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Evidence Appraisal on Indocyanine Green Lymphography's (ICG-L) Efficacy in Diagnosing Lymphedema Compared to Other Assessment Methods

Jasmin Cardenas

Catherine Daggi

Leah Parsons

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This evidence project, submitted by

Jasmin Cardenas, Catherine Daggi, & Leah Parsons

has been approved and accepted
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Shelly Norvell
Project Chairperson: Shelly Norvell, OTD, OTR/L

Renee Watling George Tomlin
OT637/737 Instructors: Renee Watling, PhD, OTR/L, FAOTA; George Tomlin, PhD, OTR/L, FAOTA;

Yvonne Swinth
Director, Occupational Therapy Program: Yvonne Swinth, PhD, OTR/L, FAOTA

Dean of Graduate Studies: Sunil Kukreja, PhD

Key words: indocyanine green lymphography, lymphedema diagnosis, lymphedema assessment

Abstract

The authors collaborated with Kate Long, OTR/L, CLT who is currently practicing at Legacy Salmon Creek Rehabilitation outpatient clinic, to answer the research question, "How effective is indocyanine green lymphography (ICG-L) in diagnosing and guiding treatment of adult clients suspected of having lymphedema compared to other assessment methods?" Results of the in-depth literature review provided moderate evidence to support the use of the ICG-L assessment method for obtaining an early, conclusive diagnosis of lymphedema. Findings also showed that imaging of individual lymphatic flow can assist certified lymphedema therapists (CLTs) in delivering personalized treatment to their clients. Compared to other diagnosing methods, ICG-L does not involve radioactive substances, is able to record lymphatics in real time, and has a higher specificity rate. Limitations of ICG-L include requiring injection of a dye and limited visualization of deep lymphatics.

An informational pamphlet product was assembled to assist our collaborator in informing clinicians about the merits of ICG-L. The literature review guided the development of the pamphlet, which consisted of a description of ICG-L, along with how it differs from other lymphedema assessments. A survey was provided to the collaborator and her colleagues to measure perceptions of the understandability and usability of the pamphlet prior to distributing it to other CLTs and referring clinicians. The goal was to ensure it contained all pertinent information required for effective use in educating CLTs and referring clinicians about the assessment method. Based on the results of this project, it is recommended that CLTs and referring clinicians consider the use of ICG-L for conclusively diagnosing lymphedema and aiding in personalized treatment for affected clients.

Executive Summary

This research project was completed in collaboration with Kate Long, OTR/L, CLT, an occupational therapist and certified lymphedema therapist (CLT) who practices at an outpatient clinic at Legacy Salmon Creek Rehabilitation in Vancouver, WA. The focus of this project was to compare lymphedema diagnostic methods, particularly ICG-L, a newer method for diagnosing lymphedema, to six other well-known methods. The main goals were to determine the pros and cons of utilizing ICG-L in diagnosing and guiding treatment of lymphedema compared to other diagnostic methods, and ultimately use information compiled to educate CLTs and referring clinicians about superior assessment methods.

To achieve our goals, a systematic review of the literature was conducted to appraise the evidence regarding ICG-L and other lymphedema diagnostic methods in their ability to diagnose lymphedema early, accurately, and safely. Our search criteria yielded 1,101 articles with sixteen meeting inclusion criteria. There were (7) level 2B, (5) level 3B, (3) level 4, and (1) qualitative articles. Findings from the literature indicate with moderate evidence that ICG-L is a superior method of diagnosing lymphedema compared to other reviewed methods due to its sensitivity, safety, utility in visualizing real-time lymphatic flow, and use in guiding personalized treatment.

The use of ICG-L on a client with the CLT administering manual lymphatic drainage (MLD) and observing lymphatic flow could enable altering the methods to be more effective while also allowing the client to become more familiar with the condition and how to perform self-management. Our collaborator works with clients who are suspected of having lymphedema, but have not all been definitively diagnosed. Lymphedema is often diagnosed by exclusion of other possible diagnoses so there are clients who are receiving services for lymphedema who do not actually have a dysfunctional lymphatic system. Ms. Long is trained in complete decongestive therapy, including MLD techniques, but without an assessment with a modality like ICG-L, which can definitively diagnose lymphedema and help guide individualized treatment, it is difficult to

determine whether the techniques she is applying are the most beneficial for each client. Due to the accuracy of the assessment methods, ICG-L and lymphoscintigraphy are the top two methods that can be used to ensure that the clients she is treating are actually in need of her services. We, therefore, recommend that efforts are made to educate potential referring providers on the merits and limitations of ICG-L in order for our collaborator, other CLTs, and lymphedema clients to benefit from what it has to offer.

Translation of the project findings occurred through an informational pamphlet about ICG-L. The pamphlet was reviewed by the project chair and then sent to our collaborator, who then reviewed the pamphlet and provided it to her colleagues. A survey created by the authors was provided to the collaborator and her colleagues to obtain data on their overall thoughts of the product. Feedback was received on how to improve the appearance of the pamphlet as well as recommendations on syntax to improve the readability. An updated version was provided to our collaborator for further dispersal at Legacy Salmon Creek Medical Center. Overall, based on the survey outcomes, the informational pamphlet has been shown to be an appropriate handout to provide to CLTs and referring clinicians.

Critically Appraised Topic

Focused Question

How effective is indocyanine green lymphography (ICG-L) in diagnosing and guiding treatment of adult clients suspected of having lymphedema compared to other assessment methods?

Prepared By

Jasmin Cardenas, OTS; Catherine Daggi, OTS; Leah Parsons, OTS

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Professional Practice Scenario

The collaborating practitioner, Kate Long, OTR/L, CLT, is an occupational therapist certified in lymphedema therapy and is employed at an outpatient clinic in Vancouver, WA. She also works on the acute care floor at an adjacent hospital when time allows. At the outpatient clinic, Ms. Long is one of two occupational therapists and her client population includes 50% non-cancer related lymphedema clients, 25% cancer related lymphedema clients (mostly breast cancer), and 25% clients with cancer who are not currently diagnosed with lymphedema. Kate expressed that her clients are often diagnosed with lymphedema by exclusion of other illnesses rather than by using a conclusive assessment method. She has done some research on the use of ICG-L and wants assistance with gathering more definitive research on the implications of using this method compared to other assessment methods, including lymphoscintigraphy, other imaging modalities, and diagnosis by exclusion. She is seeking evidence-based information regarding the effectiveness of ICG-L to ensure a thorough understanding and to illustrate the importance of conclusive diagnostic imaging tests when communicating with referring clinicians. The hope is that with the use of ICG-L, lymphedema can be diagnosed in its earlier stages and individualized treatment can be provided to those who have lymphedema.

Search Process: Procedures for the selection and appraisal of articles

Inclusion Criteria

Our inclusion criteria required that participants are adults (age 18+) because our collaborator primarily works with this population and treatment methods for children may be different from what would be done with adults. An exception was made for one article that had a participant who was 12 years old. This article was included due to the applicable information regarding the topic of lymphedema. The second inclusion requirement was that the clients must be suspected of having primary or secondary lymphedema. This is because we are comparing the ability of multiple assessments to detect lymphedema thus the clients should be suspected of being affected by it. Initial reviews have shown that some participants in the studies actually did not end up having lymphedema once lymphography was completed. Finally, the disease location must be in the limbs or neck. While lymphedema does exist in other parts of the body, our practitioner primarily works with the limbs and neck; there is also an abundance of research on these areas which served as a solid starting point for this comparison.

Exclusion Criteria

Our exclusion criteria included any articles dated prior to January 1, 2006. While ICG-L has been used for decades, it is only more recently that it has been used in detecting lymphedema. These more recent studies provide rich information regarding the use and efficacy of ICG-L along with comparisons to other methods including lymphoscintigraphy (LS), magnetic resonance imaging (MRI), computerized tomography (CT) scans, diagnosis by elimination, and even visual observations. Also excluded were articles that used ICG-L to detect cancerous lymphatic nodes or for other medical reasons. While the use of ICG injections in these articles would be to examine the lymphatics, the primary purpose was for diagnosing cancer, not to determine whether lymphedema is present. Also considered were criteria on study type, outcomes, location, and specifying specific causes of the lymphedema, however, we determined that excluding any of this data could limit the richness of obtainable information.

Search Strategy:

Categories	Key Search Terms
Patient/Client Population	adults, adult
Assessment	Indocyanine green lymphography, ICG lymphography, ICG, fluoroscopy diagnostic imaging
Comparison	Magnetic resonance imaging lymphography, MRI lymphography, MRI lymphedema, lymphoscintigraphy, computerized tomography lymphedema, CT lymphography, CT lymphedema, circumferential measures
Outcomes	lymphedema, lymphatic obstruction, lymphatic disease, lymphatic disorder, lymphatic insufficiency, diagnose, evaluation, detect, determine, identify

Databases, Sites, and Sources Searched
Medline
PubMed
Cumulative Index to Nursing and Allied Health Literature (CINAHL)
Science Direct
American Journal of Occupational Therapy (AJOT)
Collins Memorial Library Primo Search
University of Puget Sound, Sound Ideas

Search Outcomes/Quality Control/Review Process

To extract the most relevant empirical literature, we conducted comprehensive searches in online databases (*Medline, PubMed, CINAHL, and ScienceDirect*), the American Journal of Occupational Therapy, and manual searches with *Collins Memorial Library Primo Search*, the *University of Puget Sound's Sound Ideas,* and reference lists of identified articles. The search was limited to published articles from January 2006 to September 2021. The main search terms *indocyanine green lymphography*, and *lymphedema* were selected from the overall PACO question and were used in combination with other key terms to ensure we considered as many relevant articles as possible. Key players involved in this process included the library liaison who helped us to quickly obtain many articles through interlibrary loan.

Our search yielded a fair amount of results in some databases (i.e., *PubMed and CINAHL*), but very few in other databases (i.e., *ScienceDirect* and *Medline*) which may be due to the specific assessment we were researching. To determine potential relevant articles with each search, we initially screened titles and abstracts. We then reviewed the full text of articles that appeared to be relevant to decide if they met our inclusion and exclusion criteria. All members of the team reviewed the full text and noted a

"yes," "no," or "maybe", next to each article in the Master Citation Table. The "maybe" articles were then further reviewed by all members and together decided if they met the criteria.

After removal of duplicates, 1,087 potential articles remained. Screening by title and abstract resulted in 41 articles which were fully reviewed using the inclusion and exclusion criteria. Studies were excluded if they were meta-analysis, literature review, expert opinion or poster session (6), protocols for future studies (1), consisted of unrelated outcome measures (15), or did not meet inclusion criteria (3). One study was included which did not fully meet inclusion criteria (Akita et al., 2013). The study mentioned an age range as young as 9 years old. The authors of the study discussed that there is no indication of skeweds results, thus all members decided to include the study. This process resulted in 16 articles being included

in this critically appraised topic paper.

Master Citation Table (AOTA, 2016)

Evidence Project Group Member Names: Jasmin Cardenas, Catherine Daggi, Leah Parsons

Topic/PACO Question: How effective is indocyanine green lymphography (ICG-L) in diagnosing and guiding treatment of adult clients suspected of having lymphedema compared to other assessment methods?

CITATION	Level of Evidence: Pyramid; AOTA 1-5AB	Y N M	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWERS
Akita et al., 2013	O3; 2B	M/Y	Thorough study; mentions an age range as young as 9- discussed & no indication that presence skews results.		LP, JC, CD
Akita et al., 2017	O2; 4	Y			CD, JC, LP
Medina-Rodriguez et al., 2020.	D2; 4	Y			JC, LP, CD
Mihara et al.,	E3; 2B	Y			CD, JC, LP

2012					
Pigott et al., 2021	Q2c; NR	Y			LP, JC, CD
Qin et al., 2018	O3; 2B	Y			LP, JC, CD
Soga et al., 2021a	O3; 3B	Y			CD, JC, LP
Soga et al., 2021b	O3; 3B	Y			CD, JC, LP
Suami et al., 2019	O3; 2B	Y			LP, JC, CD
Unno et al., 2007	O3; 2B	Y			JC, LP, CD
Unno et al., 2010	O3; 2B	Y			CD, JC, LP
Wiser et al., 2020.	O4; 3B	Y			JC, LP, CD
Yamamoto et al., 2011	O3; 3B	Y			LP, JC, CD
Yamamoto et al., 2013	O3; 2B	Y			JC, LP, CD
Yoon et al., 2020	O2; 3B	Y			CD, JC, LP
Zalzeska et al., 2017	D3; 4	Y			JC, LP, CD
Pappalardo et al., 2019	N/A	M/N	Reviews LS for the diagnosis of extremity lymphedema	Expert opinion	CD, JC, LP
Heydon-White et al., 2020	N/A	Y/N		Initially included in proposal but excluded due to location of lymphedema in breast tissue.	CD, JC, LP
Suami et al., 2012	N/A	M/N	ICG was used on patients that already had a dx of lymphedema. Author's purpose was to use ICG to identify the location of	Does not fully meet inclusion criteria of focusing on ICG-L specifically for	JC, LP, CD

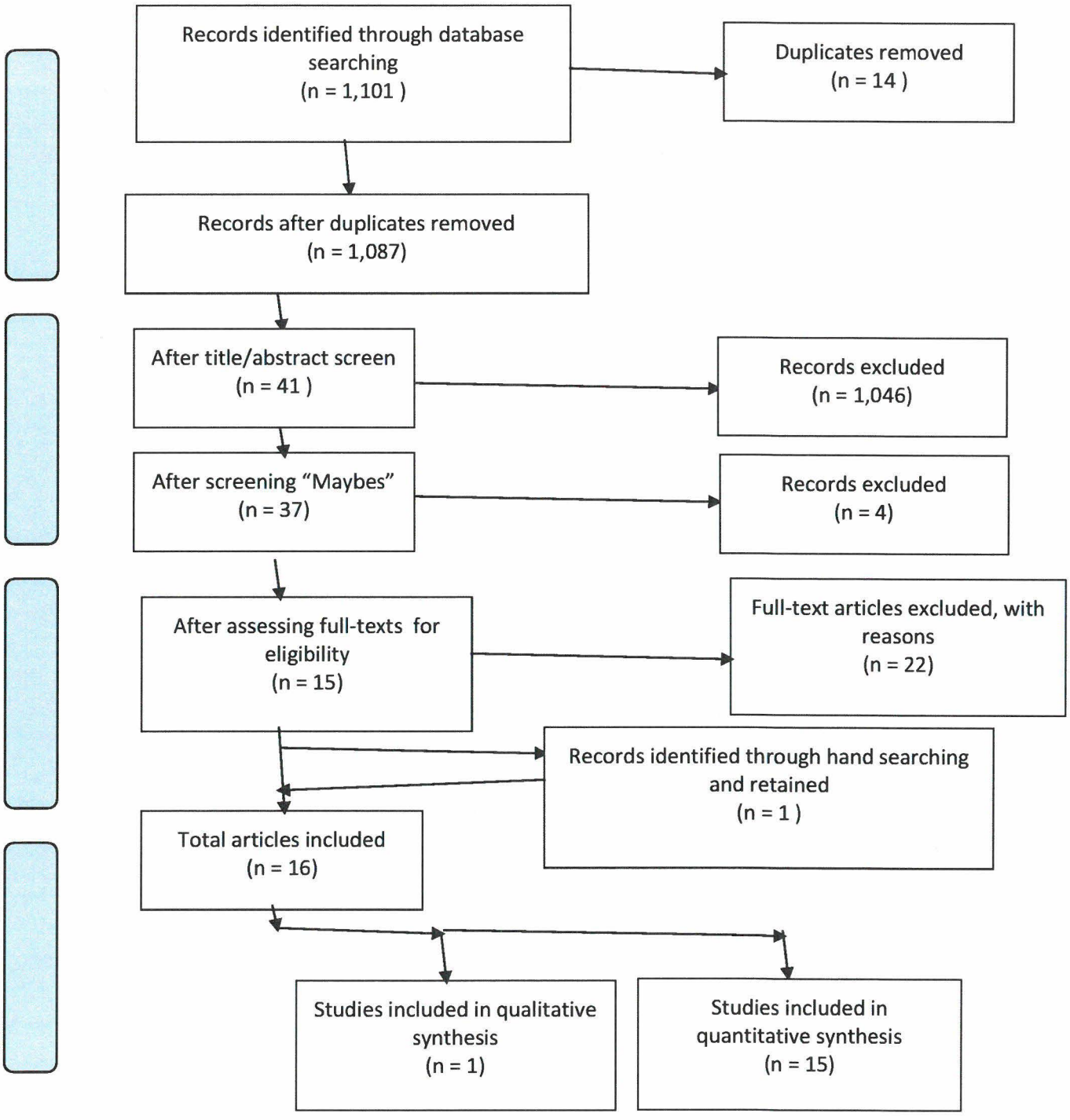
			lymphatic vessels for lymphovenous shunt. Author states the pros of ICG.	lymphedema detection	
Hidding et al., 2006	N/A	M/N	Systematic review with synthesis of information on this topic.	Decided not to use systematic reviews- mining for individual papers instead.	JC, LP, CD
Naurishima et al., 2016	N/A	M/N	Examines ICG-L findings in limb lymphedema	Does not cover results of ICG-L as an assessment for lymphedema- covers pros/cons & using ICG-L to examine dermal backflow patterns	JC, LP, CD
Yoshida et al., 2019	N/A	M/N	ICG-L findings in older patients with lower limb lymphedema	Reviews ICG-L to classify age-related deterioration in lymph drainage not enough focus on ICG-L as an assessment method for lymphedema	JC, LP, CD
O'Donnel Jr. et al., 2018	N/A	M/N	Looks at NIRF lymphatic imaging; compares diagnostic tools	Decided not to use systematic reviews- mining for individual papers instead.	JC, LP, CD
Tashiro et al., 2015	N/A	M/N	Examines patterns of indocyanine green lymphography in secondary lower extremity lymphedema	Focused on detecting vessels and patterns, not enough focus on detecting lymphedema	JC, LP, CD
Yasunaga et al., 2021	N/A	M/N	Compared MRL with ICG to detect lymphatic vessels	Focused on detecting vessels, not enough focus on	JC, LP, CD

				detecting lymphedema	
Chao et al., 2021	N/A	M/N	ICG for preoperative, intraoperative, and post-operative assessment of lymphatic system	Focus is more on detecting vessels vs detecting/ diagnosing lymphedema	JC, LP, CD
Shih et al., 2016	N/A	M/N	Use of ICG to monitor lymphatic system after anastomosis	ICG used to analyze the surgical outcome of LVA vs detecting/diag nosing lymphedema	JC, LP, CD
Chowdhry et al., 2016	N/A	M/N	Reviews various imaging methods for managing post-mastectomy lymphoedema	Excluded because did not contain assessments only on limbs	JC, LP, CD
Chang et al., 2013	N/A	M/N	Reviewed treatment of extremity lymphedema	Received full article and it was not focused on assessment methods	
Koelmeyer et al., 2021	N/A	M/N	Reviewed personalizing lymphedema management using ICG guided manual lymphatic drainage	Focuses too much on use for drainage and not for assessment of lymphedema	LP, JC, CD
Qin et al., 2020	N/A	M/N	Examines how multi-segment bioimpedance can assess patients with bilateral lymphedema	Not enough info- research poster	LP, JC, CD
Akita et al., 2020	N/A	M/N	Study to assess the usefulness of indocyanine green fluorescent lymphography in assessing secondary	Protocol	LP, JC, CD

			lymphoedema		
Abacci et al., 2019	N/A	M/N	Near-infrared fluorescence imaging for the prevention and management of breast cancer-related lymphedema	Systematic review	LP, JC, CD
Lopera et al., 2017	N/A	M/N	Investigated the short-term effects of manual lymphatic drainage (MLD) and compression garment (CG) therapies on lymphatic function using near-infrared imaging	Not enough focus on methods to assess lymphedema-more on MLD and CG	LP, JC, CD
Chen et al., 2016	N/A	M/N	ICG-L evidence of surgical efficacy following microsurgical and super-microsurgical lymphedema reconstruction	Conclusion is about ICG and its utility but not enough focus on use for diagnosing/treating lymphedema	LP, JC, CD
Forte et al., 2019	N/A	M/N	Examines LS for evaluation of lymphedema treatment	Systematic review	LP, JC, CD
Ogata et al., 2007	N/A	Y/N	Examines intraoperative lymphography using indocyanine green dye for near-infrared fluorescence labeling in lymphedema	Has 12 year old as part of study and is unclear if that skews results	JC, LP, CD
Guo et al., 2017	N/A	M/N	Self-controlled trial was designed to detect the difference in the detection efficacies of ICG, MB, and combined ICG and MB (ICG + MB) navigation methods	Focus is on using ICG to map cancerous lymph nodes	CD, LP, JC
Yamamoto et al., 2017	N/A	M/N	Examined factors associated with lower extremity dysmorphia	Not enough focus on assessment/di	CD, LP, JC

			caused by lower extremity lymphoedema	agnosis of lymphedema	

PRISMA 2009 Flow Diagram (Moher D, Liberati A, Tetzlaff J, Altman DG. (2009). The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097)



Results of Search: Summary of Study Designs of Articles Selected for the CAT Table (All Articles with Final Label "YES" from Master Citation Table)

Pyramid Side	Study Design/Methodology of Selected Articles	Number of Articles Selected
Experimental	___Meta-Analyses of Experimental Trials ___Individual Blinded Randomized Controlled Trials __1_Controlled Clinical Trials ___Single Subject Studies	1
Outcome	___Meta-Analyses of Related Outcome Studies _2__Individual Quasi-Experimental Studies w/ Covariates _9_Case-Control or Pre-existing Groups Studies _1__One Group Pre-Post Studies	12
Qualitative	___Meta-Syntheses of Related Qualitative Studies _1__Group Qualitative Studies w/ more Rigor a. prolonged engagement with informants b. triangulation of data (multiple sources) c. confirmation (peer/member-checking; audit trail) d. comparisons among individuals, w/i a person ___Group Qualitative Studies w/ less Rigor ___Qualitative Study on a Single Person	1
Descriptive	___Systematic Reviews of Related Descriptive Studies _1_Association, Correlational Studies _1_Multiple Case Series, Normative Studies, Descriptive surveys ___Individual Case Studies	2
AOTA Levels 1A- 1B- 2A- 2B- 7 3A- 3B- 5 4- 3 5- NR- 1 Comments:		*TOTAL # of articles*- 16

Risk of Bias for Non-Control Research Studies ("YES" Articles)												
Citation	Study question or objective clear	Eligibility or selection criteria clearly described	Participants representative of real-world patients	All eligible participants enrolled	Sample size appropriate for confidence in findings	Intervention clearly described and delivered consistently	Outcome measures pre-specified, defined, valid/reliable and assessed consistently	Assessors blinded to participant exposure to intervention	Loss to follow up after baseline 20% or less	Statistical methods examine changes in outcome measures from before to after intervention	Outcome measures were collected multiple times before and after intervention	Overall Risk of Bias Assessment (low, moderate, high risk)
Akita et al., 2013	Y	Y	Y	NR	Y	Y	Y	NR	NR	Y	N	M
Akita et al., 2017	Y	N	Y	NR	Y	Y	Y	NR	NR	Y	Y	M
Medina-Rodriguuez et al, 2020	Y	Y	Y	NR	NR	Y	Y	N	NR	Y	N	M
Mihara et al., 2012	Y	Y	Y	Y	N	Y	Y	NR	NR	Y	N	M
Pigott et al., 2021	Y	Y	Y	NR	N	Y	Y	N	N	N	N	M
Qin et al., 2018	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	L
Soga et al., 2021a	Y	N	N	NR	N	Y	Y	NR	NR	Y	NR	M
Soga et al., 2021b	Y	N	N	NR	N	Y	Y	NR	NR	Y	NR	M

Suami et al., 2019	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	L
Unno et al., 2007	Y	Y	Y	NR	NR	Y	Y	N	NR	Y	N	M
Unno et al., 2010	N	N	Y	NR	N	Y	Y	NR	NR	Y	Y	M
Wiser et al., 2020.	Y	Y	N	Y	Y	N	Y	NR	NR	Y	N	M
Yamamoto et al., 2011	Y	N	Y	NR	N	Y	Y	N	N	Y	N	M
Yamamoto et al., 2013	Y	Y	Y	NR	NR	Y	Y	N	NR	Y	N	M
Yoon et al., 2020	Y	Y	Y	N	Y	Y	Y	NR	NR	Y	N	M
Zalzeska & Olszewski, 2017	Y	Y	Y	NR	NR	Y	Y	Y	NR	Y	N	M

Evaluation: Y=yes, N=no, NR= Not reported
Scoring: Add Yes scores for each item together and divide by 11 Risk of bias rating: Low (L)-75-100%, Moderate (M) 25-75%, or High (H) 0-25%

Table Summarizing the *Quantitative* Evidence

Author Year Journal Country	Study Objectives	Assessment(s)	Study Design Level of Evidence	Participants: Sample Size, Description Inclusion and Exclusion Criteria	Interventions (I) & Outcome Measures (O)	Summary of Results	Study Limitations	Implications for Practice	Indicate "Shows effectiveness" or "indirect support for _____ theme"
Akita et al. **2013** *Journal of Plastic, Reconstructive, & Aesthetic Surgery* Japan	Comparison of LS and ICG-L for the diagnosis of extremity lymphedema.	ICG-L LS	Retrospective cohort study AOTA- 2B Pyramid- O3	*N*= 134 clients; 115 female, 19 male; *M* age = 58.5; age range = 9-82; *N* = 95 secondary lymphedema; *N* = 39 primary lymphedema In: primary or secondary lymphedema; consecutive clients who underwent LS & ICG-L from August 2010 to March 2012. Ex: Patients with lymphoedem	I: Injections of ICG & technetium-99m-labelled human serum albumin (for LS) done with all client in affected & unaffected limb. I: use of ICG-L and LS O: ICG-L and LS images were evaluated by identifying DBF pattern and asymmetry in inguinal /axillary nodes	ICG-L is superior to LS in detecting secondary lymphedema earlier, sensitivity = .972, specificity = .548, accuracy = .816. ICG-L Detecting primary lymphedema: sensitivity = .974, specificity = .778, accuracy = .892.	Methodology is unclear with how far apart each client was injected with each tx or if it was at the same time. All clients were recruited from one hospital. Time elapsed between administration of ICG-L and LS was not noted.	ICG-L is able to detect secondary lymphedema earlier than LS with high levels of sensitivity, specificity, and accuracy. It is also less invasive and costs less [in Japan]. Should be used for screening, especially in earlier suspected cases of lymphedema; do not use for morbidly obese clients.	Shows effectiveness of using ICG-L over LS for diagnosing lymphedema, especially in early stages of the disease.

				a secondary to filariasis, infection or trauma.					
Akita et al. **2017** *Microsurgery* Japan	To propose a novel method of screening lymphedema patients based on thickness of the subcutaneous fat measured with perioperative CT.	CT ICG-L	2-group comparison AOTA: 4 Pyramid: O2	*N*= 285 (96 gynecological cancer patients; 189 breast cancer patients); BMI 22.7 ± 3.4 before LVA surgery and 22.6 ± 3.5 after surgery In: lymphatic function was assessed with indocyanine green lymphography	I: Gynecologic-al clients had perioperative CT T-SFTI calculated from presurgical and follow - up CT data. Breast cancer clients had post-operative CT C-SFTI calculated; all clients underwent ICG-L for comparison O: assessment of T-SFTI on gynecological patients and assessment of C-SFTI on breast cancer patients	Preoperative CT T-SFTI was higher in 46 lymphedema limbs than 134 normal limbs ($p < .01$), Postoperative CT T-SFTI was higher in 11 lymphedema limbs than in 42 normal limbs ($p < .01$). CT finding sensitivity was 0.87 and specificity was .98.	A prospective study is needed to confirm reliability and reproducibility. Only early cases included; long standing cases need to be examined. CT is not recommended for screening of lymphedema only due to radiation exposure. No mention of timeline of CT scan and ICG-L admin. Exclusion criteria not specified.	Assessment of sub-cutaneous fat thickness using CT is useful for screening early stage lymphedema if already obtaining CT scan; CT is not routine after some treatments so it would need to be an additional order that includes additional radiation exposure.	Shows effectiveness of using ICG-L and CT for assessing lymphedema for gynecological and breast cancer clients.
Mihara et al.	To compare the diagnostic	CT ICG-L	Experimental controlled clinical trial	*N* = 21; 21 female; *M* age = 60.4	I: LS, ICG-L, MRI, CT	ICG-L cannot detect	Small sample size; all the clients were	ICG-L and MRI are more	Shows that ICG-L and MRI are

2012 *PLoS ONE* USA	accuracy of the imaging methods and to investigate their usefulness for identification of early-stage lymphedema.	LS MRI	AOTA- 2B Pyramid- E3	yrs.; range = 35-81 yrs. In: dx unilateral mild upper limb stage 1 lymphedema, resection of breast cancer with lymph node dissection Ex: lymphedema in the contralateral arm	O: Diagnostic accuracy of each imaging method for identification of early stage lymphedema.	vessels 2cm deep. For ICG-L and MRI all 21 cases were positive. However, on LS and CT, positive features were noted in 13 and 7 cases, respectively. Specificity for all methods = 1. Sensitivity for ICG-L and MRI = 1. Sensitivity for LS = .62. Sensitivity for CT = .33.	recruited from the same hospital and were solely female.	sensitive in diagnosing UE lymphedema than LS and CT. ICG-L is less effective than LS at displaying deeper lymphatic flow in obese clients.	more effective for diagnosing lymphedema over CT and LS.
Qin et al. **2018** *Journal of Plastic, Reconstructive, & Aesthetic Surgery* USA	To test the sensitivity, specificity, and diagnostic accuracy of BIS in diagnosing lymphedema by referencing its results with ICG-L.	BIS Circumferential Measurement ICG-L QoL Assessment	Retrospective study- record review AOTA- 2B Pyramid- O3	*N*= 62; 58 female, 4 males; *M* age = 57 In: age 18+, eval on history & physical exam, lymphedema - specific QoL assessment, BIS, and ICG-L;	I= Lymphedema- specific quality of life assessment, circumference-measurement - based index, BIS, ICG-L O: diagnostic accuracy of	BIS specificity rate= 100%; sensitivity rate= 64%; false-positivity rate of 36% when comparing BIS to ICG-L results.	All clients were evaluated for management of lymph-edema, which may have resulted in selection bias regarding client demographics and disease	BIS is not sensitive to rule out lymphedema if there is a negative test. Using a diagnostic study with a low false-negative rate will decrease missed cases,	ICG-L is more effective than BIS in diagnosing lymphedema. BIS is limited in use due to high false negative rate but can be used to track progress/ change.

				females with suspected arm or leg lymphedema or males with suspected leg lymphedema; and suspected unilateral disease Ex: inability to complete both BIS & ICG prior to surgical management; clients with bilateral disease; males with UE disease	BIS was assessed using ICG-L as a reference test on affected limb		severity; variability in BIS measurements because of electrode placement-slight discrepancies likely due to variance in client anatomy and user placement. Circumference measurements not reported. Limited info on ICG-L administration	allow for prompt management, prevention of disease sequela, and be more cost-effective over time.	
Soga et al. **2021a** *Journal of Vascular Surgery: Venous and Lymphatic Disorders* Japan	To investigate if there are any characteristic patterns for DBF and lymphatic visualization depending on the anatomic location within LE and severity of lymphedema	MRL	Retrospective study AOTA: 3B Pyramid: O3	*N*= 56 patients (112 limbs); 45 female, 11 male; *M* age = 50.9; age range = 34-67.8; *N* = 43 unilateral and *N* = 13 bilateral lymphedema of the LE	I: MRL was performed on all clients. Postcontrast imaging using 3D two-point DIXON initiated 5 minutes after administration and acquired in two	DBF was observed in 60 out of 112 LE. DBF more frequent in distal regions of LE than proximal regions ($p < .05$). Positive correlation between the ISL stage and seven MRL	All patients recruited from the same hospital. Control group was not included. Exclusion criteria were not reported.	Depending on the LE anatomic location and the severity of disease, MRL shows changes in delineation of DBF and lymphatics-may aid in assessment of the disease	Shows effectiveness of MRL in assessing severity of lymphedema.

	. Additionally, to investigate if it is possible to classify the severity of lymphedema based on MRL findings.			In: patients with LE lymphedema , must have underwent MRL between 2012 and 2018. Ex: not reported	consecutive phases O: MRL image assessment of MRL patterns conducted by two radiologists	stages (Spearman's rho = .79, *p* < .01). Visualization of DBF towards the proximal LE decreased due to contrast agent uptake is more highly impared in lymphatics.		progression. MRL DBF patterns correlate with ISL stage;. DBF patterns of proximal LE regions are not well detected with MRL- can cause under-diagnosis of lymphedema .	
Soga et al. **2021b** *Journal of Vascular Surgery: Venous and Lymphatic Surgery* Japan	Analyze MRL images for the presence or absence of collateral lymphedema to clarify the patterns of lymphatic collateral formation and the association with the clinical stages of lymphedema .	MRL	Single center, retrospective cross-sectional study AOTA: 3B Pyramid: O3	*N*= 56 (112 limbs); 45 female, 11 male; *M* age = 50.9; age range = 34-67.8; *N* = 23 primary LE lymphedema , *N*= 33 secondary LE lymphedema In: patients with LE lymphedema who underwent MRL between	I : MRL was performed on all clients. Postcontrast imaging using 3-D two-point DIXON initiated 5 minutes after administratio n and acquired in two consecutive phases O: MRL image assessment for presence or absence of collateral	3 collateral pathways (anterolatera l lymphatics, deep lymphatics, and posteromedi al lymphatics) were more frequent in ISL stage II and stage 0 (p < .05). Anterolateral lymphatics were more frequent in stage I than stage 0 (p < .05).	All participants recruited from the same hospital. Authors state the definition of collateral lymphatics is ambiguous. Control group was not included. Exclusion criteria were not reported.	Identifying the 3 collateral pathways in MRL images, can guide practitioners to identify ISL stages.	Shows effectiveness of MRL in early diagnosis and assessing the severity of lymphedema .

				2012 and 2018. Ex: not reported	lymphatic pathways was conducted by two radiologist	3 collateral pathways were more frequent in stages I-III than in stage 0 LE ($p < .05$). Results support early dx of lymphedema in asymptomatic LE.			
Suami et al. **2019** *BMC Cancer* Australia	To summarize initial findings obtained by ICG-L protocol in breast cancer related lymphoedema.	ICG-L LS	Retrospective cohort study AOTA- 2B Pyramid- O3	*N*= 103; *M* age= 57.73 ± 9.78 In: clients with BCRL who underwent ICG-L at the Australian Lymphoedema Education, Research and Treatment (ALERT) clinic at Macquarie University between February 2017 and April 2018	I: ICG-L completed in affected arm followed by MLD massage with regular imaging completed for 1 hr to view lymph movement; 3 clients repeated ICG-L after 24 hrs; 3 clients also separately underwent LS O: evaluations of lymphatic imaging of UE	ICG-L process faster and more comprehensive vs. LS in diagnosis lymphedema, especially when coupled with MLD; ICG-L provides visualization of lymph movement and personalized care ICG-L revealed three cases of falsely diagnosed lymphedema.	Photography method was not always consistent with upper arm photos missing for some participants. Participants were recruited from one treatment clinic. Exclusion criteria and gender of participants was not reported.	ICG-L is the preferred method over LS due to efficiency with time, ability to guide personalized treatment with clear visualization of drainage pathways, enabling increased effectiveness of MLD.	ICG-L is more effective than LS for personalized treatment of lymphedema.

Unno et al. **2007** *Journal of Vascular Surgery* Japan	Determine the effectiveness of ICG-L for the dx of lymphedema of the LE.	ICG-L	2 group-comparison AOTA- 2B Pyramid – O3	*N* = 22; Lymphedema = 12; 11 female, 1 male; *M* age = 64.3 yrs., range = 50.7-77.9 yrs; Control = 10; 3 female, 7 male; M age = 44.9, range = 26.6-62.2yrs. In: LE secondary lymphedema ; previous physical examination, LS, and duplex ultrasound	I: ICG-L was done to all participants O: Imaging patterns-normal or abnormal	ICG- L successful in identifying abnormal lymph drainage, DBF, and dilated lymph channels - indicate lymphedema ; 15 LE with DBF; 8 LE with proximal obliteration and dilated; 6 LE with diffused glittering. Researchers concluded ICG-L may be useful in clinical practice of lymphatic disorder.	Small sample size; sample recruited from one location; only assessed for LE secondary lymphedema ; did not state if lymphedema was early or late; and exclusion criteria were not reported.	ICG-L does not cause discomfort and is successful in identifying 3 factors that indicate lymphedema .	Shows effectiveness of ICG-L in diagnosing lymphedema at unknown stages.
Unno et al. **2010** *Journal of Vascular Surgery* Japan	Adapt the ICG-L technique for measuring superficial lymphatic pumping in the human leg and comparing the contractile	ICG-L LS	Retrospective cohort study, pre-existing groups AOTA: 2B Pyramid: O3	*N* = 65 (Secondary lymphedema = 23, *M* age = 61.8, 23 female; healthy volunteers = 15, *M* age = 58.5, 15 female; AAA clients = 27,	I: ICG-L and dynamic LS measuremen t of lymphatic pumping O: Comparison of lymphatic pumping in healthy	Lymph pumping pressure of healthy participants (*M* = 29.3, *SD* = 16.0) were higher than lymphedema participants (*M* =13.2, *SD* =14.9). ICG-L	Most patients involved underwent extended lymph node dissection which damaged lymphatic passageways and might	The pressure necessary to move lymph in the limb is a factor that can help identify obstruction in the lymphatic vessels, thus can indicate	Shows effectiveness of ICG-L in diagnosing lymphedema in the LE.

	force between healthy and lymphedematous legs.			M age = 71.9, 21 male, 6 female) In: AAA patients no lymphedema and hospitalized for treatment of AAA; secondary lymphedema.	volunteers and patients with secondary lymphedema.	is an accurate, safe, easy, and economical method of measuring lymphatic pumping.	have increased lymphatic afterload. Exclusion criteria were not reported.	a diagnosis of lymphedema. ICG-L is useful in measuring lymph pump pressure.	
Wiser et al. **2020** *Cancers* USA	Evaluate the most commonly used preoperative assessment tools for patients undergoing surgical treatment for secondary UE lymphedema.	BIS ICG-L LS Limb Circumference Perometry	Prospective cohort study, pre-existing groups AOTA- 3B Pyramid- O4	*N* = 118, *M* age =54 yrs, range = 43-65, 116 females, 2 males In: unilateral UE secondary lymphedema, pt database from the Memorial Kettering Cancer Center, all clients were evaluated for surgical management of UE swelling following axillary	I: Lymphedema was evaluated on affected and unaffected limbs by limb volume measurements, BIS measurement, LS, ICG-L O: SPSS software was used to analyze results of each measurement	Perometer more sensitive and specific than circumferential. Circumferential method under-diagnoses and under-estimates the degree of lymphedema (sensitivity = .828) BIS sensitive for early stage lymphedema (sensitivity = .912). LS alone is insufficient,	Cohort had an established lymphedema dx before assessments, no control group, ISL stages of 0 or 3 were underrepresented. Authors stated ICG-L has high sensitivity for detecting lymphedema but did not include a percentage. Exclusion criteria were not reported.	Practitioners must understand the benefits and drawbacks of common lymphedema assessments. ICG-L and BIS have the highest sensitivity for identifying lymphedema, thus they should be the main assessments used to determine diagnosis.	Shows effectiveness of ICG-L and BIS over LS for diagnosing lymphedema in the UEs.

				surgery between January 2015 and July 2018.		(sensitivity = .88, specificity= . 414). ICG-L sensitive for detecting lymphedema .			
Yamamoto et al. **2011** *American Society of Plastic Surgeons* Japan	To understand how ICG-L splash pattern precedes manifestation of clinically evident lymphedema and whether its appearance would indicate a time point at which to start tx for lymphedema .	ICG-L	Retrospective AOTA- 3B Pyramid- O3	*N* = 28 clients (27 females, 1 male; age range 22.1-66.7 years) In: secondary LE lymphedema with at least one symptomatic leg and one asymptomatic leg Ex: not reported	I: 28 symptomatic and 28 asymptomatic LE assessed using ICG-L O: ICG-L patterns of limb	Leg DBF stage of asymptomatic limb, 1.2 ± 0.4 versus 0.0 ± 0.0 ($p < .001$) of leg w/o DBF pattern; and leg DBF stage of symptomatic limb, 3.5 ±0.6 versus 2.8 ±0.8 ($p = .033$) in symptomatic leg without a DBF pattern; DBF pattern observed in 19 asymptomatic legs (16 were in backflow stage I; 3 in backflow stage II)	Small number of clients and limbs tested; currently unknown how this earlier diagnosis could impact treatment and progression of disease. Exclusion criteria was not reported	ICG-L is a minimally invasive method to assess lymphedema ; visualizes superficial lymph flow in real time without risk of radiation exposure. Both lymph circulatory condition and lymph pump function can be evaluated using ICG-L; DBF patterns enable earlier detection of secondary lymphedema	Shows effectiveness of ICG-L in diagnosing lymphedema in the LEs.

Yamamoto et al. **2013** *Annals of Plastic Surgery* Japan	Evaluate lymph pump function of unaffected and affected limbs, and analyze the relation between lymph transportation and progression of lymphedema.	ICG-L	Quasi-experimental, pre-existing groups comparison AOTA- 2B Pyramid- O3	Lymphedema group: *N* = 12, *M* age = 49.1 yrs, age range = 29-71 yrs, 12 females, 24 legs Control: *N* = 3, *M* age = 49.1yrs, age range = 29-71 yrs, 3 females, 6 legs In: secondary lymphedema from uterine cervical carcinoma, received only compression therapy with elastic stockings Ex: other treatments, i.e. manual lymph drainage, LVA	I: ICG completed on all limbs O: ISL stages based on images, ICG velocity and transit time, and lymphedema dermal backflow stage	With progression of ISL stage, ICG velocity decreased ($p < .001$). As DBF stage progresses, ICG velocity decreases ($p < .001$). ICG travel time to the knee increased with progression of ISL stage ($p < .001$). As DBF stage progressed, ICG travel time to the knee increased ($p < .001$).	Small sample size. Examinations of ICG transit and velocity were cut off at 5 min, limiting observation of more progressed lymphedema.	Velocity of lymph pump function can be evaluated using ICG-L and guide in diagnosing lymphedema.	Shows effectiveness of ICG-L of diagnosing lymphedema in all limbs.
Yoon et al. **2020** *Journal of Plastic,*	To examine the relationship between lymphedema severity	ICG-L LS	Retrospective study AOTA- 3B Pyramid- O2	*N*= 47; 47 females; *M* age = 55.85; age range = 44.34- 66.38	I: ICG-L, LS O: Spearman's correlation was applied	LS severity stage and the ADB stage on ICG-L showed a very strong	Tests were performed two weeks apart. Staging of the two	Practitioners may consider using both ICG-L and LS assessment methods to	ICG-L and LS are complementary in diagnosing lymphedema

Reconstructive & Aesthetic Surgery Korea	stages in LS and on ICG-L in patients with secondary lymphedema after breast cancer.			In: patients who underwent both LS and ICG-L for the evaluation of secondary unilateral lymphedema after breast cancer surgery. Ex: patients who had previous primary lymphedema, history of trauma, metastasis or infection of both arms and patients where staging was impossible due to poor image quality or atypical findings.	to determine the degree of association between variables. Kapa analysis was calculated between scales. The Bland-Altman plot was used to analyze the agreement between different severity scales.	positive correlation and substantial agreement ($p < .001$); both assessments can work together and be complementary for evaluation of lymphedema severity. ICG-L is more sensitive than LS and can detect earlier; LS can be used to better examine deeper lymphatics.	imaging modalities were not performed. The study analyzed two modalities for diagnosing lymphedema, LS and ICG-L. There may be other modalities that perform better that were not analyzed.	increase certainty with lymphedema diagnosis.	. Supports ICG-L's use to diagnose earlier and the use of LS to visualize deeper lymphatics.

Table Summarizing *Descriptive* Evidence

Author Year Journal Country	Purpose of the study; Level of Evidence	Assessment(s)	Sample Description	Assessment Instrument	Outcome	Conclusions	Study Limitations	Implications for Practice	Indicate "Shows effectiveness" or "indirect support for _____ theme"
Medina-Rodriguez et al. **2020** *Medicine* Spain	With ICG, determine relationship between perimetric differences among healthy and affected limbs and the type of fluoroscopic pattern present in limb AOTA- 4 Pyramid- D2	ICG-L	*N* = 19; *M* age = 59; 19 females In: unilateral secondary lymphedema due to breast cancer, undergone axillary lymph node resection, all on waitlist for physical treatment at the Lymphatic Pathology Unit Ex: suspicion or dx of deep vein thrombosis, allergy to	Limb measurements (in cm) of affected and unaffected limbs by physiotherapist and ICG-L of affected limbs.	Wrist level: difference of 2 cm or more between affected and unaffected limb is associated with a worse ICG pattern (stardust or diffuse), 80% probability Elbow level: difference of 4.25cm or less is associated with better ICG pattern (splash or linear), 100% probability Arm level: difference of 2.25 cm or less is	Quantitative data of the perimetric increase in the affected UE is a sign of system malfunction based on ICG fluoroscopic patterns. ICG-L shown to be a comfortable to use and portable method that is advantageous for the examination of the lymphatic system; allows view of lymphatic flow in all directions.	ICG patterns in the proximal UE region were difficult to assess, thus data in this region was limited. Small sample size, and only included females. Participants were recruited from one hospital.	Practitioners should be aware that measurement differences between limbs could indicate presence of lymphedema and should seek a method of obtaining a conclusive diagnosis, such as ICG-L.	Shows indirect support for using ICG-L to assess lymphedema.

			iodine or derivatives.		associated with better (splash or linear) ICG pattern				
Zaleska & Olszewski **2017** *Biophotonics* Poland	Analyze the value of lymphatic imaging methods that are currently used in practice, imaging agents include lipiodol, isotope, and ICG. AOTA - 4 Pyramid - D3	ICG-L LS	*N* = 400; 174 males, 226 females; age range = 20-76 yrs. In: UE and LE limb lymphedema, stage II to IV, duration of 2 to 15 years, post-inflammatory, post-traumatic, post-surgical etiology Ex: BMI > 30, limb lipedema, venous insufficiency and thromboses, inflammation and ulcer	I: Three different imaging agents injected to the hand or the foot. Those agents are: Iodinated oil (lipiodal), isotope labeled aggregated albumin, ICG	100 images for each lymphatic imaging type (Iodinated oil [lipiodal], isotope labeled aggregated albumin, ICG) were analyzed, each were given a clinical lymphedema stage by a practitioner.	ICG-L and LS are both useful methods to establish indicators for conservative therapy. ICG-L does not capture minor lymphatics of 100um diameter. ICG-L depicts lymphatics only to a depth of 15mm [1.5cm]; tissue thickness inches.	Assessments were all conducted by different health care providers prior to study. Not an equal number of images from each agent.	ICG-L is a useful method to visualize lymphatic pathways enabling therapists to use individualized conservative therapy options; limitation is on visualizing deeper levels of lymphatic flow.	Shows direct support for ICG-L to assess lymphedema by viewing lymphatic pathways at a depth of up to 15mm.

Table Summarizing the *Qualitative* Evidence

Author Year Journal Country	Study Objectives	Assessment(s)	Study Design Level of Evidence	Participants: Number, Description, Incl/Excl Criteria	Methods for enhancing rigor	Themes and Results	Study Limitations	Implications for Practice	Indicate "Shows effectiveness" or "indirect support for _____ theme"
Pigott et al. **2021** *Supportive Care in Cancer* Australia	To explore participant's experiences of ICG-L to inform cancer-related lymphedema therapy & understand the impact of knowledge acquired from ICG on lymphedema therapy mgt.	ICG-L	Qualitative phenomenological study AOTA - not rated Pyramid - Q2c	*N* = 17; 9 female, 8 male; *M* age 53.8 yrs.; range = 36-78 yrs; purposive sampling Primary cancer dx: 7 breast, 7 melanoma, 2 Hodgkin's lymphoma, 1 cervical; In: undergoing ICG-L; had secondary cancer-related lymphedema of UE or LE; over 18 y.o., & life expectancy > 12 mon.	Clear description of methodology, first piloted interviews then modified questions, trained interviewer, audio recordings, coded ind. by 3 researchers, addtl. coding with software, peer debriefing, member checking, and audit trial all implemented	Coding and meetings used to gain consensus on emerging themes including: 1.Experience of the ICG procedure 2. New knowledge explained symptoms and tailored treatment 3. Internal impact of knowledge ICG-L is beneficial in all 3 areas for clients and may result in improved self-management	Self-reporting on impact but no long-term follow-up to verify accuracy; objective measures needed to verify impact of changes noted by clients and therapists with gained information. Exclusion criteria not reported	ICG-L is a useful method to definitively diagnose lymphedema and provide individualized tx instead of relying on assumed compensatory drainage pathways. Participants valued the insight they gained from it and reported that it did not cause undue pain. Patients also reported greater determination to perform self-massage and wear compression garments.	Shows effectiveness of ICG-L in diagnosing lymphedema, aiding clients in understanding the disease and self-management, and guiding personalized treatment by the therapist.

Abbreviation Key

Abbreviation	Term	Abbreviation	Term
AAA	abdominal aortic aneurysms	LE	lower extremity
ADB	arm dermal backflow	LS	lymphoscintigraphy
BCT	breast-conserving therapy	LVA	lymphovenous anastomosis
BIS	bioimpedance spectroscopy	MLD	manual lymphatic drainage
CT	computed tomography	MRA	magnetic resonance angiography
C-SFTI	crosswise subcutaneous fat thickness index	MRI	magnetic resonance imaging
DBF	dermal backflow	MRL	magnetic resonance lymphography
ICG	indocyanine green	QoL	quality of life
ICG-L	indocyanine green lymphography	T-SFTI	temporal subcutaneous fat thickness index
ISL	International Society of Lymphology	UE	upper extremity

Summary of Key Findings

Summary of indocyanine green lymphography:

There is a moderate level of evidence that indocyanine green lymphography (ICG-L) allows a definite diagnosis of lymphedema due to observation of dermal backflow patterns (Mihara et al., 2012; Yoon et al., 2020). Time allocation for administration depends on severity of lymphedema with the process taking 30 minutes to 2 hours, but reimaging can take place 12-24 hours later for a more thorough understanding of lymphatic movement during that time period (Medina-Rodriguez et al. 2020; Soga et al., 2021a; Yoon et al., 2020). This method requires specialized equipment including an LED and infrared camera (Akita et al., 2013; Unno et al., 2007). ICG-L has high sensitivity (ranging from .974 to 1) and specificity (ranging from .778 to 1), especially in early stages of lymphedema, compared to all other assessed methods (Akita et al., 2013; Akita et al., 2017; Wiser et al., 2020; Yoon et al., 2020). ICG-L provides valuable insight for clients and practitioners as they can see the lymphatic flow in real-time (Akita et al., 2013; Pigott, 2021; Unno et al., 2007; Yamamoto, 2013).

One descriptive study provides low evidence that ICG-L is a better method to determine surgical treatment over LS for issues relating to lymphedema. (Zaleska & Olszewski, 2017). Two other studies provide moderate evidence that ICG-L can detect posterior regions of edema which is superior to MRL (Medina-Rodgriguez et al., 2020; Soga et al., 2021a). The ICG mixture moves faster than the LS tracer and facilitation of ICG transit with MLD can reduce examination time by specifying the lymphatic drainage pathway and providing additional direct therapeutic guidance to the client and the therapist (Suami et al., 2019). In secondary lymphedema, earlier and less severe dysfunction could be better detected by ICG-L compared to LS (Akita et al., 2013; Unno et al., 2010). As described by the client, ICG-L has minimal pain, discomfort, and invasiveness (Akita et al., 2013; Pigott, 2021; Unno et al., 2007). Additionally, there is a benefit of no radioactive material (Medina-Rodriguez et al., 2020; Mihara et al., 2012; Suami et al., 2019; Unno et al., 2010). One limitation found amongst the evidence is that ICG-L cannot detect lymphatics more than 1.5-2cm deep which indicates that it is not well-suited in

diagnosing lymphedema in obese clients (Mihara et al. 2012; Unno et al., 2010; Zaleska & Olszewski, 2017).

Summary of lymphoscintigraphy:

Lymphoscintigraphy (LS) is a method for diagnosing lymphedema by using radiotracers (Technetium-99m sulfur-colloid) that are injected, then imaged by a gamma camera (Akita et al., 2013). This method can be performed without discomfort and allows a definite diagnosis of lymphedema due to the observation of dermal backflow (Mihara et al., 2012; Unno et al., 2007; Yoon et al., 2020). LS enables visualization of the lymphatics at a deeper level than ICG-L; this is especially useful for clients who are obese (Mihara et al. 2012; Unno et al., 2010; Zaleska & Olszewski, 2017). LS severity stage and the ADB stage on ICG-L showed a very strong positive correlation and substantial agreement; both assessments can work together and can be used in a lymphedema severity evaluation (Yoon et al., 2020). LS has high sensitivity (.972 secondary; .974 primary) and specificity (.548 secondary; .778 primary) for the diagnosis of lymphedema (Akita et al., 2013; Unno et al., 2007) but not as high as ICG-L, especially in earlier stages of disease progression (Mihara et al., 2012). LS demonstrates difficulty in evaluating lymphatic vessels in the lateral region of the body due to only acquiring images in the anteroposterior direction where clients must remain supine during imaging , versus the possibility of circumferential imaging with ICG-L (Mihara et al., 2012; Unno et al., 2010).

Summary of computed tomography imaging:

Computed tomography imaging (CT) is useful for visualizing and monitoring overgrowth of fibrous tissue with the progression of lymphedema (Mihara et al., 2012). One outcome study provides low evidence in using CT scans to diagnose the presence of lymphedema in early stages by checking the change in the thickness of subcutaneous fat (Akita et al., 2017). The study also determined that it is a less optimal way to assess or guide treatment of lymphedema compared to ICG-L or LS due to (1) increased exposure to radiation compared to other methods and (2) the lack

of sensitivity .33; (Akita et al., 2017; Mihara et al., 2012). It also cannot be used to obtain real-time results (Mihara et al., 2012). One study suggests that CT shows characteristic features related to the skin changes associated with lymphedema which can only suggest abnormalities of the lymphatics, not diagnose lymphedema (Unno et al., 2007).

Summary of bioimpedance spectroscopy :

Bioimpedance spectroscopy (BIS) is a simple, non-invasive method that measures quantity of extracellular fluid by measuring tissue resistance to the flow of an electric current (Qin et al., 2018). This method is best used to track treatment efficacy and evaluate postoperative changes (Qin et al., 2018). One study indicated L-Dex scores were highly sensitive (.912) and had a high positive predictive value for diagnosing lymphedema in patients with a volume excess of 10% or more (Wiser et al., 2020). When using BIS it is important to consider that fluid manipulation by external factors including compression, temperature, and daily activities can affect BIS results (Qin et al., 2018). When comparing BIS to ICG-L results for the same clients, high specificity (100%) and low sensitivity (64%) at 3SD indicates that it is not sensitive enough to confidently rule out lymphedema if the result is negative (Qin et al., 2018).

Summary of magnetic resonance lymphography:

Using the method of magnetic resonance lymphography (MRL) to diagnose lymphedema has been found to have limited usefulness. Two quantitative studies provide moderate evidence that MRL provides visualization of preclinical lymphatic alteration and may detect early presence of lymphedema (Soga et al., 2021). This method has a short duration of administration, with images acquired up to 30 minutes after contrast administration (Soga et al., 2021a). With this method lymphatic visualization is best seen in distal limbs due to the contrast media (Soga et al., 2021a; Soga et al., 2021b). This method is best used for visualizing alterations in lymphatic flow and allows evaluation of extra-lymphatic soft tissues to assist in guiding treatment (Soga et al., 2021a; Soga et al., 2021b). This method also presents

different imaging patterns than ICG-L with seven MRL-specific patterns that significantly correlated with ISL stage and duration of lymphedema. While this method is usually "well-tolerated" by patients, some pain was reported at the injection site (Soga et al., 2021a). In addition, MRL cannot be used to obtain real-time results in lymphatic fluid flow (Mihara et al., 2012). Lastly, while there is evidence that indicates MRL may be useful in early diagnosis of lymphedema it shows characteristic features related to the skin changes associated with lymphedema which can only suggest abnormalities of the lymphatics, not diagnose lymphedema (Unno et al., 2007).

Summary of limb perometer measurement (volume):

Limb perometer measurements differ from limb circumference measurements by focusing on measuring volume rather than circumference. There are a variety of methods being employed to obtain measurements for volume and circumference, but the same methods should be used consistently over time – perometer measurements are not interchangeable with circumferential measurements (Wiser et al., 2020). When using these measurements it is best used longitudinally to assess changes in affected limb over time (Wiser et al., 2020). Limb perometer was found to be more effective than circumference measurements (Wiser et al., 2020). Therefore, when using this method it is important to be aware of the limitations and best ways to use it. Limb perometer measurements should be used to monitor lymphedema on a regular basis due to its ease of use and ability to monitor change over time.

Summary of limb circumference measurements:

Limb circumference measurements can be useful in diagnosing lymphedema by detecting abnormal conditions in lymphatic circulation before edema becomes clinically evident (Yamamoto et al., 2011). It was found to be superior in lymphedema diagnosis compared to BIS (Qin et al., 2018). However, there are some limitations to using limb circumference measurements as a tool to diagnosing lymphedema. Additionally, circumference measurements alone tend to under-diagnose and

underestimate the degree of lymphedema (Wiser et al., 2020). While limb circumference measurements can be used in the process of diagnosing lymphedema, it should be used in addition to other diagnosing tools and the practitioner should be aware of the potential underestimated results that it may produce. It is more effective at a later stage rather than being used for early detection.

Implications for Consumers

The consumers for this research are the clients who are going through the process of receiving a diagnosis of and treatment for lymphedema. The client population being researched were individuals who were suspected of having lymphedema and seeking treatment for this condition.

Our research on indocyanine green lymphography indicates with moderate confidence that this assessment and can be used to tailor treatment for clients and will help them better understand their unique lymphatic flow leading to improved self-management of their lymphedema (Akita et al., 2013; Pigott, 2021; Unno, et al., 2007; Yamamoto, 2013). Clients can advocate for themselves by discussing this assessment with their doctor and requesting it, if not already offered or recommended. Clients will need to consider time requirements, invasiveness, utility of information obtained, and how it will impact their care and prognosis.

Implications for Practitioners

Occupational therapists can apply this information to their practice by using the findings to guide their diagnosing and treatment methods, while also better educating clients on their condition. It can be used to inform physicians about assessments they may not be aware of and help occupational therapists lobby to request them for clients suspected of having, or being at risk for, lymphedema. This could allow occupational therapists and certified lymphedema therapists to begin treating clients earlier in the disease progression, which should have a positive impact on prognosis and quality of life for the client. The assessment of lymphedema is complex and multiple methods are able to provide an assortment of information that could be useful to the client, practitioner, and other members of the care team. The types of assessments that a practitioner

could advise the client to request from their physician depend on multiple client factors including likely stage of the disease, if it is primary or secondary lymphedema, body-mass index, time available for testing, willingness to be exposed to radiotracers, insurance coverage, availability of imaging modalities in their region, whether there is a control limb available, and advancement of fibrous tissue growth.

The results of this project suggest with moderate confidence that ICG-L is superior to lymphoscintigraphy, computed tomography (CT), bioimpedance spectroscopy (BIS), magnetic resonance lymphography (MRL), limb perometer measurement (volume), and limb circumference measurements in the sensitivity and specificity of diagnosing lymphedema (Akita et al., 2013; Akita et al., 2027; Wiser et al., 2020; Yoon et al., 2020). It allows the client and practitioner to visualize abnormalities in the lymphatic system in real-time (Akita et al., 2013; Pigott, 2021; Unno, 2007; Yamamoto, 2013). It is more time consuming but provides valuable information that allows the practitioner to specifically tailor treatment to that client and therefore, given that it matches all clients factors, it should be utilized when diagnosing and treating lymphedema.

Implications for Researchers

Additional research regarding ICG-L and other forms of lymphedema assessments must be conducted for stronger evidence of efficacy. Seven studies were found where ICG-L was directly compared with other lymphedema assessment methods (Akita et al., 2013; Mihara et al., 2012; Suami et al., 2019; Unno et al., 2010; Wiser et al., 2020; Yoon et al., 2020; Zaleska & Olszewski, 2017) yet results were not always consistent. Additionally, there is not currently a standardized method to administer ICG-L, which has the potential to confound research results. Among the researched articles there were a variety of ways that ICG-L was administered including differences in how often imaging was completed, whether there was MLD or massaging after injection, use of compression garments, and differences in positioning the limb (Akita et al., 2013, Akita et al., 2017, Pigott et al., 2021, Qin et al. 2018, Soga et al., 2021a, Zaleska & Olszewski, 2017). It was also

common to see different administration of other lymphedema diagnosing methods as well, including manual measurements or placement of electrodes for BIS. Thus it is also important to note the inconsistencies among the comparison diagnostic methods which affected the authors' ability to draw conclusions (Qin et al., 2018).

Practitioners need researchers to conduct studies that will help provide clear evidence about the effectiveness of ICG-L in comparison with other assessments. This will allow practitioners and consumers to advocate for the best assessment for diagnosing and later treating lymphedema.

A major component of whether a client gets one of these assessments is cost and whether their insurance will pay for it. These studies were completed in the United States, Japan, Poland, Australia, Spain, and Korea which all have varying healthcare systems. There is a gap in the literature regarding cost effectiveness of the presented assessments when it comes to both near-term and long-term treatment.

Bottom Line for Occupational Therapy Practice/ Recommendations for Best Practice

There is a growing body of evidence supporting the use of ICG-L as an assessment method for lymphedema as well as a method for guiding treatment during occupational therapy sessions. Occupational therapy is client-centered and emphasizes client education to ensure they have a better understanding of their condition which can lead to improved self-management (Akita et al., 2013; Pigott et al., 2021; Unno et al., 2007; Yamamoto et al., 2013). There is ample evidence that ICG-L is a useful method for early detection of lymphedema and allows for personalized treatment of lymphedema. Therefore, it is important for ICG-L to be considered as an initial diagnosing method by physicians. In order for this to occur, an effective method for providing this information to the diagnosing physician must be devised. Early detection of lymphedema can allow occupational therapists to start interventions earlier, therefore potentially reducing the amount of rehabilitation the client would need, improve their quality of life, and reduce costs in the long-term. In addition to

early interventions, education and prevention strategies (i.e., MLD, range of motion activities, compression garments) could be implemented earlier.

Involvement Plan

Our group met with the project collaborator, Kate Long OTR/L, CLT, on 11/22/21 to discuss the results of our research project on the question of how effective indocyanine green lymphography (ICG-L) is in diagnosing and guiding treatment of lymphedema in adult clients compared to other assessment methods. The search strategy and results were reviewed along with the PRISMA chart, CAT table format, and a summary of the findings. Ms. Long asked clarifying questions then requested that we use the research to assemble an informational product in the form of a pamphlet that describes ICG-L along with how it's distinguished from other lymphedema assessment methods. She wanted to provide it to referring physicians, and the nuclear medicine department, in order to educate them on the merits of the assessment method. Her overarching goal is to one day be able to request ICG-L for a client and use the results to guide individualized treatment.

Context

Ms. Long currently spends the majority of her work time at an outpatient clinic working with lymphedema clients at Legacy Salmon Creek Medical Center and mainly utilizes other assessment methods including circumferential measurement, which she is able to administer herself, and lymphoscintigraphy, which is accessible through other specialists. The research shows that ICG-L has a relative advantage compared to other methods when it comes to earlier diagnosing, visualizing real-time lymphatic flow, a lack of radiation exposure, and for educating clients on how their lymphatic system works, which may lead to better home care adherence. It is not a particularly complex assessment, can be observed in real-time by multiple people, has low risk, and provides an abundance of knowledge for the clients, doctors, and practitioners.

Ms. Long is currently the only certified lymphedema therapist employed in the rehabilitation center at Legacy Salmon Creek Medical Center, and is the subject matter expert in treating clients suspected of having lymphedema, therefore, it is up to her to advocate for the most beneficial treatment methods for this disease to her superiors and referring physicians. Our pamphlet can assist with introducing the assessment method, provide references to evidence-based research, and adapt knowledge of their clinic setting in order to promote understanding and the likelihood of clients obtaining this type of lymphatic imaging.

Some facilitators to the knowledge translation process include staff at Ms. Long's facility, including two occupational therapists and approximately 12 physical therapists who are willing to learn more about this newer assessment method. There are also change agents available for consultation, including Dr. Wei Chen out of the Cleveland Clinic, who regularly lobbies for the use of ICG-L and can help with the adoption process. Ms. Long also works intermittently in the acute care clinic at Legacy Salmon Creek Medical Center and has access to many of the physicians who could refer clients for this test once they become familiar with the ICG-L diagnostic tool. Barriers to implementation include cost, lack of time and motivation for referring physicians to learn about ICG-L, lack of client knowledge on ICG-L, lack of ICG-L knowledge by other medical personnel and staff, and potentially the lack of access to the specialized camera needed for imaging.

Product and Target Dates

To assist Ms. Long in meeting her goals an informational pamphlet was created to inform referring physicians about ICG-L (see Appendix A). This pamphlet includes information regarding what ICG-L is and the benefits and limitations of using it to diagnose lymphedema and its use in guiding personalized treatment in real time.. The table below provides steps used to create the product and the date each step was achieved.

Steps to Achieve Product	Date Met
Draft of concise ICG-L summary	2/2/22
Draft of concise ICG-L PROS and CONS	2/2/22
Draft of concise research summary or bullet points	2/2/22
Draft of complete brochure	2/3/22
Meeting with chair to discuss the pamphlet	2/10/22
Revise pamphlet after feedback	2/23/22
Provide collaborator with pamphlet	2/28/22
Survey review and revision with chair	3/23/22
Provide survey to collaborator to evaluate the effectiveness of pamphlet	3/24/22
Receive and analyze survey	4/4/22

Outcomes and Effectiveness

In March, we provided Ms. Long with a survey via Google Forms to evaluate the usefulness of the pamphlet in informing physicians about the use of ICG-L to diagnose and guide treatment for people suspected of having lymphedema (see Appendix B). She shared the survey link with other therapists certified in lymphatic treatment, who reviewed the pamphlet to obtain their feedback as well. The survey included questions regarding the effectiveness of the pamphlet and whether the information would affect their decision to pursue the use of ICG-L. Five questions were rated on a 5-point Likert scale, 1 = strongly disagree to 5 = strongly agree. Other questions were related to pamphlet appearance, clarity, substance, and utility. Additionally, areas for written feedback were available for respondents to provide open-ended feedback on how to improve the contents of the pamphlet. This survey, along with feedback provided via email, provided useful information toward improving the effectiveness of the pamphlet.

Once information was collected from the survey, responses were reviewed, changes were made where merited, and a revised pamphlet was created (see Appendix C). This included small grammatical changes, clarifying language, and font color changes. One participant responded with, "I think the coloring scheme can be a bit hard to distinguish," and we responded by changing the font color in some areas that were difficult to read to improve readability. Overall, we received positive feedback from our collaborator and four additional certified lymphatic therapists. Another participant commented, "I love the left hand side of the font. Very direct and to the point in an easy to read format." Sixty percent of the participants responded with "Agree" and 40 % responded with "Strongly Agree" to the question addressing the product's appropriateness to be given to physicians, indicating we met our goal of obtaining information regarding the utility of various lymphedema assessment methods and translating that knowledge into a useful product that can be shared in order to ultimately provide better care to clients living with the disease.

Evaluation of the Overall Process of Project

This project presented an opportunity to conduct research in a specialized field of occupational therapy. Our group was challenged with understanding the details of lymphedema assessment methods, including ICG-L, due to our limited knowledge in the field of lymphedema therapy. However, it allowed us the opportunity of diving into this area to aid our understanding of the value of these diagnostic tools and the positive impact they could have for patients with lymphedema. Examining research articles was difficult at times due to the unfamiliar language and lack of articles directly comparing ICG-L to other assessment methods. Our clinician collaborator and mentors were very helpful sharing their knowledge of lymphedema, sharing resources, and helping us further understand what this diagnosis and treatment process entails. Our clinician collaborator also shared insight as to why there is a lack of research on this assessment method and the barriers ICG-L faces in order to become a more common component of lymphedema practice.

The knowledge translation process was both difficult and rewarding. The realization that practitioners would be reading our pamphlet and potentially using it to guide their medical practice was nerve-racking. However, our ability to help inform other practitioners about an assessment method that could help a patient throughout their diagnosis and treatment of lymphedema was very rewarding. Being able to receive feedback on our pamphlet was insightful and helped with edits to improve our product.

Through this project we were able to assess ICG-L and a variety of other assessment methods for diagnosing lymphedema. We also were able to see the benefit that ICG-L has in the efficacy of diagnosing lymphedema and helping patients better understand their diagnosis. We are very proud of all the work we have done and the final product we have created.

Recommendations for the Future

We recommend that follow-on projects further examine the use of ICG-L in other parts of the body, complete a cost-benefit analysis, obtain information on insurance coverage of various methods, and attempt to uncover additional research that more definitively compares lymphedema assessment methods. Our collaborator shared that she has clients who are suspected of having lymphedema in their neck and groin and this research project only covered assessment of limbs. Our collaborator indicated that cost could be a barrier to obtaining ICG-L, but without more research it is unknown what the average cost is to potential clients. It could also be beneficial to obtain more qualitative research on people living with lymphedema and how ICG-L use with real-time treatment via manual lymph drainage has impacted their self-management and experience with the disease. This research mostly focused on the ability to diagnose and track changes in disease progression but did omit much detail on how it is used in treatment, therefore future studies could include additional information in that area. It could also be beneficial to include a referring

physician as a collaborator to better understand their questions and needs for referring clients for ICG-L.

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Appendix A

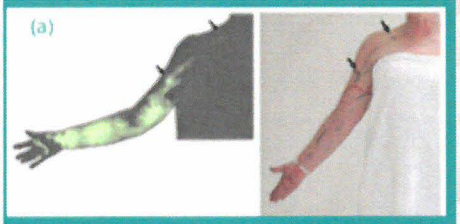
Initial Pamphlet

What is ICG lymphography?

Indocyanine green (ICG) lymphography is a method to visualize lymphatic flow in real time. A small amount of ICG florescent dye is injected near the affected site then taken up by the lymphatic system. A near infrared camera system reveals lymphatic flow patterns which can be manipulated and observed for changes. Results are visible to the physician, lymphatic therapist, and client immediately and are used to guide personalized treatment.

The ICG dye binds to plasma proteins that travel through lymphatic channels, is water soluble, and has been safely used in surgeries since the 1950s.

Assessment of the same patient using ICG lymphography (a), compared to imaging obtained from lymphoscintigraphy (b)[1]



Benefits of using ICG lymphography compared to other assessment methods:

- Highly sensitive for earlier detection (0.92)[2]
- Safe- no radiation exposure[3]
- Able to visualize realtime lymphatic flow[4]
- Patterns reveal lymphedema severity[4]
- Improve patient self-management and adherence to home programs[5]
- Can be covered by most insurances

Limitations

- 2-3cm depth[6]
- Possible allergic reaction to dye
- Requires injection

Appendix B

Pamphlet Survey

1. 1. The overall appearance of the pamphlet is appropriate for its purpose.

   Mark only one oval.

	1	2	3	4	5	
Strongly disagree	◯	◯	◯	◯	◯	Strongly agree

2. 2. The size and font of the letters make it easy to read.

   Mark only one oval.

	1	2	3	4	5	
Strongly disagree	◯	◯	◯	◯	◯	Strongly agree

3. 3. The overall content of the pamphlet is appropriate for its purpose of providing an introduction to ICG-lymphography and its use in diagnosing/treating lymphedema.

   Mark only one oval.

	1	2	3	4	5	
Strongly disagree	◯	◯	◯	◯	◯	Strongly agree

4. 4. Is there anything else you wish the pamphlet covered on ICG-lymphography or lymphatic imaging?

5. 5. The content of the pamphlet is easy to understand as presented.

   Mark only one oval.

	1	2	3	4	5	
Strongly disagree	◯	◯	◯	◯	◯	Strongly agree

6. 6. If you find some information to be unclear, please specify that here.

7. 7. This pamphlet provides the appropriate amount of information to providers who would refer patients suspected of having lymphedema for lymphatic imaging.

Mark only one oval.

	1	2	3	4	5	
Strongly disagree	◯	◯	◯	◯	◯	Strongly agree

8. 8. Were you aware of ICG-lymphography's use in diagnosing lymphedema prior to reading this pamphlet?

Mark only one oval.

- ◯ Yes
- ◯ Somewhat
- ◯ No

9. 9. Were you aware of ICG-lymphography's use in treating lymphedema prior to reading this pamphlet?

Mark only one oval.

- ◯ Yes
- ◯ Somewhat
- ◯ No

10. 10. After reading the pamphlet, are you more or less likely to pursue ICG-lymphography for patients suspected of having lymphedema?

Mark only one oval.

	1	2	3	
Less likely	◯	◯	◯	More likely

11. 11. Please provide any other comments on how to improve the contents of this pamphlet.

Appendix C

Revised Pamphlet

What is ICG lymphography?

Indocyanine green (ICG) lymphography is a method to visualize lymphatic flow in real time. A small amount of ICG florescent dye is injected near the affected site then absorbed by the lymphatic system. A near infrared camera system reveals lymphatic flow patterns which can be manipulated and observed for changes. Results are visible to the physician, lymphatic therapist, and client immediately and are used to guide personalized treatment.

The ICG dye is water soluble, and has been safely used in surgeries since the 1950s.

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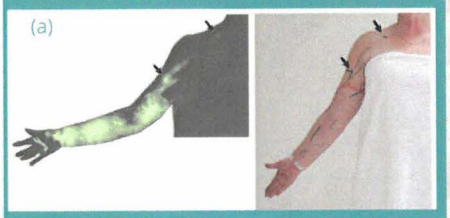

Benefits of using ICG lymphography compared to other assessment methods:

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- Safe- no radiation exposure[3]
- Able to visualize realtime lymphatic flow[4]
- Patterns reveal lymphedema severity[4]
- Improve patient self-management and adherence to home programs[5]
- Can be covered by most insurances

Limitations

- 2-3cm depth[6]
- Possible allergic reaction to dye
- Requires injection

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Name: Jasmin Cardenas Date: 5/6/2022

Jasmin Cardenas

Signature of MSOT Student

Name: Leah Parsons Date: 5/6/2022

Leah Parsons

Signature of OTD Student

Name: Catherine Daggi Date: 5/6/2022

Catherine Daggi

Signature of OTD Student