



# **Clinical Practice Guideline From the Oncology Section of APTA**

## **Diagnosis of Upper-Quadrant Lymphedema Secondary to Cancer: Practice Recommendations**

# Introduction

- Purpose of the Oncology Section CPG: aid the clinician in diagnosing secondary upper-quadrant cancer-related lymphedema
- Process:
  - Systematic review of published studies
  - Structured appraisal process
  - Written Clinical Practice Recommendations
    - Formulated based on the evidence for each diagnostic method
    - Graded based on the strength of the evidence and clinical utility
- To make the recommendations clinically applicable, written based on patient presentation including the location and stage of a patient's lymphedema
- Full Guideline: Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. [Diagnosis of Upper-Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline From the Oncology Section of APTA](#). Physical Therapy 2017; 97(7):729–745; co-published in: Rehabilitation Oncology 2017; 35(3):E1-E18.

# Clinical Questions

1. What are the evidence-based diagnostic methods and criteria for cancer-related Secondary Upper Quadrant Lymphedema (SUQL).
2. What are the gaps in the research for the diagnosis of cancer-related SUQL.

Additional Goal: Create reference publications for use by health care professionals regardless of subspecialty and setting, as well as for educators and students, identifying best practice related to the diagnosis of SUQL.

# Guideline Development Methodology

## Target Population/Target Audience

### **Target Population:**

- Cancer survivors with Secondary Upper Quadrant Lymphedema such as Breast Cancer, Lymphoma, Melanoma, and Head and Neck cancer.

### **Target Audience:**

- Physical therapists regardless of subspecialty and setting, as well as for other health care practitioners and students.

# Literature Search

- Published from January 1, 2000 through July 5, 2015
- Databases searched: PubMed, CINAHL Plus with fulltext, Cochrane, AHRQ National Guideline Clearinghouse, SCOPUS, SPORTDiscus with full text, Physiotherapy Evidence Database (PEDro), and Occupational Systematic Evaluation of Evidence (OTseeker).
- Final search terms included: *Lymphedema*, *Elephantiasis*, and truncated text words *lymphedema\**, *lymphoedema\**, *elephantiasis*.
- Search excluded: Articles including the terms *filariasis*, *parasites*, *congenital*, *hereditary*, as well as *editorial*, *letter*, and *comment*.

# Literature Search Results

- Literature Searches yielded 9247 articles
- Reviewed for relevance
  - Excluded articles not on secondary upper quadrant lymphedema
  - Excluded articles on interventions and risk factors
  - Excluded articles without measurement psychometrics reported
- 91 Articles included and reviewed for quality

# Quality Appraisal Process

- Quality Rating Tools:
  - Reliability Studies - Quality Appraisal of Diagnostic Reliability (QAREL) checklist
  - Validity and Diagnostic Accuracy Studies - Quality Assessment of Diagnostic Accuracy Studies–2 (QUADAS-2) tool
- **QAREL** evaluates participant and examiner properties, blinding, order effects, time interval and test implementation and interpretation, and appropriateness of the statistical tests used.
- **QUADAS-2** evaluates appropriateness of patients, choice and application of reference standard, blinding of testers to results of other tests, sources of potential bias, and clinical applicability.

## Quality Ratings for Individual Articles:

- Each article was assigned a level (I-III) according to criteria established by the Centre for Evidence-Based Medicine for diagnostic studies and used in other CPGs (<http://www.cebm.net/index.aspx?o=1025>)

# Quality Ratings for Individual Articles

- **I** High-quality diagnostic studies, prognostic or prospective studies, cohort studies or randomized controlled trials, meta-analyses, or systematic reviews; critical appraisal score >50%.
- **II** Lesser-quality diagnostic studies, prognostic or prospective studies, cohort studies or randomized controlled trials, meta-analyses, or systematic reviews (eg, weaker diagnostic criteria and reference standards, improper randomization, no blinding, <80% follow-up); critical appraisal score ≤50%.
- **III** Case-controlled studies, retrospective studies, or studies of only healthy control subjects.
- Based on Phillips et al 2009 and Delitto et al 2012

# Evidence Grades for a Diagnostic Method

- Evidence from Multiple Articles Synthesized to Grade Each Diagnostic Method
- Based on Delitto et al 2012 and Kaplan et al 2013

Grade	Recommendation	Criteria
A	Strong	A preponderance of level I studies, but at least 1 level I study directly on the topic supports the recommendation
B	Moderate	A preponderance of level II studies, but at least 1 level II study directly on the topic supports the recommendation
C	Weak	A single level II study at <25% critical appraisal score or a preponderance of level III and IV studies, including consensus statements by content experts, support the recommendation
D	Theoretical/ foundational	A preponderance of evidence from animal or cadaver studies, from conceptual/theoretical models/principles, or from basic science/bench research or published expert opinion in peer-reviewed journals supports the recommendation
EO	Expert Opinion	Recommended practice based on current clinical practice norms, exceptional situations where validating studies have not or cannot be performed, and there is clear benefit, harm, or cost and/or the clinical experience of the Guideline Development Group

# Clinical Practice Recommendations

- Statements generated to assist practitioners in making decisions about appropriate health care for specific patient circumstances
- Synthesis of the graded evidence and clinical utility
- Takes risks and benefits into account
- Higher evidence grade leads to stronger language
  - The clinician “should” or “should not” .....
- Lower evidence grade leads to weaker language
  - The clinician “may” or “may not” .....

# Practice Recommendations

- Recommendations were based on the characteristics of the location and stage of a patient's lymphedema within the upper quadrant.
- The categories and subcategories for practice recommendations were written for the following:
  - All patients at risk for SUQL
  - Secondary upper-extremity lymphedema
    - At risk, early (ISL stages 0-I)
    - Moderate, established (ISL stage II)
    - Late (ISL III)
  - Lymphedema primarily in the hand
  - Trunk/breast lymphedema
  - Head and neck lymphedema

# Practice Recommendations

## **All patients at risk for secondary upper-quadrant lymphedema**

- Self-reported symptoms of swelling, heaviness, and numbness should be investigated for early diagnosis. (Grade B)
- Palpation for fibrosis, pitting, and overall tissue quality may be clinically helpful for staging; however, it has not been investigated for diagnostic purposes. (Expert Opinion)
- If a questionnaire is used to assist with diagnosis, the Norman Questionnaire or Morbidity Screening Tool should be considered. (Grade B)

# Practice Recommendations

## At-risk/early-stage upper-extremity lymphedema (ISL stages 0-I)

### *Bioimpedance analysis (BIA):*

- BIA should be used to detect subclinical/early-stage lymphedema. (Grade B) Cut point of  $>7.1$  L-Dex score should be used for the diagnosis of breast cancer–related lymphedema when preoperative baseline measures are not available. (Grade B)
- Cut point of  $>10$  L-Dex score above preoperative baseline should be used for the diagnosis of breast cancer–related lymphedema. (Grade B)
- Preoperative assessment using BIA may enhance the ability to detect changes in tissue fluid earlier indicating lymphedema. (Grade B)

# Practice Recommendations

## At-risk/early-stage upper-extremity lymphedema (ISL stages 0-I) cont.

### *Volume measures:*

- Volume determined from circumferential measurements should be used to diagnose lymphedema (Grade B) but may not capture subclinical and early-stage lymphatic transport impairment. (Expert Opinion)
- When using circumferential measurements, volume should be calculated. (Grade B)
- Calculated volume differential between sides  $\geq 200$  mL, or a volume ratio of  $>1.04$  (affected:unaffected), will help rule in lymphedema, but values  $<200$  mL cannot be used to rule out. (Grade B)
- Water displacement may be used in diagnosing lymphedema but is limited by clinical utility. (Grade B)
- Volume can also be assessed by perometry, but diagnostic criteria need to be evaluated for this method. (Expert Opinion)
- Methods of volume measurement are not interchangeable; use the same method at each time point. (Grade A)

# Practice Recommendations

## Moderate- or established upper-extremity lymphedema (ISL stage II)

### *Bioimpedance analysis:*

- BIA is less useful in diagnosing lymphedema at this stage, and self-reported symptoms or volume measures should be used. (Grade B)
- Accuracy with BIA in diagnosing moderate- to late-stage lymphedema may decline due to tissue changes/fibrosis. (Expert Opinion)

# Practice Recommendations

## Moderate- or established upper-extremity lymphedema (ISL stage II) cont.

### *Volume measures:*

- Volume measurements should be taken and used in the diagnosis of lymphedema. (Grade B)
- When using circumferential measurements, volume should be calculated. (Grade B)
- Calculated volume differential between sides of  $\geq 200$  mL, or a volume ratio of  $>1.04$  (affected:unaffected), will help rule in lymphedema, but values  $<200$  mL cannot be used to rule out. (Grade B)
- Water displacement may be used in diagnosing lymphedema but is limited by clinical utility. (Grade B)
- Volume can also be assessed by perometry, but diagnostic criteria need to be evaluated for this method. (Expert Opinion)
- Methods of volume measurement are not interchangeable; use the same method at each time point. (Grade A)

# Practice Recommendations

## Late-stage upper-extremity lymphedema (ISL stage III)

- As tissue changes progress, excess fluid may decrease, but excess volume may remain because of fibrosis, increased fat deposition, and other skin changes. (Grade B)

### *Volume measures:*

- Volume measurements should be taken and used in the diagnosis of lymphedema. (Grade B)
- When using circumferential measurements, volume should be calculated. (Grade B)
- Calculated volume differential between sides of  $\geq 200$  mL, or a volume ratio of  $>1.04$  (affected:unaffected), will help rule in lymphedema, but values below 200 mL cannot be used to rule out. (Grade B)
- Water displacement may be used in diagnosing lymphedema but has limited clinical utility. (Grade B)
- Volume can also be assessed by perometry, but diagnostic criteria need to be evaluated for this method. (Expert Opinion)
- Methods of volume measurement are not interchangeable; use the same method at each time point. (Grade A)

### *Ultrasonography:*

- Ultrasonography should be used to detect underlying tissue changes. (Grade B)

# Practice Recommendations

## Hand lymphedema

- Little research is available to guide the diagnosis of hand lymphedema
- Water displacement and “figure-of-eight” method of circumferential measurement may be used for assessment but have not been studied as diagnostic tests. (Expert Opinion)

## Trunk or breast lymphedema

- Little research is available to guide the diagnosis of truncal or breast lymphedema
- Ultrasonography has the potential to determine tissue changes consistent with different stages of lymphedema. (Expert Opinion).
- Tissue dielectric constant is an emerging diagnostic tool that may be useful in assisting with assessment of lymphedema. (Grade C)

# Practice Recommendations

## Head and neck lymphedema

- Modified Head and Neck External Lymphedema and Fibrosis assessment criteria when combined with circumferential measurements may be useful for diagnostic purposes. (Expert Opinion)
- Circumferential measurements at the upper neck point may be used in assessment. (Expert Opinion)
- Tissue dielectric constant is an emerging diagnostic tool that may be useful in assessing lymphedema. (Expert Opinion)
- Recommend a combined approach involving both the Modified Head and Neck External Lymphedema and Fibrosis assessment and either circumferential measures or tissue dielectric constant. (Expert Opinion)

# Discussion

- At present, SUQL is most often diagnosed by clinical history, physical examination of tissue quality, and a measurement of increased limb volume.
- Subclinical or early-stage lymphedema may not display a sufficient or persistent volume change to meet this diagnostic criterion.
- Research indicates the importance of early detection of SUQL to minimize body function and structure impairments that may progress to functional limitations and activity and participation restrictions.
- For patients at risk for SUQL, symptoms of swelling, heaviness, and numbness should be identified during the history, as it may assist in identifying those with subclinical or early-stage lymphedema.
- The Norman Questionnaire and the MST should be considered to determine the presence or absence of lymphedema in conjunction with volume measures.
- For all patients, the physical examination should consist of observation, palpation, and other measurements.

# Discussion cont.

- For subclinical/early-stage lymphedema, BIA should be used to assist in the diagnosis of SUQL. A volume measure should also be taken but may not be consistently increased at this point.
- In the moderate and late stages, circumferential measurement should be used, and water displacement may be used in some cases, for the diagnosis of upper-extremity lymphedema (see practice recommendations below for cut points).
- Perometry may be used for upper-extremity volume assessment in the early, moderate, and late stages; however, diagnostic criteria have not been fully evaluated.
- In late stage, ultrasonography should be used to detect underlying tissue changes, which may be helpful for clinicians to determine appropriate management.
- ***Clinicians need to be aware that none of the diagnostic criteria are perfect in their diagnostic accuracy***, and especially patients whose measurement values fall just under or over a cut point have the potential to be misclassified. We encourage clinicians to cluster findings from their examination to draw a conclusion on diagnosis.

# Discussion cont.

- There are emerging diagnostic methods that detect tissue quality, visualize edema, or evaluate structural lymphatic transport capacity.
- These methods include: 3D camera, Tissue Dielectric Constant, DXA, MRI, CT, lymphoscintigraphy, lymphography, and tonometry.
- Because of lack of evidence, high costs, or the invasive nature for some of these tests, these methods are not recommended to be incorporated into general clinical practice for diagnosing SUQL at this time.
- Lymphatic system imaging, including lymphoscintigraphy and lymphography, can be useful in determining the full extent of lymphatic system impairment, and the results may assist the clinician when conservative interventions are not successful.

# Discussion cont.

- Another emerging area is the diagnosis and assessment of lymphedema in patients treated for head and neck cancer.
- A combined approach of HN-ELAF, circumferential measurement at the upper neck point, and TDC may be useful for diagnostic purposes.
- Little research is currently available to guide the diagnosis of hand, trunk, and breast lymphedema.
- Overall, on the basis of the evidence in this CPG, **there is no one diagnostic tool that can be used definitively to diagnose SUQL**, but using these recommendations can facilitate early identification and should lead to an examination of activity and participation restrictions and appropriate interventions.

# Limitations

- The literature was searched from January 1, 2000, through July 5, 2015
  - Evidence from inception and newer articles may have been missed.
  - The Oncology Section plans to update this CPG every 5 years, adding the most recent literature to the development of our recommendations.
- Articles not in the English language were excluded from this study.
- Well-published methods may not be superior to newer measures with fewer studies.
- There is no single quality rating tool for all psychometric properties of diagnostic measures; therefore, multiple tools were used to review the quality of the evidence.
- Lack of standardization in diagnostic criteria, as well as the limited study representing all stages of SUQL, may confound the findings.
- Finally, this CPG was created by physical therapists, was not piloted in clinical practice, and did not include perspectives from patients or other medical and rehabilitation professionals in its inception and conduct. The authors addressed this limitation by inviting feedback from a wider audience of other physical therapists, physicians, nurses, and occupational therapists.

# Implementation and Future Work

- Preliminary findings were presented at the Combined Section Meeting of APTA in 2016.
- In addition, the group is committed to the following:
  - Ensure open access to the CPG and reference material.
  - Develop a guide to implementation of the CPG in clinical practice, made available through the Oncology Section of APTA.
  - Present the CPG at national conferences for health care professionals, allowing dissemination to other disciplines.
  - Create a podcast or similar electronic media that can be used in physical therapy and other health care professional education.
- To further support clinical practice in this area, The Oncology Section of APTA plans to create guidelines on risk factor identification and appropriate intervention for SUQL in the near future.

# Future Research Needs

There are several important directions for future research:

- Psychometric testing needs to be completed on many tools currently being used to assess and diagnose SUQL. This includes the emerging methods that lack diagnostic accuracy studies.
- Research is needed to determine which combination of signs, symptoms, and measures is most accurate for diagnosing SUQL.
- There is a need for high-quality studies on at-risk populations, as well as on the population in various stages of lymphedema.
- The bulk of the evidence includes patients with upper-extremity lymphedema due to breast cancer treatments. Further research is needed for diagnosing lymphedema both in the trunk and in the head and neck region.
- Early diagnosis is crucial to maintain quality of life and minimize upper-quadrant morbidity for patients at risk for SUQL; therefore, there is a need for research to determine appropriate preoperative measurements and prospective monitoring protocols.

# Resources

- Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. [Diagnosis of Upper-Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline From the Oncology Section of APTA](#). *Physical Therapy* 2017; 97(7):729–745; co-published in: *Rehabilitation Oncology* 2017; 35(3):E1-E18.
- Davies C, Levenhagen K, Ryans K, Perdomo M Gilchrist L. [An Executive Summary of the Clinical Practice Guideline: Diagnosis of Upper-Quadrant Lymphedema Secondary to Cancer](#). *Rehabilitation Oncology* 2017; 35(3):114-118.
- Davies C, Levenhagen K, Ryans K, Perdomo M, Gilchrist L. [How Can a Clinical Practice Guideline Enhance My Practice?](#) *Rehabilitation Oncology* 2017; 35(3):111-113.
- **Podcast: Understanding the development and use of clinical practice guidelines** by Dr. Laura Gilchrist at <http://journals.lww.com/rehabonc/pages/podcastepisodes.aspx?podcastid=1>
- **Podcast: Diagnosis of Upper Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline from the Oncology Section of the American Physical Therapy Association** by Dr. Claire Davies at <http://journals.lww.com/rehabonc/pages/podcastepisodes.aspx?podcastid=1>
- [BREAST CANCER EDGE TASK FORCE OUTCOMES: Assessment Measures of Secondary Lymphedema in Breast Cancer Survivors](#). Perdomo, Marisa; Davies, Claire; Levenhagen, Kim; et al. *Rehabilitation Oncology*. 2014; 32(1):22-35.
- [EDGE Task Force on Head and Neck Cancer Outcomes A Systematic Review of Outcome Measures for Quantifying External Lymphedema](#). Flores, Ann Marie; Spinelli, Bryan A.; Eden, Melissa M.; et al. *Rehabilitation Oncology* 2015; 33(2):15-23.

# Guideline Panel

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# Disclaimer

- This CPG is not intended to replace clinical judgment or establish a protocol appropriate for all individuals with this condition.
- *Clinicians need to be aware that none of the diagnostic methods and criteria are perfect in their diagnostic accuracy*, and especially patients whose measurement values fall just under or over a cut point have the potential to be misclassified. We encourage clinicians to cluster findings from their examination to draw a conclusion on diagnosis.
- Prior to determining a diagnosis, clinicians need to consider other potential causes.
- As the evidence continues to evolve, clinicians need to keep abreast of new additions to the literature

# References

- Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-Based Medicine – levels of evidence. Available at: <http://www.cebm.net/index.aspx?o=1025>. Published March 2009. Accessed August 25, 2012.
- Delitto A, George SZ, Van Dillen LR, et al. Low back pain. *J Orthop Sports Phys Ther.* 2012;42:A1–A57.
- Kaplan SL, Coulter C, Feters L. Physical therapy management of congenital muscular torticollis: an evidence-based clinical practice guideline—from the Section on Pediatrics of the American Physical Therapy Association. *Pediatr Phys Ther.* 2013;25:348–394.