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Oncology Section EDGE Task Force on Urogenital Cancer Outcomes: Clinical Measures of Lymphedema—A Systematic Review

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ABSTRACT:

BACKGROUND: Valid and reliable tools to assess lymphedema are necessary to accurately evaluate status and to objectively document and measure the results of interventions. Understanding the advantages and disadvantages of each measure can inform the clinician's choice of the appropriate tool to be used in the clinic or research setting. **PURPOSE:** To identify reliable and valid measurement techniques which are sensitive to change for assessing edema volume or soft tissue change in the lower extremities or genital region of patients with lymphedema. **METHODS:** A systematic review of the literature was conducted to assess the published psychometric properties and clinical feasibility of each method identified. Task Force members independently reviewed each measure using the Cancer EDGE Rating Form. **RESULTS:** Water displacement and circumferential measurement methods by tape measure were both rated as Highly Recommended to quantify lower extremity limb volume. Water displacement was determined to be the gold standard by which all other assessments of volume are benchmarked. Optoelectric volumetry and bioelectric impedance analysis were both rated as Recommended, and ultrasound was rated Not Recommended. **CONCLUSION:** The Urogenital Cancer EDGE Task Force highly recommends water displacement and circumferential tape measurement for use as reliable methods for assessment and documentation of change of limb volume in this patient population. Early detection of subclinical lower extremity lymphedema in this patient population remains challenging as there is no 'index' limb that can be proven to be

uninvolved in a patient population with documented pelvic node dissection/irradiation. No articles were found to support valid and reliable genital lymphedema volume measurement.

KEYWORDS: Psychometrics, measurement, limb volume, edema, urogenital neoplasms

INTRODUCTION:

Urogenital cancers impact over 5 million Americans, with an estimated 426,000 new cases annually.[1] Urogenital cancers typically affect the urinary system (kidney and related anatomy, bladder) or the genitals (including ovaries, uterus, cervix, testis, vulva, prostate, and penis). Mortality estimates for 2017 are approximately 90,000 individuals, with five-year survival rates ranging from 68% for all stages of cervical cancers, to 99% for all stages of prostate cancers.[2] The magnitude of impact of effective treatments on life expectancy suggests that these individuals will live for many years after a cancer diagnosis. It is therefore important that ongoing monitoring of late and long-term effects of cancer treatment take place to help these individuals return to the level of function and quality of life prior to the cancer diagnosis.

Most urogenital cancers are treated with some combination of surgery, radiation, and chemotherapy. Surgeries range from removal of the involved organ (oophorectomy, hysterectomy, prostatectomy, etc.), and often involve pelvic lymph node dissection to determine the extent of cancer. Radiation to either the tumor bed and/or the groin lymph nodes impacts the tissues treated as well, with well documented radiation fibrosis resulting from treatment further compromising the pelvic/groin lymphatic flow.[3] The incidence of lymphedema of the lower extremities and groin varies from 21-36%[4,5] among women surgically treated for endometrial, cervical, or ovarian cancer, and 34% among a mixed population of urogenital cancers.[6] The development of lymphedema of the lower extremities and genitalia results in both functional impairments and marked decline in quality of life. In a study investigating the prevalence of symptoms associated with lower limb lymphedema, all of participants with lymphedema reported difficulty walking, and more than 75% reported achiness and pain.[6] Furthermore, among a population of individuals with lower extremity lymphedema, participants' baseline

quality of life scores on the 36-Item Short Form Survey (SF-36) were approximately 20% lower than that of a healthy population.[7,8] The presence of lower extremity lymphedema negatively impacts both functional abilities and quality of life, and the need to identify and manage this chronic disease is clear in order to mitigate these negative effects.

While no universally accepted standards exist to clinically diagnose the presence of lymphedema, evidence exists to guide this clinical judgement. Typically, a clinical diagnosis of lymphedema is based on a difference in limb volume, either from a baseline measure or in comparison to a contralateral limb. The International Society of Lymphology (ISL), in their 2016 Consensus Document on the Diagnosis and Treatment of Peripheral Lymphedema, identifies a multi-stage classification system for lymphedema: Stage 0 is subclinical, such that while some symptoms of heaviness, achiness, or sense of tightness are felt by the individual, the lymphedema is not visible; Stage I is early lymphoma that reverses with elevation; Stage II manifests pitting without reversal with elevation; and Stage III is considered lymphostatic elephantitis.[9] Furthermore, the ISL Consensus Document suggests that minimal change is greater than 5% but less than 20%, moderate is 20-40%, and severe is greater than 40%.[9] Other evidence suggests that preclinical lymphedema is characterized by a 3-5% difference in limb volume, while a 5% difference is considered indicative of early lymphedema.[10,11] Still others have used differences of 10%, 200 ml, or 2cm of circumference as the onset of lymphedema.[12] The monitoring of limb volume change is the most common method to identify lymphedema and its earliest development, although indirect methods of measuring lymphedema are also employed. Most direct limb volume measurements are completed using water displacement, tape measure circumferential measurement, or optoelectric volumetry, while indirect measures include bioelectrical impedance analysis or ultrasound.

Accurate assessment of an individual is critical to identify impairments which drive rehabilitation treatment decisions and to monitor effectiveness of interventions. Following a call by Rebecca Craik in the 2005 McMillan lecture that the profession of physical therapy agree on the best outcome measures, the American Physical Therapy Association (APTA) Section on Research advocated for the determination of a core set of valid and reliable measurement tools. The identification of and support for particular tools are incorporated into the Evidence Database to Guide Effectiveness (EDGE). The Neurology Section (now the Academy of Neurological Physical Therapy) led the inaugural reviews of outcomes measures for stroke, traumatic brain injury, and multiple sclerosis populations. These reviews used a four-point ranking scale from Highly Recommended to Not Recommended. The Oncology Section adopted the procedures of the Neurology EDGE task forces, modifying the ranking scale to five levels, expanding the definition of "Unable to Recommend" (Figure 1).[13] To date, the Oncology Section has completed 14 reviews in breast cancer, three reviews in prostate cancer, five reviews in head and neck cancer, and one review in colon cancer. In 2016, the Academy of Neurologic Physical Therapy modified the ranking scale, and the Oncology Section adopted the new scale (Figure 2) for reviews going forward.[14] While this review was completed prior to the adoption of the new rating scale, the original rankings determined by the task force remain consistent with the new ratings. In light of the need to identify a core set of outcome measures for lymphedema among the urogenital cancer population, the purpose of this systematic review is to identify reliable, valid, responsive, and clinically feasible methods to measure lower limb and genital lymphedema.

METHODS

Search Strategy

The authors conducted a systematic review of methods and tools to clinically measure lower extremity limb and genital lymphedema in urogenital cancers in order to identify reliable, valid, and clinically feasible methods to employ in daily practice. The primary literature search took place August through September 2015 using six electronic databases: Google Scholar, PubMed/Medline, CINAHL, Web of Science, Cochrane Review, and PEDro. Primary search terms that were used included: lymphedema, lower extremity, limb volume, measurement of limb volume, and genital lymphedema. Additional search terms that described the measurement of lower extremity limb volume and lymphedema, and genital lymphedema in addition to the names of specific clinical measuring tools can be found in Appendix A. Secondary searches through bibliographic review of oncology journals and key research articles took place between October and December 2015.

Article Selection

To be included in this review, studies (1) were published in English; (2) clinically measured limb volume by direct or indirect means preferably of the lower extremity, and/or genital lymphedema; (3) reported psychometric properties; (4) presented methods considered clinically feasible in a typical physical therapy practice; and (5) included adults (≥ 18 years). Measures which are not available to the physical therapist, such as lymphoscintography, fluorescence lymphography, or magnetic resonance imaging, were not included. Additionally, self-reported measures of measuring lymphedema were not included, as this review is focused specifically on objective clinical measures. Included articles were considered if published from January 1, 1996 – present, unless a study published prior to 1996 was deemed a key article. Research focusing on participants with lower extremity or genital lymphedema as a result of urogenital cancers took first priority, followed by upper extremity lymphedema and/or vascular disorders and venous

insufficiency. While searching the databases, when other patient populations in which limb volume measurements were investigated, such as lower extremity amputations, met all other inclusion criteria, these articles were included when no other evidence in the cancer population was available. While it may appear that the research in upper extremity lymphedema, vascular disorders or venous insufficiency, and residual limbs are not applicable to this review, the methods of volume measurement, whether water displacement or use of a truncated cone, are based in principles of physics and mathematics and do not change based on the item measured. After retrieving all articles, duplicates were removed, and studies were screened on the basis of title and abstract initially, followed by review of full-text.

Data Extraction and Analysis

Teams of two reviewers independently performed data extraction using the Cancer EDGE Task Force Rating Form (available online). Psychometrics included in the Cancer EDGE Task Force Rating Form consisted of reliability, validity, ceiling/floor effects, sensitivity to change, and clinical utility. The following criteria were applied to determine the strength of the psychometric properties: excellent reliability = >0.90; good reliability = 0.76-0.89; moderate reliability = 0.50-0.75; and poor reliability <0.50.[15] Concurrent, discriminative, criterion-related, and construct validity values are reported when available, as well as measures assessing responsiveness to change such as minimal detectable change (MDC) and minimal clinically important difference (MCID). In the absence of these common statistical calculations, the coefficient of variation was reported. Determining clinical usefulness was based on equipment needed, cost, ease of use, scoring/interpretation, and availability of normative data. Outcome measures that directly or indirectly measured lower extremity and genital lymphedema were categorized into one of five tools: (1) Water Displacement, (2) Tape Measure, (3) Optoelectric Volumetry, (4)

Bioimpedence, and (5) Ultrasound. Each reviewer then rated the measure using the original Cancer EDGE Rating Scale. Any discrepancies in ratings were discussed with all four reviewers until consensus was obtained.

RESULTS:

The initial literature search using terms outlined in Appendix A, alone or in combination, yielded 181,658 articles. After screening for titles and abstracts and removing any duplicates, 66 articles were identified for subsequent review. An additional eight studies were found on secondary search. No articles were found that met eligibility criteria for measurement of genital lymphedema. After applying inclusion/exclusion criteria (articles were removed which did not have psychometric properties of interest, or were not published in the date range specified, or were not conducted within populations previously identified), a total of 33 articles were reviewed. Some of the studies included psychometric analysis of more than one measure of lymphedema such that the number of articles reviewed for each tool is not mutually exclusive. The numbers reviewed by category are: Water Displacement (11), Tape Measure (15), Optoelectric Volumetry (6), Bioimpedence (12), and Ultrasound (1). Figure 3 outlines the flow diagram for the literature search.

The outcome measures, ratings, and strengths and weaknesses are summarized in Table 1, while Table 2 presents the psychometric properties of the Highly Recommended and Recommended measures for measurement of lower extremity lymphedema. Lastly, Table 3 summarizes the clinical usefulness of the recommended measures for lower leg lymphedema.

Water displacement and tape measure circumferential measurement methods scored a 4, and are Highly Recommended by the EDGE Task Force on Urogenital Cancers. Both measures have been extensively tested and used to measure limb volume in persons with lower extremity

edema or lymphedema. Two other measures, optoelectric volumetry and bioimpedance, are rated 3, or Recommended, based on limitations in clinical utility. The use of ultrasound was not recommended (rating of 1) as a measure of lower extremity lymphedema due to a lack of available psychometric evidence for use and poor clinical utility. Furthermore, no clinical method can be recommended to measure genital lymphedema as measures reported on in the literature are limited to lymphangiography and magnetic resonance lymphography.

DISCUSSION

Based on the chronic nature of lymphedema, the accurate and reliable assessment of limb volume is crucial to detect lymphedema, and to monitor change in limb volume or amount of lymphedema over time. As lymphedema may not be visibly apparent in its earliest stages, ongoing monitoring of the limb at risk is important to detect any change over time. Limb volume as changes as small as 3% have been documented as pre-clinical lymphedema in a population of women with breast cancer related lymphedema.[10] It is reasonable to extrapolate these findings in lower extremity lymphedema in the absence of other research support, and support the need to continue to monitor the limb at risk. Direct or indirect measures of lymphedema (limb volume or impedance ratios) can be recorded at baseline prior to medical intervention, and used in comparison to a contralateral normal limb, if available, or the same limb over time, to assess and track the response to treatment. Long term, measurements allow for monitoring of the success of the self-management skills which the individual employs. Water displacement, circumferential measurement with a tape measure, optoelectric volumetry, and bioelectrical impedance analysis are recommended tools to monitor lower extremity limb volume. While the research available lacks specific data indicating how responsive each of these measures are, those measures which

can accurately detect small levels of change, such as a 3% volume change or a difference in impedance ratios between limbs, are indicated for use to monitor change in this population. .

Water Displacement

Water displacement is a method for assessing volume used since first described by Archimedes in Ancient Greece. Archimedes Principle, a body submersed in a liquid loses weight equal to that of the volume of liquid that it displaces, provides the basis for limb volume measurement in water.[16] Water displacement as a method to calculate the volume of a limb is reproducible using a standardized container, standardized temperature of the water and room, standardized immersion of the limb at the same depth and position, and a standardized way to measure the displaced water.[17,18] Measuring displaced water is most often done by volume, including the use of a transducer equipped volumeter, although some studies used the weight of the displaced water.[17,18] In either method, the involved limb is submerged in a container of water, generally a volumeter, in the same position and to the same depth on each measurement occasion. Limb volume is then based on the measurement of the water displaced.

Water displacement is considered the 'gold standard' of volume measurement to which all other methods are compared.[19] Most studies reviewed which described the use of water displacement measured volumes to the level of the knee, and were done in patients with venous insufficiency or peripheral vascular disease.[17,18] There were no studies found for full leg water displacement, most likely reflecting the difficulty that would be encountered in creating a container for volumetric measurement of differing length legs and the attendant difficulty in achieving insertion of a full leg into the device. Water displacement was found to have a high day to day reliability in repeated measures done over five episodes. Test-retest values ranged from r=.95-.99, and the mean percent change in volume measurements ranged between 0-

.37%.[16] Overall inter-rater reliability of this method varies from ρ=0.95, where ρ is the intrasubject correlation coefficient, based on an analysis of variance,[20] to ICC=0.99.[21] One study examined the minimum percent change of the volume of the leg and determined the MDC to be 22.2-23.4%.[22] These excellent psychometric properties make water displacement a Highly Recommended measure of lower extremity limb volume.

The advantages of water displacement as a method for volume assessment are low cost (generally less than $400) with high accuracy in assessing the most distal portion of the limb.[19] Volumeters are generally made of plexiglass with a spout and come with a calibrated cylinder collecting vessel. High clinical feasibility, however, may be hindered by the time investment to measure (filling, draining, cleaning), the potential excess size of a limb not fitting a volumeter, and the inability to measure the full limb to the groin.

It should be noted that a contraindication to using water displacement is the immersion of limbs with open wounds. A compelling reason for the importance of infectious disease precautions is due to the fact that those with lymphedema have a known compromise in their immune response with a greater risk of cellulitis.[23] Another limitation in the use of volumeters for individuals with lower extremity lymphedema is the possibility of an excessive size of the patient's leg. It is not unusual in some clinical settings to see patients with calf circumferences in excess of 120 cm, far exceeding the size of volumeters that are available commercially.

Circumferential Measurement by Tape Measure

Taking circumferential measurements at regular intervals with a non-elastic tape measure is the most widely used clinical method to determine the presence of lymphedema and assess volume changes when monitoring response to treatment. The best tape measures have several

important attributes: are made of non-stretch material, are easily cleaned with alcohol swabs, and have clearly and easily discernible markings and an easily seen zero mark. The need for consistent tensioning of the tape can be addressed by the use of a tape measure with a spring tension gauge at the zero end assuring the exact same pull with each application. However, studies done of circumferential measurement without the use of this tension gauge have demonstrated good inter- (ICC=0.97) and intrarater reliability (ICC=0.92-0.99) in both upper and lower limb measurement.[24,25]

Reliable and reproducible measurements require a standardized positioning of the patient and establishment of reproducible landmarks for marking intervals of measurement. It is important to utilize a straight measure of intervals marked for measurement rather than a contoured laying on of the tape on the limb as the contour of an abnormally shaped lymphedematous limb can change dramatically during treatment and lead to errors in subsequent markings of intervals for repeated measurement. Boards with a footplate provide this rigid straight method to mark intervals more consistently. Landmarks for the zero interval also improve the reliability of the resultant and subsequent measurements. In several studies, the landmark chosen is the malleoli ,[17-19] while in others[26,27] the heel is the landmark. In practice, the malleoli can be almost obliterated in the lymphedema patient at evaluation, so that a base of heel or distance from the floor (the footplate) to the bend of the ankle is least likely to change with treatment and should be used as the zero interval.[28] The distance between intervals varies depending on the study; 4 cm and 10 cm intervals are reported.[17,27,29] Both methods are reliable and valid, and correlate highly with each other (r>.99) however, the 4 cm method may better account for abnormal lobules in advanced lymphedema.[24,29] Whichever interval is used for measurement, values are typically entered into an appropriate truncated cone formula to

determine limb volume. The Frustrum or truncated cone formula is more accurate in assessing limb volume than a cylinder formula, as the limb is roughly the shape of a cone.[30]

The advantages of using a tape measure for volume measurement are cost (low) and accessibility (high) in the clinical setting. This measurement can also be done even if the patient has wounds or is unable to assume a standardized position for measurement by water displacement. When compared to the gold standard water displacement, the validity is excellent, (ICC=0.93 – 0.98), except in grade 1 edema where the correlation between measures was moderate (r=0.45).[17,26,27] Reliability is also excellent: test-retest reliability in a 1-2 week timeframe was excellent (ICC=0.94) and good (ICC=0.82) long term; interrater and interrater reliability were both excellent (ICC=0.89-0.99 and ICC=0.82-99, respectively).[19] Minimal ceiling or floor effects are present using a tape measure measurement, however one study reported that when the leg volume difference is >11%, tape measurement overestimated the volume difference as compared to water displacement.[17] One study examined the SEM and determined this to approximately 84 ml or 0.64% of lower leg volume.[31] These sound psychometric properties and high clinical utility make this tool highly recommended by the EDGE task force.

The disadvantage of tape measurement method is time needed for multiple measurements and then calculation for comparison with contralateral 'normal' limb or for comparison to pre-treatment volumes. The time to calculate volume can be mitigated through the use of previously formatted spreadsheets such that simply entering circumferential values will render total volume and percent volume difference. Of clinical importance is the consideration that in lower extremity lymphedema, the lymphatic compromise is often bilateral despite presentation of swelling in only one limb. Post treatment measurements often demonstrate a volume reduction in

what was thought to be a 'normal' limb due to the focus in Complete Decongestive Therapy (CDT) on the proximal, intact lymphatic system. This is consistent with the physiological fact that there needs to be an increase of 20-30% in the normal interstitial volume before it is clinically apparent.[32] Therefore, comparison over time may be a more clinically relevant measure.

Optoelectric Volumetry

Optoelectric volumetry, or perometery, is an assessment of limb volume that utilizes an array of infrared beams oriented via a square frame at right angles to each other. As the frame, tracking on a carriage, is passed over a limb in either a horizontal or vertical configuration, the limb volume is calculated using a computerized algorithm. The validity of optoelectric volumetry was established in comparison to water displacement and ranges from r=0.97-0.99.[33-35] Test-retest reliability is excellent with an ICC=0.99.[18,36] Intrarater reliability is reported as excellent, with an ICC≥0.99.[37,38] The repeated measures coefficient of variation was reported as 0.13.[36]

The advantage of optoelectric volumetry is that a highly accurate limb volume can be calculated very quickly once the equipment is on and ready for use. For the commercially available Perometer, additional benefits include optional compression garment measurement as the software reports the actual circumference at the standardized landmarks used by German manufacturers for garment manufacturing.

The main disadvantages to the Perometer being used in the clinical setting are the cost and size of the equipment. The equipment is large, requiring approximately half of the size of a typical treatment room. The purchase price in 2015 was $16,000-26,000 USD, with one primary

manufacturer: Pero-System GmbH in Germany (Wuppertal, Germany). Whether to utilize a horizontal or a vertical system is dependent on the primary population to be measured. Although either unit can measure both upper extremity and lower extremity, a horizontal unit requires that the mid-frame be positioned at chair height for the lower extremity while the individual must bend over to measure the upper extremity in a vertical unit. The size of the frame limits the extent to which the unit can traverse proximally up the limb and reduces the volume calculation possible for the limb. Accuracy of the measurements depend on correct horizontal positioning of the limb and patients with limited range of motion may not be able to be correctly positioned.[34,35,37] Newer optoelectric volumetry units, such as that designed by Skanlab, are being developed for clincial use.[39] It is possible that other optoelectric volumeter units may be available commercially in the future.

Bioelectrical Impedance Analysis

Multi-frequency bioelectrical impedance analysis (BIA) is a non-invasive assessment technique that utilizes a very small alternating current which is passed through tissue creating a measure of impedance, or resistance to flow of the current. The current moves through the path of least resistance in the tissues measuring the resistance through the water content of the intracellular and extracellular portions of the soft tissue. Low frequency current passes through the extracellular fluid, while high frequency current passes through the intracellular fluid. BIA then measures both total resistance and the resistance of the extracellular fluid quantify the impedance. This resistance is compared to an unaffected limb, creating an impedance ratio.[22] Originally tested in women with breast cancer-related lymphedema, if this inter limb impedance ratio exceeds the mean ratio plus three standard deviations, a diagnosis of lymphedema is

confirmed.[40,41] Like other methods of volume assessment, pre-operative values for comparison post-surgery are helpful for early diagnosis.[40]

Bioimpedance devices utilize four or eight electrode arrays; the eight electrode systems are considered to be more accurate.[42] Recommendations for reproducibility included: taking measurements at the same time with a constant ambient temperature, and cleaning the sites with alcohol or wet wipes before standardized application of the electrodes.[41,42] In a study comparing bioelectrical impedance values between individuals diagnosed with lymphedema via lymphoscintography and controls, BIA accurately identified those with lymphedema.[43] Intra-tester reliability ICC=0.88 in a population with lymphedema due to filariasis.[44] The predictive value of BIA was 53.2% in this same population.[44] The sensitivity of BIA to monitor change was excellent in two studies: 100% sensitivity is reported in a population with lymphatic filariasis, and treatment differences compared to baseline were highly significant ($p<.001$) in patients with pedal edema.[22,44]

The most prominent advantage of BIA is that it can detect the onset of lymphedema before clinical signs of swelling become apparent.[40] It can be completed in 5-15 min depending on the number of repeated measures made and is an accessible technology for pre-operative values for reference in the post-operative period. A reference range has been established for the impedance ratio for the legs without pathology, allowing for criteria for the diagnosis of early lymphedema in the leg.[41]

The disadvantages of BIA are that it remains an assessment that, with the current bioelectrical impedance protocol which creates a ratio comparing the unaffected and affected limb, is useful only for unilateral lymphedema risk.[41] In most urogenital cancers, pelvic lymph node dissection and/or radiation affects the lymphatic drainage patterns of both lower extremities

even in a patient who presents with unilateral swelling. Another disadvantage of BIA is that it is useful primarily for the assessment of early stage (0-1) lymphedemas, as in the later stages of lymphedema the extracellular fluid has been replaced to a large degree by fibrous tissue.[45] When this has occurred, BIA is not helpful for diagnosis or monitoring of change over time. Lastly, the electrodes are single use and therefore have a cost associated with each use.

Considerations in measuring limb volume

Two cautionary issues arise when monitoring the lower limb at risk in urogenital cancer. First, there is a significant difference in volume assessments in the lower extremity when the entire limb is included in the measurements since the majority of swelling is often only below the knee.[27] The length of the limb being measured, whether to the knee as is typical in water displacement, or to the groin including the thigh, can also impact accuracy and interpretation. Specifically, as the amount of change in the smaller lower leg may be only a small percentage of the whole limb, the size of the thigh may mask the amount of change of the lower leg. Rather, using clinical judgment incorporating patient symptom report and clinician expertise, the measures used should be to the level of greatest involvement. If this is not amenable to water displacement, clinical judgment then determines that water displacement should not be used. However, if only the lower leg is involved, then this method may be appropriate. Ideally it is clinically important to have measurements of the full thigh pre-treatment because there is also a possibility of 'fluid shift' into the proximal limb or genitals during treatment which must be recognized and addressed, and this is most easily accomplished via circumferential measurements with a tape measure.

The second consideration is the possibility of bilateral lower limb involvement because this limits the usefulness of limb to limb comparisons. For this reason, it is essential that

baseline measures are taken prior to medical intervention. The Prospective Surveillance Model developed for women with breast cancer includes baseline assessment and ongoing periodic monitoring.[46] This model could easily be adopted for use in the urogenital population. These baseline measures, then, would serve as a comparison for any changes in the lower limbs.

Ultrasound is not recommended by the urogenital cancer EDGE Task Force. The limited psychometric properties, in conjunction with decreased clinical utility, particularly cost and training, do not support its use for assessment of limb volume in this population. In a study examining the diagnostic validity of ultrasound, skin thickness was greater in the involved limb compared to the non-involved limb ($p<0.05$) among women with breast cancer related lymphedema,[47,48] yet examining the ability to detect change over time was poor as the change in skin thickness with a decrease in volume was only minimally correlated ($r=.37$).[49] Furthermore, no studies examining reliability were found.

Limitations

This topic of lower limb lymphedema in the urogenital cancer population has not been studied to the extent seen in secondary lymphedema related to breast cancer. This resulted in far fewer studies in which the population of interest was available. The authors recommend that research be focused on accurately measuring lymphedema, whether directly or indirectly, in the urogenital cancer population. Additional research in the development of optoelectric volumetric tools is warranted in order for these tools to become more clinical useful. Furthermore, it is essential to develop reliable and valid clinical methods to measure genital lymphedema, and as this research need is significant, it should be prioritized. This literature search was completed in September of 2015, and therefore any studies published thereafter with psychometric properties may not be included in this review. Newer studies may provide additional information to

evaluate these measures, and the use of bioelectrical impedance analysis is a growing in use as measurement technique of lymphedema. We recommend these ratings be reviewed in approximately five years as new evidence becomes available. As lymphedema is a world-wide problem, limiting the search to the English language may have resulted in eliminating important research published elsewhere. All recommendations made by this Task Force are issued based on the best available evidence at the time of analysis. The reader is encouraged to employ clinical judgment, expertise, and to take into account patient values when implementing these recommendations.

CONCLUSION

This systematic review evaluated methods to measure lymphedema in the urogenital cancer population, focusing on lower limb edema/lymphedema. Use of water displacement or circumferential measures with a tape measure were Highly Recommended by the Urogenital Cancer EDGE Task Force. These measures have sound psychometric properties, and high clinical feasibility. Further research is needed in valid and reliable methods to measure genital lymphedema.

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Table Legends:

Table 1. Summary of Outcome Measures

Table 2. Psychometric Properties of Recommended Measures for Lower Extremity Lymphedema

Table 3. Clinical Usefulness of Recommended Measures

Figure Legends:

Figure 1: Cancer EDGE Rating Scale

Figure 2: Cancer EDGE Rating Scale, Updated 2016

Figure 3. PRISMA Flow of literature search.

Table 1: Summary of Outcome Measures

Measure	EDGE Rating	Strengths/Weaknesses
Water Displacement	4	• Gold standard method to measure volume • Valid in multiple populations • Inexpensive • Inconvenient – requires a wet room • Time investment for infection control practices • Difficult to submerge full lower limb
Tape Measure	4	• Inexpensive • Accurate • Reliable • Validated against the gold standard
Optoelectric volumetry	3	• Validated against the gold standard • Highly accurate • Quick • Very expensive for clinical use • Requires space • Not able to acquire as a medical device outside of Europe
Bioelectrical Impedance	3	• Effective in early determination of volume changes • Expensive – unit and electrodes • Not as useful in later stage lymphedema
Ultrasound	1	• High cost • High level of training • Poor responsiveness

Table 3: Clinical Usefulness of Recommended Measures

Measure	Equipment Needed	Cost	Ease of Use	Scoring/ Interpretation	Normative Data
Water Displacement	Yes	Minimal	High	Easy	No
Tape Measure	Yes	Minimal	High	Easy	No
Perometer	Yes	High	Moderate	Easy	No
Bioelectrical Impedance	Yes	High	High	Easy	Yes

Table 2: Psychometric Properties of Recommended Measures for Lower Extremity Lymphedema

Measure	Test/Re-Test Reliability (ICC)	Inter-rater Reliability (ICC)	Intra-rater Reliability (ICC)	Responsiveness to Change	Validity
Urogenital Lymphedema Measures – Highly Recommended					
Water Displacement	ICC = 0.97-0.98[16] (leg) r = .95-.99[16] (leg)	ICC = 0.94-0.98[20] (arm) ICC=0.99[21] (arm)	ICC ≥0.98[20,24] (arm)	CV = 0.72%[16] MDC (leg) = 22.2 - 23.4%[22]	Gold-standard Effect size (pedal edema): 0.64-0.85[22] (leg)

Tape Measure	ICC=0.94 (1-2 weeks)
	ICC = 0.82 (long term)[19] (leg)
	
	ICC=0.96 (0.92 -1.00 $_{CI95}$)[50] (leg)
	
	ICC = 0.91-0.97[25] (leg)
		Short term (1 week)
		ICC=0.90[19]
		Medium term (2 weeks)
		ICC=0.89[19] (leg)
		Long term (12 weeks)
		ICC=0.78[19] (leg)
		
		ICC=0.97 - 0.98 (0.97 – 1.00 $_{CI95}$)[25,50] (leg)
		
		ICC = 0.97-0.99[20] (arm)
			Short term (1 week)
			ICC=0.94[19] (leg)
			
			Long term (12 weeks)
			ICC=0.82[19] (leg)
			
			ICC=0.99 (0.97 - 1.00 $_{CI95}$)[25,50] (leg)
			
			ICC = 0.95 (0.96-0.99)[24,38] (arm)
				SEM = 83.6 ml or .64% (lower limb lymphedema)[31]	Pearson CC of residual limb's volume and level:[51] (leg)
					Tibial tubercle= 0.814
					4-cm from tibial tubercle=0.892
					8-cm from tibial tubercle=0.878
					Distal end=0.715
					
					Concurrent Validity:
					- water displacement r=.32,[52] (leg) r=.93-.98[17,27] (arm and leg)
					- water displacement for normal limb: r=.55-.61[26] (leg)
					- water displacement affected limb: r=.75-.80[26] (leg)
					- CLEMS (computerized volume measurement system): r = 0.341[52] (leg)
					- automated volume estimates of legs: r=0.977[35] (arm and leg)
					- with water displacement for[17,26,27] (leg)
					  - grade 1 lymphedema: r=0.45;
					  - grade 2 lymphedema: r=0.92;
					  - grade 3 lymphedema: r=0.92

Optoelectric volumetry	ICC=0.99 (0.98 - 0.99 $_{CI95}$)[18,36] (leg)	ICC ≥ 0.99 (0.99 to 1.00)[37,38] (arm)	ICC=0.997[37] (leg)	CV = .13[36]	Concurrent Validity:
					- water displacement r=.97[33] (leg)
					- circumferential measurement with tape measure[34] (arm)
					  - r=.999 for mannequin limbs
					  - r=.985 for normal human arms
					  - r=.988 for upper extremity lymphedema
					- strain gauge: r=0.63[34] (arm)
					- with tape measure ICC=0.997[35] (arm and leg)
					- with truncated cone total limb volume r=0.98[38] (arm)

Urogenital Lymphedema Measures – Recommended					
Bioimpedance		ICC= 0.95 (0.90 to 0.98)[38] (arm) ICC = 0.88[44] (leg)	ICC=0.88[44] (leg)	CV = 15.6 to 17.2[22] (leg)	In lymphatic filariasis[44] (leg) - Sensitivity = 100% - Specificity= 21.4% Validity: - Bipolar and tetrapolar technique Cronbach's alpha = .668 (coefficient of variability <5% variability in 93% of measures)[45] (arm) - Concordance correlation with perometer r=0.92[38] (arm) - Concordance correlation with truncated cone total limb volume r=0.89[38] (arm) Positive predictive value = 53.2% (lymphatic filariasis)[44] (leg) Pedal Edema:[22] (leg) - Effect size = .64 to .93

CV – coefficient of variation; ICC – intraclass correlation coefficient; P = intrasubject correlation coefficient; r – Pearson's correlation coefficient; UE – upper extremity

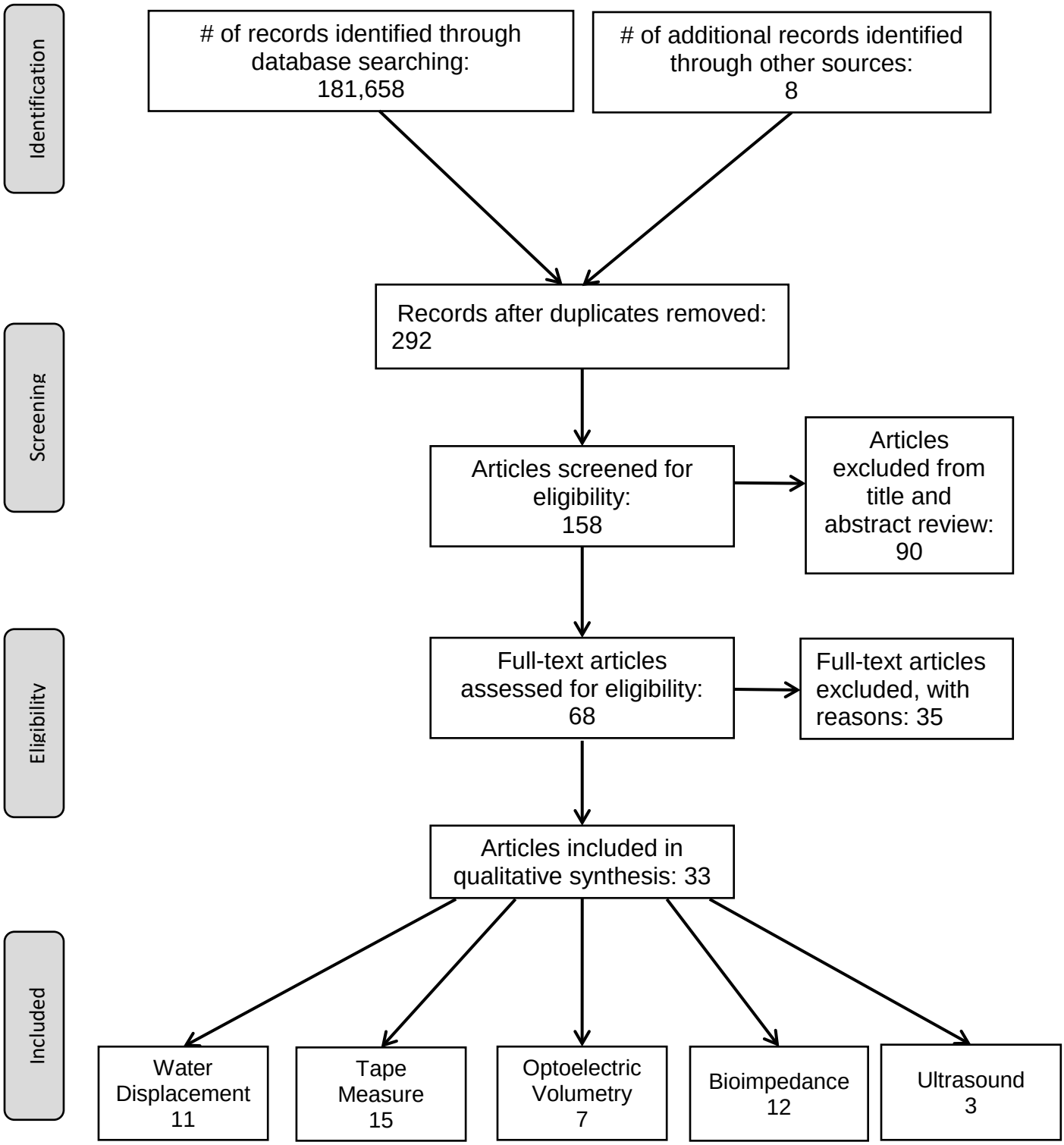
Figure 1: Cancer EDGE Rating Scale

4	**Highly Recommend**	The outcome has good psychometric properties and good clinical utility; the measure has been used in research on individuals with or post cancer.
3	**Recommend**	The outcome measure has good psychometric properties and good clinical utility; no published evidence that the measure has been applied to research on individuals with or post cancer.
2A	**Unable to Recommend at this time**	There is insufficient information to support a recommendation of this outcome measure; the measure has been used in research on individuals with or post cancer.
2B	**Unable to Recommend at this time**	There is insufficient information to support a recommendation of this outcome measure; no published evidence that the measure has been applied to research on individuals with or post cancer.
1	**Do not Recommend**	Poor psychometrics &/or poor clinical utility (time, equipment, cost, etc.)

Figure 2: Cancer EDGE Rating Scale, Updated 2016

4	**Highly Recommended**	The outcome measure has excellent psychometric properties (reliability and validity AND have available data to guide interpretation) in condition of interest and excellent clinical utility (≤20 min, equip in clinic, no copyright payments, easy to score); the measure is free or reasonably accessible to a broad range of providers.
3	**Recommended**	The outcome measure has good psychometric properties (may lack some info about reliability, validity, responsiveness) in the population of interest and good clinical utility (>20 min, some equip, training, copyright fee); OR has excellent psychometric properties but is not free and may require access to specialized testing equipment that is beyond the means of many clinicians or clinics.
2	**Reasonable to Use**	Limited study in target group; the outcome measure has good or excellent psychometric properties and clinical utility in a related population, but insufficient study in target population to support higher recommendation.
1	**Not Recommended**	The outcome measure has poor psychometric properties and/or poor clinical utility

Figure 3. PRISMA Flow of literature search.



Appendix A

Secondary search terms:

Reliability of lymphedema

Reliability of lower extremity

Lower extremity lymphedema

Lower extremity limb volume treatments

Lymphedema treatments

Measure AND lymphedema

Measure AND limb volume

Limb volume AND tape measure

Limb volume AND volumeter

Limb volume AND bioimpedence

Limb volume AND ultrasound

Limb volume AND perometer

Limb volume AND water displacement