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SECONDARY LYMPHEDEMA AFTER HEAD AND NECK CANCER THERAPY: A REVIEW

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ABSTRACT

Secondary head and neck lymphedema (SHNL) is a chronic condition affecting patients who have undergone treatment for head and neck cancers. It results from the disruption of normal lymphatic flow by surgery and/or radiation. The incidence of secondary head and neck lymphedema varies anywhere between 12 and 54% of all patients treated for head and neck cancer, but it is still commonly under-diagnosed in routine clinical practice. In spite of awareness of this condition, treatment has been difficult as definitive staging, diagnostic, and assessment tools are still under development. This review article is aimed at looking at the evidence, standards of management, and deficiencies in current literature related to SHNL to optimize management of these patients and improve their quality of life.

Keywords: cancer, head and neck lymphedema, diagnosis, imaging, treatment, MLD, CDT, quality-of-life

Swelling caused by an impaired tissue drainage resulting from lymphatic dysfunction with accumulation of fluid in the interstitial spaces is called lymphedema (1). Primary lymphedema is a result of an inherent developmental anomaly of the lymphatic system whereas secondary lymphedema is a result of damage caused to the lymphatic system by surgery, radiotherapy, trauma, infection or other systemic disorders. Lymphedema visible to the clinician is referred to as 'external' whereas that affecting the mucosal surface of the body is 'internal'; however, these conditions are not independent and can occur concomitantly in some patients. Secondary head and neck lymphedema (SHNL) is a significant complication of treatment for head and neck cancer (HNC), but has not gained widespread recognition. Some of the reasons include: (i) less than 50% of patients treated for HNC develop SHNL and the priority of the treating clinician is more on the oncological outcomes, and (ii) most patients with complex tumors of the head and neck are treated in large tertiary centers, thus few clinicians routinely encounter HNL.

With the evolution of newer aggressive multimodality treatment strategies, increased incidence of human papilloma virus-related cancers, and improved survival outcomes, patients often live longer and develop late functional sequelae of treatment. This lymphedema is often progressive (2-4). The literature suggests that the incidence of secondary lymphedema after HNC treatment varies from 12%-54%. This wide variation in incidence of

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SHNL may reflect differences in grading criteria, variations in the structures assessed for manifestations of lymphedema (e.g., internal vs external), differences in the duration of follow-up, and differences in cancer treatment regimens among the studies (5,6).

PATHOPHYSIOLOGY

A functional lymphatic system is crucial and serves many important functions such as regulation of tissue fluid homeostasis, removal of cellular debris, immune cell trafficking, lipid absorption, and transport from the gastric system. A systematic fluid exchange mechanism occurring at the blood capillary-interstitial-lymphatic interface coordinates all these functions. Four forces interact together and drive this capillary filtration namely capillary pressure, negative interstitial pressure, interstitial fluid colloid osmotic pressure, and plasma colloid osmotic pressure. Variation in any of these can lead to edema. Other factors, such as alteration of either extrinsic or intrinsic propulsion mechanisms (e.g., fibrosis impeding muscle movement) or of lymphatic structures (e.g., neck dissection or radiation induced fibrosis of nodes) can decrease lymph flow, impede fluid egress, and result in lymphedema. (7)

Surgery decreases both the carrying capacity and efficiency of the transport mechanism. The head and neck region requires substantial lymph drainage to maintain vital function and has about 300 lymph nodes, roughly a third of those in the body. Although chemotherapy was historically not thought to be a risk factor for lymphedema, it compounds the radiation-induced damage to the lymphatic system. Recently, published literature points out the association between taxane group of chemotherapeutic agents and lymphedema, though the exact causative mechanism is not yet understood. The acute effects of radiotherapy are inflammatory-mediated and cytokine-propelled, which usually subsides. The final factor in lymphedema severity depends on the extent of tissue damage. When tissue damage is more severe, the repair process is pathogenic with resultant over-production of the extracellular matrix and a permanent fibrotic scar. This occurs when new collagen synthesis by myofibroblasts exceeds the degradation rate and places cancer survivors at risk for late-effect fibrosis and/or lymphedema (7).

The manifestation of disease occurs in stages, the first being heaviness or tightness with no visible edema, progressing to visible edema which is non-pitting, and subsequently edema that pits on pressure. The final stage is fibrosis and serious functional impairment such as impaired speaking, swallowing, breathing, poor cosmesis, and even impaired vision.

SECONDARY HEAD AND NECK LYMPHEDEMA AND ITS IMPACT ON QUALITY OF LIFE

The effects of SHNL are far from only cosmetic. Significant lymphedema of the face, mouth, and neck can result in severe functional disturbances in communication (speaking, reading, writing, and hearing), alimentation, and respiration (8). Severe head and neck lymphedema may also impede ambulation when vision is impaired. In extreme cases, respiratory obstruction may require a tracheostomy (9,10). Laryngectomized patients may experience difficulty with stomal access for hygiene purposes, respiration, and management of a tracheo-esophageal voice prosthesis. Intra-oral and pharyngeal edema can impede swallowing safety and efficiency (11-12) and may mandate a gastrostomy tube for feeding. The psychological effects of facial disfiguration may be grave, including frustration, embarrassment, and depression due to both functional and cosmetic changes (9,13). The treatment of SHNL is essential for the rehabilitation of these deficits and improvement of the patient's quality of life (13,14).

Deng et al (8) has reported on the quality of life (QoL) in 103 HNC patients who were ≥3 months post treatment. The variables assessed included severity of internal and external

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lymphedema, physical, psychological symptoms, functional status, and overall QoL. The severity of internal and external lymphedema correlated with both physical and psychological symptoms. Patients with more severe external lymphedema were more likely to have a decrease in neck movement, and the combined effects of external and internal lymphedema severity were associated with hearing impairment and decreased QoL. Overall severity correlated well with symptom burden, functional status, and QoL (8).

ASSESSMENT OF HNL

Lack of a common evaluation algorithm had until recently impeded the reporting and staging of lymphedema, Measurement of SHNL is important as it forms an integral part in diagnosis, management planning, and monitoring progress of treatment. There is a wide variation in use of assessment tools between the various institutions which are currently managing the disease. Deng et al (15) have reviewed various assessment tools and have divided these into three main groups as follows.

Patient Reported Outcomes (PRO)

These unfortunately have been vastly ignored. The majority of patient reported outcome measures take into account the symptom burden associated with HNC, however outcomes pertaining specific to SHNL have not been included in any of these measures.

Lymphedema Symptom Intensity & Distress Survey-Head & Neck (LSIDS-H&N) is the only known existing PRO measure directed specifically at head and neck lymphedema (16). It is a 65-item symptom tool and was developed via a rigorous instrument development process. Deng et al reported that: (a) the LSIDS- H&N was feasible to administer, readable, and easy to use; (b) content validity was supported by expert panel review; and (c) an initial test indicated that the tool captured critical and unique symptoms related to lymphedema (17). The authors concluded that further psychometric testing of the tool in larger sample size studies was needed

Clinician reported outcome measures (CRO)

There are various CRO measuring tools described for external lymphedema with Földi's scale being the predominant measurement tool. The MD Anderson Cancer Center Lymphedema Scale (MDACCLS), which has been modified from the Földi's scale, is another measuring tool. However, validity and reliability data are not available. Other common head and neck specific scales for grading head/neck lymphedema are the Common Terminology Criteria for Adverse Events (CTCAE) (18) and the American Cancer Society (ACS) Scale.

Deng et al comparing these scales found the following: (1) none of these measures have been validated; (2) each failed to capture important features of external lymphedema; and (3) none capture edema and fibrosis that coexist in some patients (18). Lymphedema and fibrosis are now considered as two different pathophysiologic entities associated with HNC treatment which may co-exist in the same patient with one causing progress of the other. So there is a need for measuring both problems differently and scaling them appropriately (19).

Internal lymphedema measurements are largely based on both physical and functional assessment. The Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) system (20) and the Late Effects Normal Tissues-Subjective Objective Management Analytic (LENT-SOMA) (21) systems have been used for grading the internal laryngeal edema, but they have neither been validated nor do they consider other mucosal sites like the tongue or pharynx. Patterson's scale uses endoscopic visualization to grade edema of eleven structures and two spaces in the pharynx and larynx (22) and has good intra-rater reliability (weighted kappa = 0.84)

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and moderate inter-rater reliability (weighted kappa = 0.54). A weakness of the Patterson scale, however, is that it fails to capture important anatomical sites (e.g., tongue) in the oral cavity that may develop internal edema. Also, the inter-rater reliability of the Patterson Scale needs to be improved for clinical use.

Technical Measurement Tools

Tape measurements

MDACCLS (9) utilizes tape measurements of various facial and neck landmarks in their management of lymphedema *(Fig. 1)*. The inter-rater reliability of these measurements has been studied in the ALOHA trial by Purcell et al (23), who reported excellent inter-rater reliability for 3 of the 4 tape measurements *(Fig. 2)*.

Digital photography

Digital photography offers an excellent subjective method that can be used to assess the progress of the treatment. Exacting methodology must be used to ensure that the photos are taken in the same positions so accurate comparisons may be made.

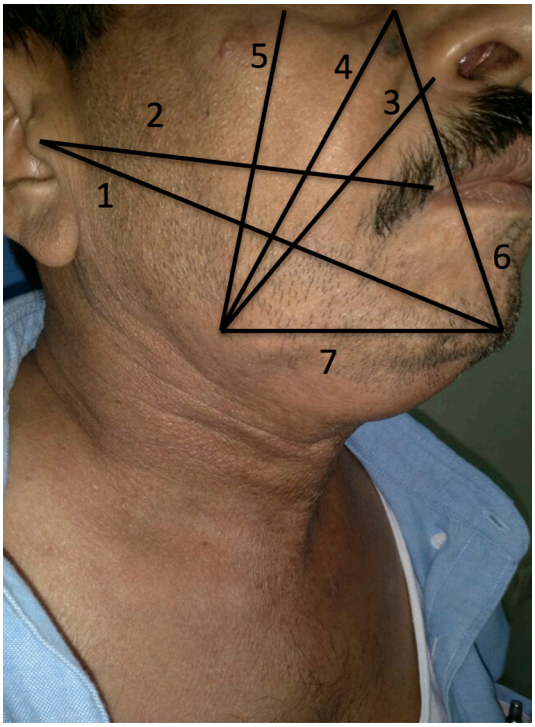

Fig. 1. The MD Anderson Cancer Centre Lymphedema Scale measurements utilizes tape measurements to assess and follow treatment for head and neck lymphedema. Multiple points are included (see lines overlaid on subject's face) including those for facial circumference (diagonal from chin to crown of head and submental from < 1 cm in front of ear with vertical tape alignment) and point to point (mandibular angle to mandibular angle and tragus to tragus).

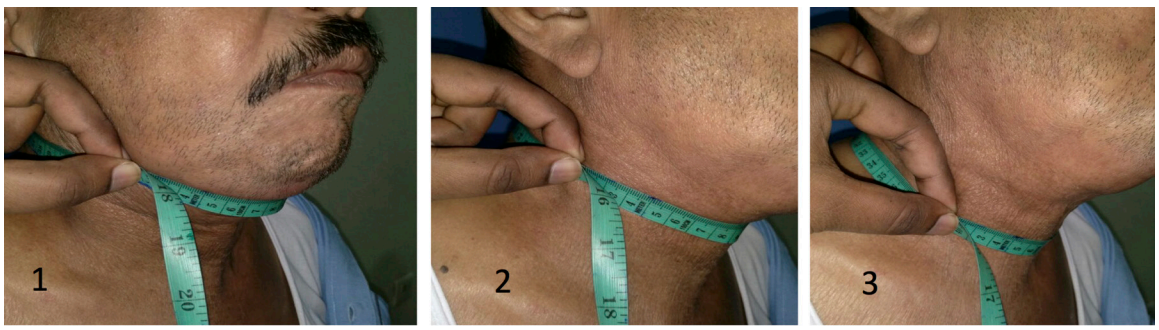

Fig. 2. Location of measurement points on the neck include: 1) Upper neck circumference taken at the highest point inferior to the mandible; 2) Length from ear to ear measured at the inferior junction of ear lobe and face on left to inferior junction of ear lobe and face on right intersecting a point 8 cm inferior to the lower lip edge; and 3) lower neck circumference taken at the lowest possible point superior to the angle of the neck and shoulder.

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Moisture meter D (MMD)

Another promising objective assessment of SHNL is the tissue dielectric constant (TDC), which can be assessed using the MoistureMeterD (MMD; Delfin Technologies Ltd, Kuopio, Finland). TDC reflects the content of local tissue water and is sensitive to both free and bound water contained within the tissue volume being measured. The MMD generates an ultrahigh-frequency electromagnetic wave of 300 MHz, which is transmitted into a coaxial line and further into an open-ended coaxial probe. The probe is placed in contact with the skin and the electromagnetic wave is transmitted to a specified depth in the area of tissue beneath the probe. A portion of the electromagnetic energy is absorbed by tissue water and the remainder is reflected back into the coaxial line. The amount of signal reflected represents the TDC. TDC is used as an index of local tissue water. As a reference, pure water has a TDC value of 78.5. The MMD readings range from 1 to 80 with a higher reading indicating the presence of more swelling.

Purcell et al (23) reported excellent inter-rater and intra-rater reliability for MMD use in the measurement of SHNL. The MMD discriminated well between patients with head and neck lymphedema and healthy controls ($p < .001$). Correlation between MMD score and SHNL level ratings was significant indicating convergent validity. The trial confirmed the potential of MMD as an objective measurement tool for diagnosis and assessment of SHNL.

Imaging

As a measurement tool, imaging is not reliable in the evaluation of HNL. Lymphangiography, lymphoscintigraphy, and near-infrared fluorescence imaging may aid in functional mapping of the lymphatic system, but for detection of tissue changes, other imaging modalities like CT, MRI, and ultrasound may be used. When compared to CT and MRI, high-resolution ultrasonography is a noninvasive, harmless, and inexpensive technique to visualize the dermal and subcutaneous tissue (24-34). Studies have reported that high-resolution ultrasonography is a sensitive method for assessment of changes in skin/soft tissue edema in the breast cancer population. Strain elastography is a newer imaging technique that allows noninvasive estimation and imaging of tissue elasticity distribution within biological tissues using conventional real-time ultrasound equipment and elastography software. Conceptually, elastography measures tissue elasticity, potentially adding significantly to our ability to measure the fibrotic component of lymphedema in an objective manner but it requires validation.

TREATMENT OF SHNL

Manual Lymphatic Drainage (MLD)

MLD was developed by Danish massage therapist Emil Vodder for the treatment of chronic sinusitis in the 1930s (35). It was later adapted to the treatment of lymphedema. MLD consists of series of gentle, circular massage strokes that are applied to the skin to promote increased lymphatic flow (36,37). Through this technique the lymphatic fluid is directed towards the normal lymphatic system. MLD is now used as part of the complete decongestive therapy.

Complete Decongestive Therapy (CDT)

Although the MLD technique decreases lymphedema by directing the fluid to be drained to the normal area, the already malformed interstitial space and altered lymphatic system results in rapid redevelopment of lymphedema. Földi is credited with combining MLD technique with compression bandages and physical exercises, along with skin care, labeling it CDT which is the standard of care in the management of lymphedema (38). Traditional CDT is typically provided by a certified lymphedema therapist in two phases: a primary intensive phase of outpatient treat-

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ment provided 3-5 days weekly over a period of 2-4 weeks and the subsequent maintenance phase which begins as treatment transitions from the outpatient setting to the home environment. The basic components of the program continue to be emphasized, however the performance of the program becomes the responsibility of the patient or caregiver (39). Daily adherence to a home treatment program may be required for the remainder of the patient's life depending on the severity of the edema.

In the early stages, patients are encouraged to carry out Simple Lymphatic Drainage (SLD), a modified form of MLD, at least once a day not only to enhance benefits of other forms of lymphedema treatment but also to help accurate recall of the routine and technique. The basic goals of CDT are to decongest the edematous region, prevent refilling of the tissues, and promote improved drainage. MLD relieves the edema, and exercises combined with compression bandaging enhance the movement of lymph to adjacent areas with intact drainage.

Smith et al from MD Anderson Cancer Center have reported their 6-year experience with the HNL CDT program in 1,202 patients. Most patients (62%) had soft, reversible pitting edema (MDACC Stage 1b). Treatment response was evaluated in 733 patients after receiving therapy; 439 (60%) improved after complete decongestive therapy. Treatment adherence independently predicted complete decongestive therapy response ($p<0.001$) (40).

Pharmacotherapy

The use of drugs in the treatment of lymphedema is still experimental. One of the commonest agents used is selenium. Bruns et al have suggested a short positive effect of sodium selenite on SHNL caused by radiotherapy, alone or in combination with surgery. 36 patients with SHNL (20 of whom had severe internal lymphedema) received 350 µg/m^2 body surface area of sodium selenite orally daily (up to 500 µg per day) for a period of 4-6 weeks after radiotherapy. 75% of the patients had an improvement of the score by one stage or more. The self-assessment of QoL using the visual analogue scale improved significantly after selenium treatment with a reduction of 4.4 points ($p < 0.05$) (41,42).

Anti-inflammatory drugs (corticosteroids, D-penicillamine, colchicine, etc), vascular targeted therapies (pentoxifylline, hyperbaric oxygen therapy, ACE inhibitors) and anti-oxidants (liposomal super oxide dismutase, vitamin E) are some of the drugs/techniques that have also been tried in both pre-clinical and clinical studies for the management of radiation induced fibrosis with promising results. But their role in the management of SHNL is doubtful, although fibrosis is a continuum of the process (43-63).

Low Level Light Therapy (LLLT)

Lee et al (64) has reported the use of LLLT in treatment of HNL. It is the application of light (usually a low-power laser or light emitting diode (LED)) to promote tissue repair, reduce inflammation, reduce edema, and induce analgesia. The laser or LED device typically emits light in the red and near-infrared light spectrum (600 nm-1000 nm), the power output is usually in the range of 1-500 µW and the irradiance is generally in the range of 5 µW-5 W/cm^2. Treatment time per point is typically in the range of 30-60 seconds per point and most pathologies require the treatment of multiple points (65). Treatments can be weekly, though more frequent treatments may be more effective with a maximum possible after which effectiveness is decreased. For acute and post-operative pathologies, one treatment may be all that is necessary, but for chronic pain, degenerative conditions, and lymphedema, ten or more sessions may be necessary. Although LLLT have been more routinely used in breast cancer related lymphedema, the efficacy of its use in SHNL has not been proved.

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Surgical Management of SHNL

Lymphatico-venous anastomosis has been reported for the treatment of SHNL not responding to MLD techniques. Mihara et al (66) have reported the technique and outcomes. Functional and dilated lymph vessels were identified using pre- and intra-operative fluorescent lymphography, using indocyanine green dye for near-infrared fluorescence labeling and reliable anastomosis of the lymph vessel with the venous circulation (superficial temporal vein). A super-microsurgical anastomosis technique is used because the diameters of the lymph vessel and vein are approximately 0.3- 0.5 mm. Capillary lymph vessels in the head and neck region have fewer valves compared with lymph vessels in the limbs, and lymph flows relatively freely. A follow-up of 8-12 months after anastomosis is needed to investigate changes in the postoperative course as the therapeutic effect may not appear rapidly. Similar techniques and results have also been reported by Ayestaray et al (67).

A lymphatic bridge is the last option in the most severe cases of SHNL. It has been reported in patients who were completely functionally impaired with no feasible therapeutic options. A pedicled (usually a deltopectoral) flap draining into a normal lymphatic system is harvested and bridged into the upper part of the lymphedematous area (usually cheek) and CDT or MLD is initiated so that the lymph flows from the collected area to the normal lymphatic system (axilla) through the pedicled flap (68).

CONCLUSION

SHNL is a common morbidity associated with head and neck cancer treatment. There is an urgent need to validate the various evaluation tools and standardize measurements. Comprehensive decongestive therapy is the current treatment of choice in patients with SHNL, with medical therapies being a possible adjunct therapy and surgery a potential last resort.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist and have no disclosures.

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