulation and fibrosis) (Bruns et al., 2004; Micke et al., 2003; Warren et al., 2007).

Three studies (Bruns et al., 2004; Micke et al., 2003; Zimmermann et al., 2005) examined the effect of selenium in the treatment of lymphedema of the head and neck region. Results suggested a short-term positive effect on secondary head and neck lymphedema. As a result of small sample sizes in the studies, limited study designs (e.g., Zimmermann et al. [2005] was the only randomized, clinical trial), and different regimens of selenium among the studies (including different dosages: 500 mcg versus 1,000 mcg daily; different treatment period: three weeks versus four to six weeks), the results of the studies cannot be generalized to other patients.

If lymphedema persists for protracted periods or is untreated, patients may develop fibrosis (Davis et al., 2003). Once fibrosis develops, managing lymphedema is much more difficult. Secondary chronic lymphedema may be refractory to therapy (Lymphoedema Framework, 2006) and it requires aggressive management of

resulting conditions such as impaired swallowing and voice alterations (Murphy et al., 2007).

Cost to Patients and Society

HNC-related lymphedema results in direct (e.g., rehabilitation, compression garments) (Foldi et al., 2006; Lymphoedema Framework, 2006) and indirect costs (e.g., loss of work, sequelae of function loss). To date, no data exist regarding the cost of lymphedema treatment in patients with HNC. However, available data regarding the cost of lymphedema therapy in patients with breast cancer may provide some indication as to the cost to patients with HNC. A cohort study review of insurance data demonstrated significantly higher costs among women in the breast cancer-related lymphedema group, with an estimated increase in the two-year medical costs ranging from \$14,877–\$23,167 when compared to patients without lymphedema (Shih et al., 2009). Although secondary lymphedema is a recognized complication of breast cancer treatment, insurance coverage often is inadequate; therefore, existing data may substantially underestimate the cost of lymphedema. In patients with HNC in which lymphedema is underappreciated and poorly studied, insurance reimbursement issues are likely to be greater.

In addition to the direct costs incurred from treatment, secondary lymphedema in patients with HNC may cause moderate to severe alterations in critical functions such as cervical range of motion, swallowing, and speaking. These changes may affect work ability and efficiency for some individuals. For example, patients with secondary lymphedema may have difficulties with driving because of limited neck range of motion. Again, data related to work ability and efficiency in patients with HNC are not available. In patients with breast cancer and lymphedema, a significant increase was found in the number of days in which usual activities were interrupted by either hospitalization or office visits (58.7 days versus 46.5 days, $p < 0.001$) (Shih et al., 2009). The issues of potential loss of income and additional costs related to secondary lymphedema in patients with HNC, determined via data extrapolation from patients with breast cancer, are likely to be significant.

Influences on Quality of Life

Quality of life is a major concern throughout the treatment and survival trajectory; therefore, numerous studies have focused on treatment-related quality of life. However, studies on quality of life suggest that the type of HNC treatment alone may not be the major contributing factor to poorer quality of life, and the symptoms and secondary complications may affect quality of life (Donatelli-Lassig et al., 2008; El-Deiry, Futran, McDowell, Weymuller, & Yueh, 2009; Langendijk et al., 2008). Throughout the literature review, only two studies

(Bruns et al., 2004; Micke et al., 2003) are available in relation to secondary lymphedema affecting quality of life of patients with HNC. Both studies used self-designed visual analog scales (VAS), rated from 0–10, to assess patients' overall quality of life related to secondary lymphedema and found that patients with secondary lymphedema have a lower quality of life. Higher VAS values mean a lower quality of life, and the self-reported quality-of-life values of the patients in the two studies were 7.9 ± 2.3 and 7.3 ± 1.9 , respectively. The authors of the two studies, however, did not report detailed information on the quality-of-life assessment scale (e.g., reliability, validity). No other instruments were reported in the literature to measure secondary lymphedema-related quality of life after HNC treatment.

Conclusions

Many gaps in the current state of the science related to secondary lymphedema in patients with HNC were identified in this review. These gaps include incidence and prevalence, mechanisms, measurement, risk factors, cost, symptoms, body functions, and quality-of-life issues.

The incidence and prevalence of secondary lymphedema in patients with HNC are unknown in the United States, likely related to the lack of unique measurement tools to assess symptoms associated with secondary lymphedema and resulting in a complete lack of information on lymphedema incidence after the treatment of HNC (Cheville et al., 2003).

Although some studies have developed instruments for measuring external and internal lymphedema, these instruments' psychometric characteristics require additional verification. Therefore, to date, no specific tests are available to diagnose lymphedema. Clinicians must rely solely on patient presentation and medical history to make a diagnosis. In addition, a lack of systematic research exists that focuses on mechanisms leading to lymphedema development, the relationship of lymphedema and fibrosis, and the possible risk factors (e.g., polymorphisms) for secondary lymphedema in patients with HNC.

A lack of systematic research focusing on the effects of secondary lymphedema on patients' physical and psychological symptoms and body function was apparent throughout the literature review. Likewise, the cost of lymphedema (both personal and healthcare system cost) is unknown. The available data are from studies with small sample sizes. Secondary lymphedema after HNC treatment may be associated with numerous symptom issues (e.g., tension in the face) and functional impairment (e.g., impaired hearing). These complications may disrupt function and affect quality of life.

Although early detection and multimodality treatments have decreased the mortality of patients with

cancer, the secondary complications from cancer and cancer treatment affect patients' quality of life. Patients with HNC suffer unpleasant and distressful symptoms that are not explained and are hard to control by current symptom-management strategies. A clear need exists to develop an evidence base that will provide oncology nurses and other healthcare professionals with empirical evidence to better manage secondary lymphedema. Therefore, studies should be conducted to address the gaps identified in the literature.

Implications for Nursing

Nursing Research

Nurse scientists can fill critical and unique roles in the research related to patients with HNC with secondary lymphedema. Research should be focused on gaps in the current literature. The following research areas associated with secondary lymphedema after HNC treatment are needed: (a) examination of incidence and prevalence of secondary lymphedema, (b) exploration of risk factors contributing to the development of secondary lymphedema, (c) descriptions of symptom burden and symptom transitions of secondary lymphedema, (d) psychometric validation of measurement instruments, (e) investigation of the relationships among secondary lymphedema, functional status, and quality of life, (f) exploration of effective interventions and management strategies, (g) assessment of patients' self-management and healthcare professionals' awareness or knowledge, and (h) examination of the cost of lymphedema therapy. In addition, biomarkers that may explain the possible mechanism of secondary lymphedema in the population should be explored.

Nursing Practice

Recommending specific nursing interventions for this patient population is difficult because of a lack of information. Oncology nurses should be aware that some patients may develop secondary lymphedema after treatment for HNC. Minimally, nurses should look for external swelling and tissue fibrosis. They also should assess symptoms and functional impairments that may relate to lymphedema and document any abnormalities. The nursing staff should work with the treatment team to identify appropriate methods to reduce the impact of secondary lymphedema on these patients and help facilitate appropriate referrals for specialty services.

Jie Deng, PhD, RN, OCN[®], is a postdoctoral fellow and Sheila H. Ridner, PhD, RN, FAAN, is an assistant professor, both in the School of Nursing at Vanderbilt University, and Barbara A. Murphy, MD, is an associate professor at the Vanderbilt-Ingram Cancer Center, all in Nashville, TN. Deng can be reached at jie.deng@vanderbilt.edu, with copy to editor at ONFEditor@ons.org. (Submitted August 2009. Accepted for publication December 28, 2009.)

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