

Head and neck lymphoedema and fibrosis: a case study

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Key words

Head and neck cancer, lymphoedema, fibrosis, shear wave elastography

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Patients with locally advanced head and neck cancer (HNC) are at risk of the development of secondary lymphoedema and fibrosis (LEF), inclusive of physiological changes that represent a continuum of conditions, from swelling to hardening of fibrotic tissue (Földi et al, 2006; Avraham et al, 2013). These changes are associated with damage to the lymphatic system and its surrounding soft tissues from tumour infiltration, surgery, and radiation (Földi et al, 2006; Smith and Lewin, 2010). The literature has reported that 75% of HNC patients >3 months post-treatment developed some degree of lymphoedema (Deng et al, 2012a). It is important to understand that the earlier stages of lymphoedema are typically reversible; however, without appropriate and timely management, lymphoedema may progress to late stages, i.e., the development of fibrotic changes, which are refractory to standard rehabilitation treatment.

LEF is associated with substantial symptom burden and functional deficits; furthermore, it may have a devastating

Abstract

Introduction: Accurate techniques for measurement of head and neck lymphoedema and fibrosis (LEF) are lacking. Shear wave elastography (SWE) is a new sonographic method to assess soft tissue elasticity. **Objective:** To present a case report of a head and neck cancer (HNC) patient with LEF whom was assessed using SWE. **Methods:** A 41-year-old patient with HNC developed LEF after his cancer treatment. The patient underwent LEF therapy in a timely fashion and self-care for LEF; nonetheless, the patient developed severe fibrosis. **Results:** This case describes the patient with progressive skin/soft tissue changes related to LEF. SWE demonstrated dramatically increased shear wave velocity, which corresponded to a marked decrease in the soft tissue elasticity of the neck. **Conclusion:** This case report highlights the importance of monitoring and managing LEF long term in the HNC population. SWE may prove to be a useful tool for clinicians to identify skin/soft tissue changes related to LEF that require intervention. Further investigation of this tool is ongoing.

impact on long-term quality of life (Stubblefield and O'Dell, 2009; Smith and Lewin, 2010; Deng et al, 2013). Although level I evidence is lacking, clinical experience indicates that early and aggressive therapy for LEF results in improvement in musculoskeletal symptoms and decreased functional deficits. Unfortunately, accurate and quantitative techniques for measurement of head and neck LEF are lacking. This may adversely impact early identification, timely referral for therapy, and continued monitoring of therapeutic response. In addition, the lack of quantitative measures results in methodological limitations for therapeutic clinical trials.

Ultrasonography is a non-invasive, harmless, and relatively inexpensive technique that can be used to visualise the dermal and subcutaneous tissues (International Society of Lymphology, 2013; Lee et al, 2013; Suehiro et al, 2013). Studies have reported that ultrasonography may be a sensitive method for assessment of changes in skin and soft tissue oedema in

the breast cancer population (Tassenoy et al, 2009; Tassenoy et al, 2011). Applicability and utility of this measurement technique for assessment of LEF in the HNC population has yet to be established.

Shear wave elastography (SWE) is a sonographic technique that allows for the objective measure of soft tissue elasticity expressed in meters per second (shear wave velocity) or kilopascals (Young's modulus) (Garra, 2015; Liu et al, 2015; Scoutt and Miller, 2014; Shiina et al, 2015). In SWE, a push pulse, often referred to as an acoustic radiation force impulse, is used to generate shear waves within the tissues, which is similar to dropping a stone into a pond (the push pulse) and generating waves on the water (shear waves). Conventional B-mode imaging is used to monitor the shear waves generated through the tissue and calculate the shear wave speed. Using SWE, an absolute stiffness value can be obtained and used for lesion characterisation. Higher shear wave speed indicates increased soft tissue stiffness. Currently, no literature has been available

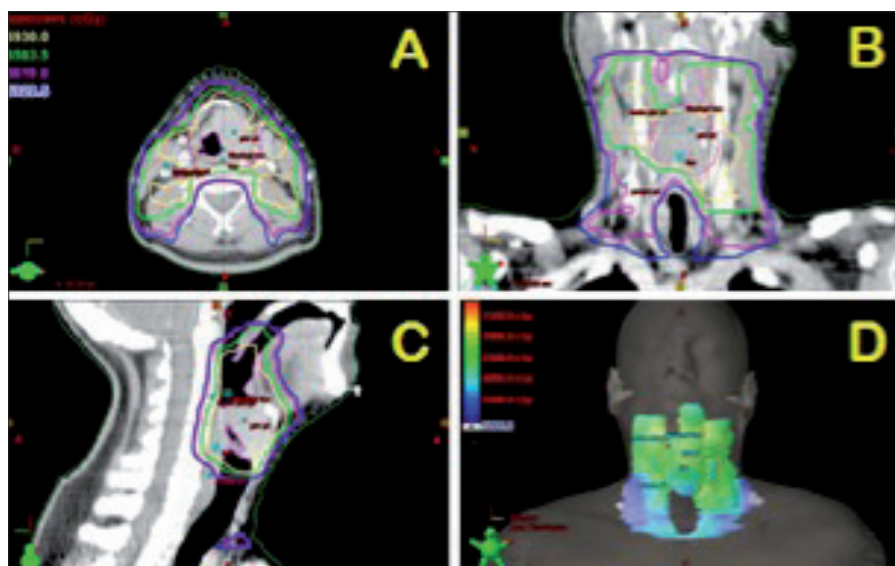


Figure 1. Images of the Patient's Radiation dosimetry. Notes: Panels A, B, and C show axial, sagittal, and coronal isodose curves, respectively. The yellow line and green lines represent 100% and 95%, respectively, of the prescribed dose of 6930 cGy for the primary tumor site and the grossly involved lymph nodes. The magenta and green lines represent 100% and 95%, respectively, of the prescribed dose of 5610 cGy for the prophylactic coverage of the uninvolved cervical lymph nodes. Panel D shows a three-dimensional rendering of the cumulative radiation dose cloud.

to report using SWE to measure LEF in HNC patients. Research efforts need to be considered to examine if SWE is capable of identifying skin and soft tissue elasticity changes related to early lymphoedema, the progression of lymphoedema, as well as late-stage lymphoedema (fibrotic changes). Most recently, SWE has been successfully applied in identification and staging of liver fibrosis, thus providing clinicians with a useful tool to guide treatment decision making (Samir et al, 2015; Zheng et al, 2015). Thus, SWE may potentially provide us with a tool to quantify the fibrotic component of LEF in an objective manner. This paper presents a case report of a patient with severe HNC-related LEF assessed using SWE.

Case Presentation

Disease/treatment/recovery history

The patient was a 41-year-old white male who presented in January 2005 with a 4-month history of sore throat, hoarseness, left-sided otalgia and throat pain. He was diagnosed with a T4N2cM0 squamous cell carcinoma of the left supraglottis. The patient did not have any other chronic or significant medical conditions.

The patient was treated with induction chemotherapy, followed by concurrent chemoradiation at a large academic cancer centre. Intensity-modulated radiation therapy (IMRT) was delivered over 33

fractions using differential dose painting at two dose levels: 1) the primary tumour site and grossly involved lymph nodes received a total dose of 6,930 cGy divided into 33 equal daily doses of 210 cGy; 2) the clinically uninvolved cervical lymph node regions at risk for subclinical spread received a total dose of 5,610 cGy, divided into 33 equal daily fractions of 170 cGy. An image of the radiation dosimetry (defined as measurement of radiation exposure from X-rays, gamma rays, or other types of radiation used in the treatment or detection of diseases, including cancer) (National Cancer Institute, 2016) for this patient is provided (Figure 1).

The patient completed cancer therapy in June 2005. The patient's treatment course was complicated by: grade I hoarseness, grade II dysphagia, grade II xerostomia, grade II skin reaction, and grade III mucositis. Pain was well-controlled with lortab elixir (hydrocodone bitartrate and acetaminophen oral solution), duragesic (fentanyl transdermal skin patch), and roxanol (morphine). Mucositis was well-controlled with salt and soda wash (2 tea spoon (tsp) of salt and 2tsp of baking soda per 1 gallon of water – 15 ml swish and spit q 2 hours prn) and Miracle Mouthwash (1/3 lidocaine, 1/3 Maalox, 1/3 benadryl – 15 ml swish and spit every 6 hours as needed. Skin reactions responded well to thermazene (silver sulfadiazine).

Overall, the patient did well post-treatment, with rapid recovery of ECOG performance status 0 from a nadir of 3 during treatment. Late effects included: musculoskeletal impairment (i.e., decreased neck and shoulder range of motion), hoarseness, hypothyroidism, anxiety, and depression (well-controlled on medication). During each post-treatment clinical follow-up visit (every 4–6 weeks for the first year post treatment, then every 3 months for year 2 post treatment then a minimum of every 6 months thereafter), the patient was educated about the importance of performing neck-shoulder exercises and maintaining proper body alignment and posture.

LEF changes over time: patient report, physical exam and imaging findings

In 2007, the patient developed noticeable swelling on the bilateral neck from level 2 through level 4 and in the submental region. He was diagnosed with face and neck LEF based on medical history and physical examination in the head and neck region. He underwent lymphoedema therapy with reduction in soft tissue swelling. In 2008, the patient was noted to have increased restriction of movement in the neck and shoulders, with worsening posture. He was referred for physical therapy to treat poor posture and decreased neck and shoulder range of motion, secondary to treatment-associated LEF. Since that time and through 2016 when the patient was last seen, he maintained an aggressive exercise regimen with resultant retention of good postural alignment and functional range of motion in the neck and shoulders. However, the texture of the soft tissues of the neck remained woody in character and range of motion is diminished over time.

Due to the patient's chronic LEF, he participated in two LEF research studies conducted in December 2012 and September 2015. Both studies were approved by the Institutional Review Board at the study site and the participant signed the informed consents. As part of the research activities, the authors were able to assess the patient's symptom burden, LEF characteristics and neck range of motion over time. Additionally, in September 2015, tissue elasticity was assessed using a newly-developed protocol for SWE. This protocol measured skin/soft tissue thickness and

Case report

elasticity at nine defined anatomical sites within the face and neck region.

Symptoms

The Lymphedema Symptom Intensity and Distress Survey-Head and Neck (LSIDS-H&N) (64-item) was used to measure lymphoedema symptoms in the study. When filling out this tool, the patient needs to indicate whether he/she has a symptom (“yes” or “no”) and if “yes”, he/she needs to further rate intensity and distress levels of the symptoms on two separate 10-point scales. Content and face validity of the tool was reported during the development and preliminary testing of the tool (Deng et al, 2012b).

Based upon the LSIDS-H&N measure, there was no significant change in the number or type of symptoms that the patient experienced between 2012 and 2015. The patient reported the following symptom burden: 1) local effects in the head/neck (tightness, spasm, lack of endurance, firmness or hardness of skin, stiffness, change in skin texture, and limited head/neck movement); 2) body image disturbance (concern about how one looks, feeling unattractive, and lack of confidence in one’s body); 3) psychosocial issues (feeling anxious and grouchy); and 4) altered head-and-neck-specific functions (problems swallowing, voice changes, hoarseness, hard to move tongue, trouble breathing, stopped up sinuses, and ringing in ears). The patient’s symptom severity was variable and ranged from mild to severe. In general, the symptom severity increased over time.

Neck range of motion

The Cervical Range of Motion (CROM) device, manufactured by Performance Attainment Associates, was used to measure the patient’s neck range of motion in degrees (Reynolds et al, 2009; Williams et al, 2010). The patient’s neck range of motion was assessed in six directions: forward flexion, extension, left and right lateral movement, and left and right rotation. Based on the literature report, the average neck ranges of motion in healthy, normal individuals are: forward flexion (45–60 degrees), extension (45–75 degrees), left and right lateral flexion (45 degrees), and left and right lateral rotation (60–80 degrees) (Hoffman, 2006). Using the CROM measure, the patient’s neck

Table 1. Measurement sites and speeds using shear wave elastograph.

| Measure sites | Right Speed (m/s) | Left Speed (m/s) |
|--|-------------------|------------------|
| Maxillary Prominence | 4.97 ± 1.60 | 3.26 ± .35 |
| Middle Mandible | 8.01 ± .38 | 2.24 ± .13 |
| Middle sternocleidomastoid muscle (SCM) | 7.07 ± .40 | 8.22 ± .15 |
| Superior SCM | 7.36 ± .30 | 7.87 ± .14 |
| Middle submental* | 7.39 ± .18 | |
| *Submental measurement performed at midline generating a single value. | | |

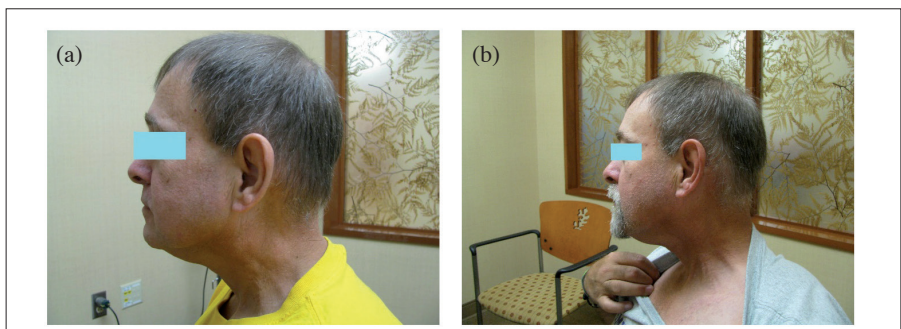


Figure 2. Patient left lateral neck images. Note: lateral neck photograph of atrophic and fibrotic changes noted in 2012 (a) and 2015 (b).

range of motion decreased from 2012 to 2015 in 4/6 directions: forward flexion (from 50 to 36 degrees), extension (from 44 to 32 degrees), left lateral rotation (from 62 to 40 degrees), and right lateral rotation (from 48 to 42 degrees).

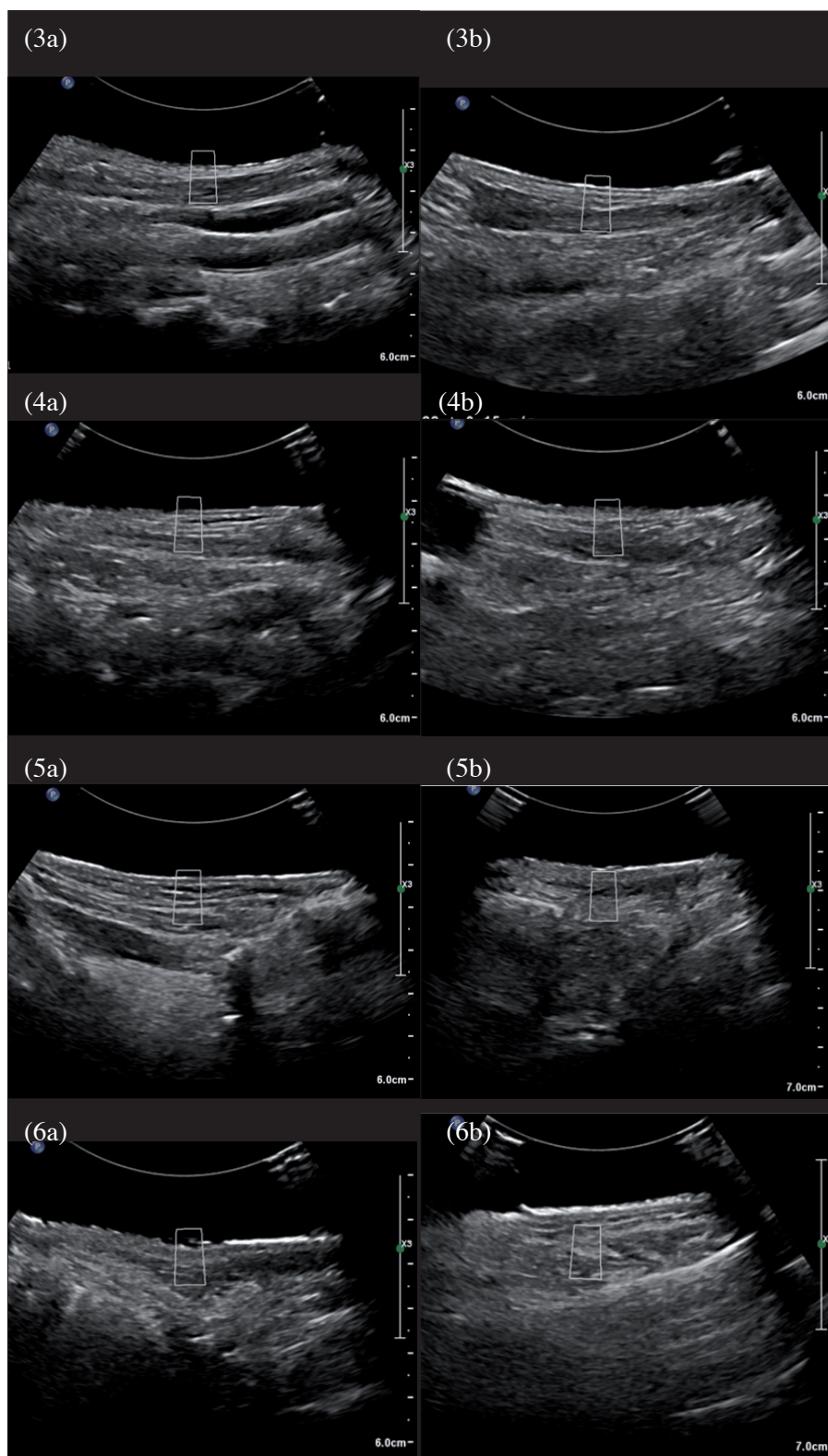
Physical examination

The patient’s skin and soft tissue abnormalities were graded using Head and Neck External Lymphedema Fibrosis Grading Criteria (HN-LEF Grading Criteria), a clinician report outcome measure (Deng et al, 2015). The tool includes four types of soft tissue abnormalities found during physical examinations, including type A, B, C and D. Type A is defined as “palpable thickening and/or tightness of the dermis without visible soft tissue swelling”; type B is defined as “visible soft tissue swelling, with involved tissues feeling soft to touch and tissue swelling reducible and fluctuating in severity”; type C is defined as “visible soft tissue swelling with involved tissues firm to touch, tissue swelling that is non-reducible and persistent”; and type D is described as “firm skin with increased density and decreased compliance in the absence of

swelling.” Under each type (except for type A), a grade is used to describe the severity of the soft tissue abnormalities, ranging from mild to severe (Deng et al, 2015). Using the criteria, the patient’s skin and soft tissue abnormalities progress over time. In 2012, the patient had moderate fibrotic changes (type D) involving the bilateral neck and bilateral peri-clavicular regions (Figure 2a). By 2015, the patient developed more extensive skin/soft tissue fibrosis (type D) in the head and neck (Figure 2b), including moderate fibrosis on the submental region, and severe fibrosis on the bilateral posterior auricular, bilateral neck, and bilateral peri-clavicular regions (please note: per the HN-LEF Grading Criteria, moderate fibrosis is defined as soft tissues that are extremely hard and have a woody texture, while severe fibrosis is defined as soft tissue fibrosis associated with contracture).

Skin and soft tissue elasticity

SWE was performed by an experienced sonographer in nine anatomical sites within the face and neck region using an EPIC scanner (C5-2 transducer) (Philips Healthcare Bothell) with an aqueous, disposable ultrasound standoff gel pad.



Figures 3–6. Paired shear wave elastography images with corresponding calculated velocities (mean + standard deviation). Figure 3(a) Right maxillary prominence. Figure 3(b) Left maxillary prominence. Figure 4(a) Right middle mandible. Figure 4(b) Left middle mandible. Figure 5(a) Right middle sternocleidomastoid muscle (SCM). Figure 5(b) Left middle SCM. Figure 6(a) Right superior SCM. Figure 6(b) Left superior SCM. Notes: The box (region of interest) within each image shows how measurement of shear wave velocity on each anatomical site was made.

Table 1 depicts the speed of shear waves at the nine measurement sites used in the current protocol. The results demonstrated dramatically increased speeds (e.g., middle submental SWE: 7.39 ± 1.18 m/s), which is consistent with and reflective of a marked decrease in the soft tissue elasticity (Figures 3–7), compared to shear wave speeds (ranged from 1.89 ± 0.32 m/s to 2.38 ± 0.58 m/s) reported in the healthy normal participants' gastrocnemius medialis skeletal muscle (Dorado Cortez et al, 2016).

Discussion

This case depicts the insidious and progressive skin and soft tissue changes that may develop in post-treatment HNC patients, as demonstrated by self-reported symptoms, physical examination and elastography. It is important to note that this patient was informed and advised with respect to preventative neck and shoulder exercises from the time he completed radiation. Therapy was initiated during the early developmental stages of the patient's lymphoedema. When the patient began to develop range of motion and postural deficits, he was referred for physical therapy in a timely manner. Even with aggressive intervention, the patient developed marked fibrosis characterised by soft tissues with a woody texture. Despite the progressive soft tissue changes, aggressive intervention and self-care activities resulted in maintenance of good postural alignment and functional neck and shoulder range of motion.

Using SWE, the authors were able to quantify skin and soft tissue elasticity in the affected tissues within the head and neck region. The degree of fibrosis as measured by shear wave speed was strikingly severe. Speeds were dramatically higher than those reported in other normal soft tissues or pathologic states in the literature. For instance, a study reported that ultrasound shear wave velocity in the healthy normal participants' gastrocnemius medialis skeletal muscle ranged from 1.89 ± 0.32 m/s to 2.38 ± 0.58 m/s in the longitudinal plane (Dorado Cortez et al, 2016). In a study conducted in patients with chronic hepatitis C, the optimal cutoff values were 1.54 m/s for significant fibrosis, 1.70 m/s for advanced fibrosis, and 1.86 m/s for cirrhosis (Ferraioli et al, 2012). Another recent study reported that the

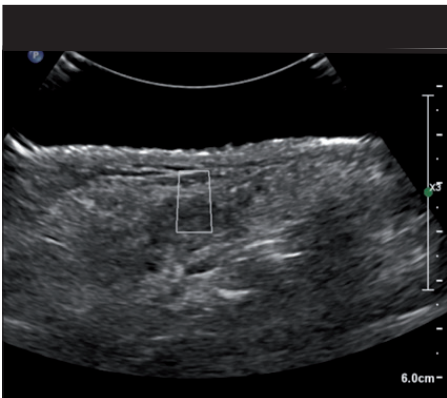


Figure 7. Middle submental.

shear wave velocity was 1.59±0.41 m/s for normal thyroid lobes, and 2.47±0.57 m/s for chronic autoimmune thyroiditis (Fukuhara et al, 2015).

This case report highlights the importance of monitoring and managing LEF long term in the HNC patient population. Accurate diagnosis and measurement of LEF is important to the direction of appropriate clinical therapy. Available evidence shows that early interventions are more effective when soft tissue abnormalities are composed predominantly of reducible lymphatic fluid (Földi et al, 2006; Lee et al, 2011). Once fibro-fatty scar tissue or fibrosis develops, the impact of therapy is more limited (Stubblefield and O’Dell, 2009). Current therapy for LEF includes education, manual lymphatic drainage, compression garments, exercise and skin care (Zuther, 2009). Both an experienced therapist and aggressive patient self-care are required in order to maximise favourable outcomes. In addition, therapy must be instituted early in the course of the disease process. Lymphoedema responds to positioning, manual lymphatic drainage, and compression garments; however, once tissues become fibrotic, it is less likely to respond to therapy. Since this can be a chronic and progressive process (Földi et al, 2006; Lee et al, 2011), ongoing assessment and management by the treating clinician is critical.

Based on the preliminary data from this case report, a clinical trial is currently under way to determine if SWE

is an effective tool for assessment and quantification of LEF-related soft tissue changes in the setting of clinical trials. The trial aims to examine the associations among results from SWE, self-reported symptoms, and outcomes based on clinical skin and soft tissue physical examinations, which could facilitate in establishing clinical utility of the SWE. In addition, given that there are no valid tools available for monitoring soft tissue changes across the trajectory of cancer treatment, recovery, and survival, longitudinal studies are warranted to conclude if SWE is a useful tool for clinicians to make early identification of skin and soft tissue changes related to LEF that require intervention, as well as to monitor effects of therapeutic interventions for LEF management.

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