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"QUALITY OF LIFE OUTCOMES AFTER OPERATIVE MANAGEMENT OF PRIMARY AND SECONDARY LYMPHOEDEMA – A SYSTEMATIC REVIEW"

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SUMMARY

Background: Lymphoedema is an incurable and progressive disease that affects not only physical function but overall quality of life. Surgical treatment options for the management of Lymphoedema are being increasingly performed. This study aims to review post-operative health-related quality of life (HRQOL) following surgical treatment of Lymphoedema.

Methods: A systematic search of the PubMed and Medline databases was performed from the date of their inception until September 2018 to evaluate HRQOL following different surgical options for the treatment of Lymphoedema.

Results: One hundred and thirteen articles were identified. Twenty-one articles were included in the final review, comprising a total of 736 patients. HRQOL improvements appear to be sustained for at least six to 12 months post-operatively. In particular, major benefits were noted in the domains based around physical functioning. Patient satisfaction similarly mirrors HRQOL improvements, following an initial dip in the immediate post-operative period.

Conclusion: All surgical treatment modalities for the management of Lymphoedema confer significant HRQOL improvements across a diverse range of health domains, with this critical outcome of surgery an important pre-operative consideration. Recommendations for ongoing research are suggested.

INTRODUCTION

Lymphoedema, the accumulation of lymphatic fluid in areas of poorly drained interstitium and its inflammatory sequelae [1], presents its sufferers with a chronic and progressive deterioration in both their function and overall quality of life. Lymphoedema affects approximately 140 to 200 million people worldwide[2]. On a global scale, especially in sub-tropical areas of the world, filarial disease is the most common cause of secondary lymphoedema [3], however in developed countries, lymphoedema most frequently arises following oncologic resection and adjuvant therapy in malignancy[4]. It is estimated that more than 8000 patients each year are expected to develop secondary lymphoedema in the course cancer in Australia alone each year[5].

Despite the lack of a definitive treatment option, surgical and non-surgical treatments for the symptomatic management of lymphoedema have been developed[6-9]. Conservative measures often involve some form of compressive garment and physiotherapy, including manual lymphatic drainage or complete decongestive therapy, in addition to basic skin care. The current options for surgical management are divided into either ablative or physiologically restorative procedures. Ablative procedures involve the direct removal of excess tissues, directly reducing bulk to improve function and QOL. Early ablative procedures included Charles procedure, which involve radical excisional debulking and re-coverage with skin grafting[10]. More recently (1970s onward) liposuction or suction-assisted lipectomy have become increasing popular as minimally invasive debulking procedures. Physiological procedures aim to improve symptoms through the reconstruction of a functional lymphatic system through microsurgery. Among these, the lymphaticovenular/venous anastomosis (LVA) and vascularised lymph node transfer have gained acceptance among the lymphoedema surgical community[11].

Technical quantitative measures of surgical success following these procedures are subjectively reported by the surgical practitioner as excellent, with the majority of literature demonstrating some

post-operative volume and circumferential reductions[12]. However, such traditional indicators of surgical outcome may not always reflect a patient's own post-operative experience[13]. Globally, there has been a paradigm shift towards a more holistic assessment of physical, functional, emotional and mental health wellbeing in determining surgical success[14]. The evaluation of Health-Related Quality of Life (HRQOL) in the immediate and long-term post-operative setting has thus become a key indicator of surgical success. In particular, given the broad health implications of lymphoedema and symptom-directed surgical options[15], a multi-dimensional assessment is crucial to properly evaluating a treatment's efficacy.

The goal of this study was to investigate, in patients with either primary or secondary lymphoedema, the effect of surgical interventions as compared to a non-operative control group on HRQOL throughout the literature. Therefore, the authors conducted a systematic review focusing on generic and disease-specific HRQOL changes following the use of the operative treatment options for lymphoedema.

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and structured around existing recommended guidelines. A PRISMA checklist has been incorporated.

Definition and measurement of HRQOL in lymphoedema

Health Related Quality of Life (HRQOL) is a multi-dimensional concept that encapsulates an individual's physical, emotional, mental and social functioning status[16]. This assessment places emphasis on a patient's subjective perception of their health status through key-related questions. Cumulatively, these domains enable a comprehensive evaluation of the broad health-related impacts

of lymphoedema and its treatment. A number of validated questionnaires have been developed to reliably measure all HRQOL domains.

Disease-specific HRQOL questionnaires are those tailored to more accurately reflect a patient's experience with respect to lymphoedema and has the advantage of detecting even subtle effects from interventions. Disease-specific or Region Specific scoring systems used in the included studies were Modified Blepharoplasty Outcomes Evaluation (MBOE)[17], Derriford Appearance Scale (DAS-59)[18], Upper Limb Lymphoedema-27 Questionnaire (ULL27)[19], A quality of life measure for limb lymphoedema (LYMQOL)[20], Lymphoedema Quality of life Inventory (LyQLI)[21], Lymphoedema Life-Impact Scale (LLIS)[22], Lymphoedema International Classification of Functioning (Lymph-ICF)[23], Visual Analogue Scale pain score (VAS)[24] and Lower Extremity Functional Scale (LEFS)[25].

Generic HRQOL questionnaires allows for comparison of HRQOL in other diseases, chronic conditions and against the general population, but are regarded as less sensitive for measuring population-specific changes following a particular treatment or therapy. Generic scoring systems used in the included studies were Medical Outcomes 36-Item Short-Form Survey (SF-36)[26], a modified 12-item short form health survey (SF-12)[27], Hospital Anxiety and Depression Score (HADS)[28], Nottingham Health Profile (NHP)[29], Patient Specific Functional Scale (PSFS)[30]

A summary of HRQOL instruments used in included studies is found in Table 1.

Eligibility Criteria

Study types that were considered appropriate for inclusion included randomized controlled trials, quasi-randomized studies, controlled studies and two-arm cohort studies. If a study reported clinically relevant outcomes as outlined by our objectives, they were included regardless of study type of methodological outcomes. Only clinical articles written in the English language were considered for inclusion. Study inclusion criteria were 1) any form of lymphoedema as the primary indication for

surgery 3) any form of surgical management for lymphoedema 4), a validated HRQOL tool, either generic or disease-specific, with data adequately reported and 5) comparisons with pre-operative QOL status or appropriate control.

Literature Search and Information Sources

The primary literature search was conducted using a MeSH (Medical Subject Heading) keyword search of the following databases up until November 30th 2020 with no restriction on date of publication in order to identify all relevant studies:

- MEDLINE (1950 to 15th of December 2020);
- EMBASE (1947 to 15th of December 2020);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 15th of December 2020);
- ClinicalTrials.gov (to 15th of December 2020)

This search strategy is described in our PRISMA flow diagram (Fig 1).

Additional manual searches of the reference lists of included studies, textbooks as well as other review articles for relevant studies was undertaken. The number of articles identified from this additional search is also described in our PRISMA flow diagram

Study Selection

Articles' abstracts and/or complete articles were then screened by the primary reviewer in accordance with existing systematic review guidelines[31, 32]. Articles were assessed for suitability and excluded if they did not meet the aforementioned inclusion criteria. If the abstract did not contain adequate information to determine eligibility, a secondary screen was performed following initial data extraction. Disagreements regarding suitability for inclusion and data extraction were resolved by discussion between the two reviewers until a consensus was met.

Data Items and Collection Process

Data variables were pre-determined and extraction was performed via the use of a structured data collection form. These variables included general patient demographics, duration of lymphoedema, stage of lymphoedema, follow-up period, type of surgery, validated HRQOL scoring system used, pre- and post-operative HRQOL scores and patient satisfaction. Variables were grouped according to the study's use of either a generic or disease-specific HRQOL instrument. All included studies were assessed for both study quality and HRQOL results (Table 2).

Risk of Bias

The risk of bias in individual studies was assessed using the U.S Preventive Services Task Force Quality Rating Criteria, with studies rated as 'good', 'fair' or 'poor' according to pre-determined criteria[33]. Two reviewers independently rated the quality of included studies with subsequent synthesis of ratings. Further quality assessment was evaluated through study design, follow-up consistency and level of evidence as outlined by the Agency for Healthcare Research and Quality (AHRQ)[34].

RESULTS

Study Selection

Twenty-five studies were selected for review following the search strategy outlined in the PRISMA flow diagram. Complete results of the included articles are provided in Table 2.[14, 35-58]

Assessment of Bias

Strength of evidence in included studies was systematically assessed in this review. Reporting bias was minimized through a comprehensive search of the literature for all eligible studies, however, this search was limited by the requirement of English articles. Furthermore, in studies assessing HRQOL, poor responsiveness among patients may arise as a result of worsening of the condition and functional

impairment, which may alter true HRQOL results. Similarly, surgeon preference with regards to choice of treatment for individuals patients introduces a degree of selection bias which cannot be controlled for. Follow-up consistency and study design are described below. In accordance with the AHRQ, the majority studies identified were graded evidence level II with four level I studies. Overall quality of studies was assessed using the *US Preventive Services Task Force Quality Rating Criteria* given the varied study designs, with most studies meeting "fair" or "good" study quality.

Study Characteristics

Lymphoedema surgery was performed in a total of 861 patients with a primary diagnosis of lymphoedema. Two hundred and six of these underwent liposuction with or without additional compression therapy; two hundred and twelve of these underwent either vascularized lymph node transfer alone or in combination with a free flap or scar release with fat graft; one hundred and eight five of these underwent lymphaticovenular anastomosis; two hundred and twelve underwent lymphatic vessel transplantation and twenty-six patients underwent an excisional lymphoedema procedure, such as a Homan's or Charles procedure. Studies reviewed included two randomised trial[36, 45], seventeen prospective studies[14, 37-42, 46, 47, 50, 51, 54-56], with one of these a combination prospective and retrospective study in which only the prospective cohort met inclusion criteria[50], five retrospective observational studies[48, 49, 57, 58] and one cross-sectional survey[44]. Twenty three studies assessed treatment outcomes in extremity lymphoedema, either upper limb alone or both upper limb and lower limb, with only two studies assessing treatment of submental lymphoedema[36, 38] and only one study describing management of genital lymphoedema[50].

The follow-up period varied from as early as one month to five years with follow-up occurring through outpatient clinics, mailout surveys, telephone surveys, online surveys or retrospective hospital chart review of a prospectively maintained databases. In accordance with existing guidelines, a response rate greater than 85% is considered ideal for a study assessing a post-treatment outcome[59].

Follow-up consistency was reasonable across the study population, with only five studies[42, 46, 48, 49, 58] not reaching this ideal value.

Patient Characteristics

The typical lymphoedema patient was on average 55.5 years old at the time of surgery (ranging from 18 to 89) with an approximate female-to-male ratio of 2:1 across the entire study population. Lymphoedema aetiology comprised both primary and secondary causes. Over 70% of cases occurred secondary to breast cancer, followed by head and neck cancer, genitourinary cancer and then lastly congenital causes. Not all studies described the stage of lymphoedema and the classification system used was inconsistent across all studies, reporting severity using either the Campisi or International Society of Lymphology (ISL) classification systems[60, 61]. All patients in included studies appeared to be in Stage three or less of the ISL classification system. The average pre-operative lymphoedema duration was 64 months across the study cohort.

HRQOL

A complete set of results for the included studies with regards to HRQOL is summarised in Table 2. With limited numbers when categorising HRQOL benefits based upon procedure type or patient characteristics such as lymphoedema severity and location, it was decided to group patients by the study's use of either generic or disease-specific HRQOL instrument alone as long as a fundamental diagnosis of lymphoedema had been made as per the inclusion criteria.

Generic HRQOL Instruments

Generic HRQOL scoring systems were utilised in four studies[39, 48, 50, 55, 58]. With the use of SF-36 score, PSFS, modified SF-12 and the NHP, all QOL subdomains were equal to or better than pre-operatively levels in four studies over a one-year follow-up[37, 39, 48, 50]. Major benefits were noted in primarily the physical activity [50], physical functioning, bodily pain, vitality, social functioning and mental health[48] domains. Notably, at 1-month post liposuction there was an initial decrease in role physical, bodily pain and role emotional domains attributed to immediate post-operative

discomfort, with subsequent improvements at the 3- and 6-month follow-up[48]. Studies utilising HADS to assess psychological wellbeing demonstrated a significant reduction in anxiety scores compared with pre-operative baseline, however no significant change with depression scores[39, 55]. One study examined the disease-specific change in the burden of conservative therapy following lymphatic vessel transplantation via the modified SF-12, showing significant improvements in the upper limb and insignificant improvements in lower limb patients[58].

Disease-specific or region-specific HRQOL instruments

Disease-specific or region-specific HRQOL scoring systems were utilised in 16 studies[12, 33-43, 45, 47, 48, 50]. LYMQOL scores showed significantly increased overall perceived QOL in nine studies, with significant reduction in all four assessed domains, compared to pre-operative QOL as early as 1-month post-intervention[40, 42, 47, 51, 54, 56]. Similarly, four studies utilising VAS scores showed improvement at 1-year follow-up compared to pre-operative QOL, with two of these studies additionally demonstrating statistically significant increased HRQOL when compared with a control group undergoing only conservative and non-operative treatments[39, 45, 46, 55]. Physical, Psychological, Social, Practical and Functional/Activities of Daily Living (ADL)-type domains in the LyQLI, LLIS, ULL27, LYMPH-ICF, LEFS HRQOL scales demonstrated significant benefits following surgical intervention at follow-up ranging from one month to 64 months[14, 41, 44, 49, 57]. In addition, MBOE and DAS-59 scoring systems were used in two studies[36, 38], with overall summation of HRQOL demonstrating statistically significant improvements compared to a matched control group or pre-operative outcomes at six months post-operatively.

Patient Satisfaction

Six studies evaluated patient satisfaction post-operatively and their views towards the operation[40, 44, 49, 50, 54, 57]. Subjective reports of ‘high levels of satisfaction’ among assessed patients were reported in four studies[40, 44, 54, 57]. Another study reported a satisfaction rate of up to 70% at a median follow-up time period of five years following surgical reduction of lymphoedema, with most of these patients having had documented reduction in limb size[50]. Similarly, another study reported

patient satisfaction to be directly correlated with both HRQOL and volume reduction. In this retrospective study, reduction in volume was noted to be 45%, 28% and then 46% at three, six and 12 months respectively, with satisfaction mirroring this trend[49]. This satisfaction and HRQOL trend was attributed to a commonly reported reversal in function following an initial improvement with increasing activity.

Predictors of post-operative HRQOL

Five studies reported on factors that may influence HRQOL post-operatively[41, 44, 51, 54, 56]. *De Brucker et al.* identified no significant relationship between breast-cancer related lymphoedema risk factors, including BMI greater than 25, smoking, age greater than 50 and greater than 12 months duration of lymphoedema, and HRQOL as reported on the ULL27 scoring system. In contrast, another study demonstrated that in patients with low pre-operative QOL scores, post-operative improvement and QOL outcomes would be less significant and impactful[41]. Location of lymphoedema in two studies, both of which assessed surgical intervention in upper and lower limb lymphoedema, was found to influence the functional domain in the LYMQOL scale, with increased and earlier improvements seen in upper limb surgery compared with lower limb[51, 54]. Similarly, the impact of lymphatic vessel transplantation demonstrated a greater improvement in the physiological subdomain of the modified SF-12 in UL compared with LL candidates[58].

Type of surgery and HRQOL

Maruccia et al. presented the only study comparing a combination of two different surgical techniques, with vascularized lymph node transfer undertaken alone or with a concurrent scar release with fat grafting. All domains in the LYMQOL scale demonstrated significantly better scores in a combination approach[35].

Discussion

Summary of evidence and interpretation

This systematic review aims to summarize the literature to date regarding the efficacy and impact of surgical therapy for lymphoedema, including excisional, microsurgical lymphatic reconstruction and tissue transfer procedures. *Cormier et al.*, in a systematic review of surgical treatments for lymphoedema, highlights reduction in limb volume or circumference as the most utilised measure of surgical success in the contemporary literature [12]. With the shift away from these traditional outcomes of success, HRQOL metrics are arguably the more important primary measure of intervention effectiveness in the lymphoedema patient[62]. *Kim et al.*, in a prospective study examining complex decongestive therapy in 53 patients with breast cancer-related lymphoedema, suggested that a reduction in oedema volume to be only partially correlated with improvements in HRQOL. Significant improvements in QOL were demonstrated at one and six months without relative reductions in limb volumes[63]. Beyond one-dimensional physical parameters, the experience of lymphoedema encompasses functional, social and emotional difficulties, and as such, the monitoring of HRQOL before and after surgery is critical both as an outcome measure and to monitor patient progress[64].

This review demonstrated that patients who undergo surgical treatment of lymphoedema, including lymphaticovenular-anastomosis, lymph node transfer and excisional procedures (radical and liposuction), report significant improvement in HRQOL from as early as one month and up to 64 months following initial surgery[44]. Almost all domains screened using disease-specific HRQOL instruments demonstrated improvements following operative intervention. Similarly, generic HRQOL systems showed significant improvements in a broad range of domains, not only in physical but also social and mental health[48, 50]. The improvements shown in non-physical dimensions reinforce the understanding that lymphoedema treatment should not be measured purely on circumferential or volume reductions alone[65]. An initial decline in HRQOL in the immediate post-operative period up to one month was found to potentially occur, but such a downturn was then typically followed by significant improvements. In clinical consultations, it may be advisable for patients to be made aware of this initial decline as a trade-off for eventual longer-term improvement in HRQOL[48].

Factors affecting and therefore predicting post-operative HRQOL for lymphoedema are only defined in a few of the studies. Pre-operative HRQOL and site of operation were implicated as predictors of change in overall HRQOL and its domains after the operation[41, 51, 54]. *Dionyssiou et al.* comment on the relationship between duration of lymphoedema and its response to CDT as measured by HRQOL. They suggest chronic lymphoedema with tissue fibrosis is unresponsive to a compression regimen alone but requires the addition of gentle massage to break down fibrosis[45]. Contrasting this, *De Brucker et al.* found no significant relationship between duration of lymphoedema and HRQOL measured by the ULL27 scoring system in their cross-sectional survey of 25 patients undergoing VLNT[44]. Not all HRQOL instruments survey patient satisfaction, another important indicator of surgical success. In those studies that did assess this parameter, the majority of patients reported satisfaction up to a time period of five years with satisfaction rates often mirroring HRQOL levels. These results again reinforced the HRQOL improvements that operative interventions can confer in the treatment of lymphoedema.

Given the plethora of treatment options, ascertaining the interventions that are most likely to provide the greatest benefits for the patient is a crucial aspect of lymphoedema management. On the basis of limb volume alone, *Cormier et al.* reported that the benefit of excisional procedures(91.1% reduction) outweigh both lymphatic reconstruction(54.9%) and tissue transfer procedures(47.6%)[12]. A meta-analysis undertaken by *Basta et al* comparing LVA and VLNT reported similar pre-operative and post-operative outcomes on the basis of circumference and volume parameters, however suggested a greater subjective improvement with the use of VLNT compared to that of LVA surgery. This is mirrored by the results in our review, where, with the use of the LYMQOL, an improved overall QOL was demonstrated with the use of VLNT compared with LVA for upper limb lymphoedema specifically. As expected, appearance is initially more improved in minimally invasive ablative techniques compared with physiologic techniques, however this gap is reduced with greater follow-up times. Only one study compared a combination of physiological and ablative operative techniques, with an expected improvement in both physical and psychosocial domains in the assessment of quality of life improved by a combination approach. Overall, however, there is minimal information

reported in the literature comparing improvements in validated HRQOL measures between the surgical lymphoedema techniques, especially in the comparison of ablative and physiologic procedures. Moreover, the statistical, clinical and methodological heterogeneity in the form of HRQOL scales used inherent to each of the included studies prevents pooled analysis and makes quantitative and even qualitative comparisons difficult. Similar difficulties comparing post-intervention HRQOL between operative and non-operative treatment modalities for lymphoedema has been described in the literature[66]. Given the significant variety in surgical procedures, we do recognize that patients are likely to respond differently with regard to their post-operative HRQOL scores. However, given the significance of HRQOL in a condition such as lymphoedema, further prospective comparisons assessing uniform QOL outcomes is required.

Limitations

The authors acknowledge that a key limitation of this systematic review is the inability to perform a meta-analysis. This was secondary to statistical heterogeneity (mean, median, standard error, etc.), inconsistent reporting of data items including basic demographic and lymphoedema-specific data, non-uniform use of HRQOL scoring systems and varying follow-up times. While the decision to stratify results according to HRQOL-instrument alone without regard for patient characteristics or procedure types was made as a result of the limited literature available, the authors recognize the significant clinical heterogeneity that has been introduced into the review. As such, given the varying extent and severity of lymphoedema as well as the amalgam of various procedure types that have been combined under the HRQOL subheadings, the overall improved HRQOL findings in this review may not apply to all patients. In addition to this, an inherent limitation to every systematic review is the level of evidence and quality of included studies, which we aimed to reduce through quality appraisal of each study. Despite these limitations, the significance of the qualitative analyses with regards to the benefits of surgical intervention on post-operative HRQOL in lymphoedema patients is evident in light of the number of both articles and patients included in the final results of this article. Similarly, the scope of the article incorporating all potential anatomical areas affected as well as all current

surgical techniques provides the first broad, all-encompassing review of the current literature, while highlighting clear targets for future research.

Implications for future research

This review demonstrates a significant heterogeneity in the use of HRQOL scoring systems across included studies, and thus identifies a need for consistent and validated HRQOL instruments in future studies. Furthermore, consistency with pre-determined follow-up times is also recommended. In addition to this, the lack of data directly comparing HRQOL outcomes following different operative interventions for lymphoedema is made apparent in this review, and identifies an area of potential future research. As such, large, robust prospective clinical trials with consistent reporting of preferably disease-specific HRQOL outcomes as well as pre- and post-operative edema volume is necessary to glean the true benefits of each operative intervention. These trials should aim to include long-term follow-up of up to 48 months in order to determine the true benefits of physiologic techniques, and the potential for re-accumulation in ablative techniques. Additionally, comparison of conservative treatment options and combined approaches will also assist in ascertaining the ideal treatment regimen for lymphoedema.

Conclusion

Both ablative and physiologic interventions for management of lymphoedema appear to provide an improvement in both generic and disease-specific HRQOL domains. Improvements in overall HRQOL appear to be sustained to at least six to 12 months post-operatively. The choice of intervention that maximizes HRQOL in each particular patient is not clear, and should be determined by an experienced team on a case-by-case basis.

Figure Legends

Figure 1 – PRISMA flow diagram

Author Contributions

- Nicholas Tang – Writing, Article Collation, Data Extraction, Review of Articles
- Anand Ramakrishnan – Expert Opinion, Writing up and Editing of Manuscript
- Ramin Shayan – Expert Opinion, Writing up and Editing of Manuscript

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