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A meta-analysis of the efficacy of vascularised lymph node transfer in reducing limb volume and cellulitis episodes in patients with cancer treatment-related lymphoedema

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Abstract:	Background: Lymphoedema after cancer treatment is a chronic and disabling complication that presents a significant healthcare burden during survivorship with limited treatment options. Vascularised lymph node transfer (VLNT) can reconstruct lymphatic flow to reduce limb volumes but limited higher-order evidence exists to support its effectiveness. Aim : To systematically review and meta-analyse the effectiveness of VLNT in reducing upper (UL) or lower (LL) limb volume and cellulitis episodes in patients with cancer-treatment-related lymphoedema (CTRL). Methods: PubMed, Medline (Ovid) and EMBASE databases were searched between January 1974 - December 2019. Full-length articles where VLNT was the sole therapeutic procedure for CTRL reporting volumetric limb, frequency of infection episodes and/or lymphoedema specific quality-of-life data were included in a random-effects meta-analysis on circumferential reduction rate (CRR). Methodological quality was assessed using STROBE/CONSORT and a novel, lymphoedema-specific scoring tool was used to assess lymphoedema-specific methodological reporting. Sensitivity analyses on site of VLNT harvest and recipient location were performed. Results: Thirty-one studies (581 patients) were eligible for inclusion. VLNT led to significant limb volume reductions in UL (above elbow pooled circumferential reduction rates (CRR P) = 42.7 % (95% CI: 36.5-48.8); below elbow CRR P = 34.1 % (95% CI: 33.0-35.1)) and LL (above knee CRR P = 46.8 % (95% CI: 43.2-50.4); below knee CRR P = 54.6 % (95% CI: 39.0-70.2)) CTRL. VLNT flaps from extra-abdominal donor sites were associated with greater volume reductions (CRR P = 49.5% (95% CI: 46.5-52.5)) compared to intra-abdominal donor sites (CRR P = 39.6% (95% CI: 37.2-42.0)) and combined DIEP/VLNT flaps (CRR P = 32.7% (95% CI: 11.1-54.4)) ($p<0.05$). VLNT was also found to reduce the mean number of cellulitis episodes by 2.1 per year (95% CI: -2.7- -1.4) and increased lymphoedema-specific quality-of-life scores (mean difference in LYMQOL “overall domain” = +4.26). Conclusions: VLNT is effective in reducing excess limb volume and cellulitis episodes in both UL and LL lymphoedema following cancer treatment. However, significant heterogeneity exists in outcome reporting and standardisation of reporting processes is recommended.

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Dr Alexander Eggermont, MD, PhD
Editor, *European Journal of Cancer*

13th February 2021

Re: Manuscript submission ("A meta-analysis of the efficacy of vascularised lymph node transfer in reducing limb volume and cellulitis episodes in patients with cancer treatment-related lymphoedema")

Dear Dr Eggermont,

Please find enclosed our systematic review and meta-analysis of volumetric and infection outcomes following vascularised lymph node transfer (VLNT) for cancer treatment-related lymphoedema (CTRL), which we hope you will consider for publication in *European Journal of Cancer*.

VLNT is an emerging surgical procedure for the treatment of lymphoedema that aims to reconstruct the physiological lymphatic circulation within lymphoedematous limbs through the free tissue transfer of lymph node flaps. Observational studies evaluating VLNT have shown that it reduces limb volumes and episodes of cellulitis in both upper and lower limbs, however, there remains an evidence void surrounding its efficacy to support wider uptake.

Our systematic review and meta-analysis of VLNT is the largest and most comprehensive meta-analysis of VLNT to date (581 patients derived from 31 different studies) and is the only one to specifically address the efficacy of VLNT in CTRL. To this end, our data demonstrates that VLNT results in sustained reductions in limb volume (upper and lower limb), reductions in episodes of cellulitis and improvements in lymphoedema-specific quality-of-life in cancer patients affected by lymphoedema.

Furthermore, in undertaking this work we highlight the need for more consistent reporting of outcomes in clinical studies of lymphoedema. To this end, in our manuscript we develop and utilise a novel tool to score the methodological quality of VLNT studies derived from the International Lymphology Society (ILS) recommendations.

We feel our work would be of interest to the breadth of *European Journal of Cancer's* readership because lymphoedema remains one of the most-feared complications in surgical oncology affecting a wide range of tumour types. Furthermore, as cancer survival continues to improve so will the prevalence of patients with lymphoedema and this represents a significant healthcare burden for all healthcare systems, and, for patients. Thus, there is a clinical imperative to establish the efficacy of novel surgical techniques, such as VLNT, which could be utilised in the early stages of lymphoedema to mitigate adverse outcomes in the longer-term. Finally, patients and healthcare professionals frequently question the possible

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surgical treatment options for lymphoedema and so we feel that *European Journal of Cancer* would be the ideal platform through which we could engage the wider surgical community to raise awareness of novel treatment options for lymphoedema and their potential clinical utility.

As a unit, we are committed to developing a robust evidence base for surgical interventions for lymphoedema and are cultivating a portfolio of randomised clinical trials evaluating both VLNT and lymphaticovenous anastomosis for the treatment of CTRL at The Royal Marsden hospital. Therefore, we feel that we have the experience, expertise and resources to undertake the work in this submission.

In light of the novel nature of VLNT, the broad appeal of the topic and the methodologically robust nature of our data-synthesis, we would be grateful if you would consider our work for publication in *European Journal of Cancer*.

Thank you for taking the time to consider our work.

Yours sincerely,

Mr Aadil Khan
Consultant Plastic Surgeon

Highlights

- Lymphoedema is a disabling complication of cancer treatment that burdens survivorship
- Vascularised lymph node transfer is used to reconstruct disrupted lymphatic flow and reduce excess limb volumes
- Meta-analysis demonstrated that VLNT is effective in reducing limb volume and cellulitis episodes in both upper and lower limbs and associated with quality-of-life gains
- VLNTs performed from extra-abdominal donor sites were found to be more effective in reducing excess limb volumes compared to intra-abdominal VLNT donor sites.
- Further appraisal of VLNT would benefit from standardised outcome reporting and randomised controlled trials

A meta-analysis of the efficacy of vascularised lymph node transfer in reducing limb volume and cellulitis episodes in patients with cancer treatment-related lymphoedema

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Keywords: lymphoedema, vascularised lymph node transfer, systematic review, meta-analysis

Abstract

Background: Lymphoedema after cancer treatment is a chronic and disabling complication that presents a significant healthcare burden during survivorship with limited treatment options. Vascularised lymph node transfer (VLNT) can reconstruct lymphatic flow to reduce limb volumes but limited higher-order evidence exists to support its effectiveness.

Aim: To systematically review and meta-analyse the effectiveness of VLNT in reducing upper (UL) or lower (LL) limb volume and cellulitis episodes in patients with cancer-treatment-related lymphoedema (CTRL).

Methods: PubMed, Medline (Ovid) and EMBASE databases were searched between January 1974 - December 2019. Full-length articles where VLNT was the sole therapeutic procedure for CTRL reporting volumetric limb, frequency of infection episodes and/or lymphoedema specific quality-of-life data were included in a random-effects meta-analysis on circumferential reduction rate (CRR). Methodological quality was assessed using STROBE/CONSORT and a novel, lymphoedema-specific scoring tool was used to assess lymphoedema-specific methodological reporting. Sensitivity analyses on site of VLNT harvest and recipient location were performed.

Results: Thirty-one studies (581 patients) were eligible for inclusion. VLNT led to significant limb volume reductions in UL (above elbow pooled circumferential reduction rates (CRR_P) = 42.7 % (95% CI: 36.5-48.8); below elbow CRR_P = 34.1 % (95% CI: 33.0-35.1)) and LL (above knee CRR_P = 46.8 % (95% CI: 43.2-50.4); below knee CRR_P = 54.6 % (95% CI: 39.0-70.2)) CTRL. VLNT flaps from extra-abdominal donor sites were associated with greater volume reductions (CRR_P = 49.5% (95% CI: 46.5-52.5)) compared to intra-abdominal donor sites (CRR_P = 39.6% (95% CI: 37.2-42.0)) and combined DIEP/VLNT flaps (CRR_P = 32.7% (95% CI: 11.1-54.4)) ($p<0.05$). VLNT was also found to reduce the mean number of cellulitis episodes by 2.1 per year (95% CI: -2.7- -1.4) and increased lymphoedema-specific quality-of-life scores (mean difference in LYMQOL “overall domain” = +4.26).

Conclusions: VLNT is effective in reducing excess limb volume and cellulitis episodes in both UL and LL lymphoedema following cancer treatment. However, significant heterogeneity exists in outcome reporting and standardisation of reporting processes is recommended.

Key Points

Question

Is vascularised lymph node transfer an effective procedure for reducing limb volume, infection and lymphoedema-related quality of life outcomes following cancer-treatment related lymphoedema?

Findings

In a systematic review and meta-analysis of 31 studies encompassing 581 patients we found that vascularised lymph node transfer for cancer treatment related lymphoedema can achieve reductions in limb volume and episodes of cellulitis in both the upper and lower limbs, indicating it is an effective therapy. Included studies were methodologically heterogeneous and judged to be of low quality highlighting the need for standardized outcome reporting and further well-designed randomised controlled trials in this area.

Meaning

Vascularised lymph node transfer is an effective procedure for reducing limb volume and episodes of cellulitis as well as improving lymphoedema-related quality of life

Introduction

Lymphoedema is the accumulation of extracellular fluid within the interstitial space of an extremity that leads to increased limb volume and susceptibility to cutaneous infections.[1] In higher-income countries, the most common causes are locoregional cancer treatments, such as surgery or radiotherapy. Surveys suggest a prevalence for chronic lymphoedema of 1.33-3.99 individuals per 1,000[2,3] with 50 % of cases being cancer treatment-related[4]. The incidence of cancer treatment-related lymphoedema (CTRL) varies across tumour types: breast cancer (20 %), gynaecological cancers (25 %), head and neck (75 %), urological cancers with pelvic node clearance (10 %) and melanoma (25 %)[5-9]. CTRL patients are at higher risk of developing skin infections (cellulitis), decreased limb function and, rarely, secondary cancers such as lymphangiosarcoma (Stewart-Treves syndrome). The economic impact of CTRL is significant. Cost-analysis of one US cohort demonstrated, on average, patients bore direct care costs of $2,306-2,574, and indirect costs of £3,325-5,545[10], annually, through lost productivity and earnings. Medical costs were also higher ($14,877-23,167; cumulative 2-year)[11] compared to breast cancer patients not suffering CTRL. As survival outcomes across all cancers improves with advancements in care, CTRL will become a significant survivorship burden.

The mainstays of lymphoedema management include patient education, skin care and control of co-morbidities that compound limb swelling. Conservative measures such as compression garment therapy (CGT) and complete decongestive therapy (CDT) are most effective for early lymphoedema (ISL stages 1 or 2)[12] (Supplementary Table 1) but commit patients to a lifetime of therapy. As lymphoedema becomes established (ISL stages 2b and 3), compressive regimens become less efficient and palliative surgical treatments (debulking procedures or liposuction) are the only treatment options[13].There is, thus, a strong imperative for the development of more effective surgical therapies that can be deployed in the early stages of lymphoedema. Examples of such 'physiological' procedures include lymphaticovenous anastomosis (LVA)[13] or vascularised lymph node transfer (VLNT), which aim to bypass lymphatic drainage and induce new lymphatic growth into lymph nodes, respectively[14].

VLNT is the free transfer of lymph nodes from a donor site into a lymphoedematous limb to reconstruct physiological lymphatic return.[15] Whilst precise mechanisms of action remain unclear, VLNTs are thought to promote lymphangiogenesis and either wick lymphatic fluid for transport into proximal lymphatic channels[16], or, act as pumps pushing lymphatic fluid into the venous circulation[17,18]. Donor sites examples for VLNT include groin, lateral chest wall, omental, supraclavicular and submental lymph node basins (Supplementary Figure 1a), where lymph nodes are harvested with a vascular pedicle for recipient site anastomosis. Reverse mapping techniques[19] (a modification of the axillary technique described by Klimberg[20]) have more recently been introduced to reduce donor limb lymphoedema risk (Supplementary Figure 1b). Whilst clinical experience with VLNT develops, there remains an evidence gap to support uptake into routine clinical practice.

A number of systematic reviews have been published examining VLNT efficacy [14,21-23,15,24-28]. However, none have focused solely on CTRL and just two were meta-analyses. One focused exclusively on the impact of

delayed breast reconstruction with and without VLNT for breast cancer-related lymphoedema[22]. The other, in contrast, broadly compared surgical excision, LVA, liposuction, VLNT and combination procedures for any form of secondary lymphoedema presenting heterogeneous volumetric outcomes[24]. The specific research question posed by this study was, therefore, whether VLNT was effective in CTRL for: 1) reducing limb volume, 2) reducing infection complications and 3) improving lymphoedema-specific quality of life.

Methods

We conducted this systematic review and meta-analysis in in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was prospectively registered on the PROSPERO systematic review database (CRD42020204080).

Search strategy and inclusion criteria

Pubmed, Medline (Ovid) and EMBASE databases were searched in January 2020 for studies published between 1974 and 2019 using the following Medical Subject Headings terms: [lymph node transfer OR lymph node flap OR omental flap OR omentum flap] AND [lymphoedema OR lymphedema] AND [volume OR reduction OR efficacy OR treatment] AND [human AND patient]. The references of all relevant studies were screened for further studies not identified by the original search. The inclusion criteria were: (1) any published full-length article describing lymphoedema treatment resulting from the therapeutic cancer management (2) VLNT undertaken as sole therapeutic procedure (3) reporting of volumetric limb, infection episode and/or patient-reported lymphoedema specific quality of life outcome data. The exclusion criteria were: (1) non-English language articles (2) reporting management of patients that had undergone previous surgical interventions for lymphoedema (3) anatomical/cadaveric studies, and/or systematic reviews presenting no original data (4) conference proceedings, abstracts and letters (Figure 1a). The title and abstract of each article were screened independently by two co-authors to ensure compliance. The full-text of all compliant studies were then re-reviewed to determine, definitively, selection for the systematic review. Where discordance occurred, both co-authors jointly reviewed the article to reach concordance.

Data extraction

The following data was extracted: study design, causative pathology, lymphoedema duration and site, peri-operative diagnostic imaging, procedural intervention, volumetric outcome measured, infection episodes, reported donor morbidity and complications, compression garment regimen and follow-up duration. Where available summative volumetric outcomes were grouped for analysis according to measure and where raw data was presented this was converted to circumferential reduction rate (CRR). Similarly, patient-reported lymphoedema-specific health-related quality of life data was extracted and grouped into respective LYMQOL domains. Where data presented was insufficient or unclear, authors were contact for clarification.

Meta-analysis

A random-effects meta-analysis was used to calculate summative treatment effect (pooled CRR ± 95% CI) in STATA/IC 15.1 (Texas, USA). The I^2 measure was used to demonstrate study heterogeneity. Studies were categorized according to the volumetric outcome (CRR, 21 studies (includes 7 studies where raw data converted to CRR); lymphoedema index (LI), 3 studies; excess volume reduction (EVR), 3 studies; percentage difference (PD), 3 studies) prior to meta-analysis. Meta-analyses were performed separately for upper (UL) and lower limbs (LL) with stratification according to measurement location (above elbow (AE) v below elbow (BE); above knee (AK) v below knee (BK)). Further subset analyses were performed for cellulitis episodes and to determine whether summative differences existed between VLNTs from extra-abdominal ($VLNT_{extra}$; groin, thoracic, submental, supra-clavicular), abdominal ($VLNT_{abdo}$; omental, jejunal, ileocaecal, appendiceal) and groin VLNT with synchronous autologous breast reconstruction ($VLNT_{DIEP}$; deep inferior epigastric artery perforator flap with superficial inferior epigastric artery lymph node VLNT) donor sites. It was not possible to meta-analyse peri-operative changes in patient-reported lymphoedema-specific health-related quality-of-life due to heterogenous interpretation and reporting of the LYMQOL instrument but a mean score for the "overall" domain was reported.

Quality evaluation of studies

We evaluated the methodological quality of studies in 2 ways. Firstly, all articles were scored against pre-defined STROBE (observational studies) and CONSORT (randomised controlled trials, RCTs) initiative checklists to assess study reporting quality[29,30]. For each checklist, individual items (or sub-item where appropriate) were allocated a single point. The maximum number of points available was 34 (STROBE) and 37 (CONSORT). Studies were graded as low (STROBE < 20; CONSORT <15), moderate (STROBE 20-25; CONSORT 15-20) or high quality (STROBE > 25; CONSORT > 20).

Secondly, we assessed lymphoedema-specific quality of data reporting (JW) using a scoring system ("ILS score") developed from the International Lymphology Society 2016 Consensus guidelines[13] (outlined in Supplementary Table 2). Studies were scored dependent upon whether authors reported: reverse mapping techniques, pre- and post-op CGT regimens (grade and duration), calculation of volume excess, evidence of post-operative lymphatic flow in VLNT, adjunctive imaging (e.g. bioimpedance), quality-of-life outcomes and a minimum of 12-month follow-up.

Results

Search Findings

The search identified 277 articles (Figure 1 b) of which 163 articles were excluded following title screening. A further 56 articles were excluded following title and abstract review. The full texts of 58 articles were then read with 31 deemed suitable for inclusion[17,31-62]. Of these, 13 studies were undertaken in Taiwan, 4 in the USA, 3 in China, 3 in Italy, 2 in Finland and 1 each in Belgium, France, Greece, Iran, Japan and Singapore

(Table 1). The sample consisted of 2 case reports, 2 case-series, 25 cohort studies, 1 cross-sectional patient survey and 1 RCT published 2011-2019 encompassing 581 patients.

Sample characteristics

The mean study population size was 18.7 patients (SD: 17.0, Range: 1-83). CRR was the most commonly reported volumetric outcome and available (or calculable from raw data) in 21 studies (Table 1). VLNT was undertaken in the UL for the majority of patients (81.9%). Lymphoedema aetiologies were breast (79.5 %), gynaecological (11.9 %), skin (2.4 %), urological (1.0 %), and not otherwise specified (0.5 %) cancer related (Table 2). Twenty-seven patients (4.7 %) were included with extra-CTRL aetiologies because exclusion would have led to loss of greater numbers of co-reported CTRL patients from the sample. Extra-abdominal VLNT ($VLNT_{extra}$) was undertaken for 293 patients, abdominal ($VLNT_{abdo}$) for 99 patients and VLNT in conjunction with breast reconstruction ($VLNT_{DIEP}$) for 106 patients. VLNT donor site was undefined for 83 patients. The mean pre-operative symptomatic duration was 55.6 months (SD: 38.2) and the majority of studies (16 studies) followed patients up for 6-12 months (Table 2). For 395 patients where lymphoedema staging was reported in accordance with the International Society of Lymphology Lymphoedema Classification (Supplementary Table 1)[13], lymphoedema stages were: 1 (0.8 %), 1 or 2 (33.4 %), 2 (35.7 %), 2 or 3 (21.0 %), 3 (9.1 %) (Supplementary Table 3).

Methodological quality

The mean STROBE score for the 30 observational studies was 15.4 (SD: 3.6). Twenty-seven studies were low-quality (STROBE < 20), 2 moderate-quality (STROBE: 20-25) and 1 high-quality (STROBE > 25). The single RCT included was assessed as moderate quality (CONSORT 15-20) (Figure 2). For lymphoedema-specific quality of data reporting, 30 studies were graded as low quality (ILS score < 3) and 1 study as moderate (4-6). In > 90% of studies we were unable to award points for: 1) reverse mapping undertaken, 2) duration, frequency and grade of compression garments described pre- and post-operatively, 5) adjunctive imaging or assessment of tissue composition outcomes quantified and reported.

Volumetric Outcomes

Meta-analysis was performed for 21 studies that either reported CRR, or where raw data was converted. Meta-analysis was performed for 3 studies reporting lymphoedema index (LI) (Supplementary Figure 3) but not for studies reporting EVR or PD due to insufficient study numbers and/or reporting of data.

Upper and Lower Limb

We meta-analysed outcomes for AE and BE CRRs separately observing CRRs of 42.7 % (95% CI: 36.5-48.8, 153 patients, 10 studies) and 34.1 % (95% CI: 33.0-35.1, 144 patients, 9 studies), respectively (Figure 3 a-b). Four studies[17,41,48,61] reported UL CRR outcomes globally without differentiating between AE or BE (Supplementary Figure 2 a-b). We also meta-analysed outcomes for AK and BK CRRs separately and observed CRRs of 46.8 % (95% CI: 43.2-50.4, 26 patients, 3 studies) and 54.6 % (95% CI: 39.0-70.2, 26

patients, 3 studies) respectively (Figure 3 c-d). Two studies[41,61] reported lower limb CRR outcomes globally (supplementary Figure 2 c-d).

VLNT Donor Site

To investigate whether significant differences exist between VLNT donor sites, we undertook a further meta-analysis and performed means testing of pooled summary estimates for patients undergoing $VLNT_{extra}$, $VLNT_{abdo}$ and $VLNT_{DIEP}$ for UL lymphoedema. It was not possible to present data for lower limb lymphoedema due to low study numbers and heterogeneous outcome reporting. Any measure of CRR (AE, BE or mean UL) was accepted in the analysis. The pooled summary CRR estimates of 49.5 % (95% CI: 46.5-52.5, 7 studies, 108 patients), 39.6 % (95% CI: 37.2-42.0, 3 studies, 15 patients) and 32.7 % (95% CI: 11.1-54.4, 3 studies, 29 patients) were observed for $VLNT_{extra}$, $VLNT_{abdo}$ and $VLNT_{DIEP}$ respectively (Figure 4 a-c). One-way analysis of variance showed significant differences between donor site groups and post-hoc analysis using Tukey's correction showed significant differences in CRR between patients undergoing $VLNT_{extra}$ and $VLNT_{DIEP}$ ($p<0.05$) but no difference between patients undergoing $VLNT_{extra}$ and $VLNT_{abdo}$ or $VLNT_{abdo}$ and $VLNT_{DIEP}$ (Supplementary Table 4).

Measurement Site

To determine the impact of measurement site, we performed means testing using the unpaired two-way T-test of pooled summary CRRs estimates comparing outcomes measured proximal (CRR_{AE} or CRR_{AK}) to those measured distal to the joint (CRR_{BE} or CRR_{BK}) for UL and LLs. For the UL, comparing CRR_{AE} versus CRR_{BE}, we observed patients undergoing VLNT where CRR measurements were taken proximal to the elbow had a greater CRR ($p<0.01$) compared to distal. For LL outcomes, we observed no difference in CRR when measurements were taken proximal or distal to the knee (Supplementary Table 4).

Cellulitis Episodes

Cellulitis episodes for 6 studies (219 patients) comprising both UL and LL VLNTs were meta-analysed. Following any-form of VLNT, cellulitis episodes were reduced by 2.1 (95% CI: -2.7 - -1.4, Figure 4 d) annually**.**

Lymphoedema-related quality of life

Whilst it was not possible to meta-analyse lymphoedema-related quality of life outcomes due to study heterogeneity in how the LYMQOL tool[63] was interpreted and presented, we analysed pre- and post-op differences qualitatively (6 studies, 108 patients). We compared the overall domain score as this was most consistently reported and found an improvement in the overall domain score (mean difference = 4.26 (SD 1.48)) (Supplementary Table 5).

Donor site complications

Post-operative donor site morbidity and complications data were extracted but due to its qualitative format were unsuitable for meta-analysis. Donor site complications were grouped into ‘minor’ or ‘major’ categories. Six studies reported ‘minor’ complications in 42 patients (seroma, donor site lymphorrhoea, pain, delayed wound healing dehiscence, post-operative infection), 1 study reported a single ‘major’ complication of post-operative donor-site lymphoedema treated with LVA[39]. Therefore, the estimated donor site lymphoedema rate in patients undergoing $VLNT_{extra}$ ranged between 1 in 399 to 1 in 482 (0.20-0.25%). Nineteen studies denied donor site complications and 5 studies did not state any data. No studies formally evaluated the donor site. Separately two flap losses were reported in two studies giving a flap loss rate of 0.35% (although one study excluded the affected patient)[33,53].

Discussion

CTRL is a chronic, incurable and disabling complication that reduces the quality of life during survivorship and increases the risk of acute infection complications. Traditional management options do not address the underlying pathophysiology and commit patients to a lifetime of conservative treatment. As the largest meta-analysis quantifying volumetric and cellulitis outcomes post-VLNT, in CTRL, this work defines the existing evidence base. It demonstrates VLNT reduces UL and LL volumes and infection complications. In summary, we report pooled CRRs of 42.7 % (AE) and 34.1 % (BE) in the UL and 46.8% (AK) and 54.6% (BK) in the LL post-VLNT. In addition, we found patients experienced fewer cellulitis episodes (approximately 2 episodes/year) post-VLNT and had improved LYMQOL scores. The therapeutic effect was seen for all donor sites. In the UL, pooled summary CRR estimates of 49.5 %, 39.6 % and 32.7 % were observed for $VLNT_{extra}$, $VLNT_{abdo}$ and $VLNT_{DIEP}$, respectively. Furthermore, our results suggest that $VLNT_{extra}$ results in greater CRRs compared to $VLNT_{DIEP}$. The choice of VLNT is therefore consequential and must be considered when balancing choices of donor site lymphoedema risk and post-op functional efficacy. Economic analysis is beyond this study but clearly reductions in infections and limb volume have significant financial implications.

The majority of studies were observational (30 out of 31) with only one RCT. Twenty-seven observational studies were judged low quality (STROBE < 20) with just one judged high quality (STROBE > 25). Evaluating quality of lymphoedema-specific data reporting, we found low adherence with 30 out of 31 studies scoring 0-3 points. In particular, the lack of clarity regarding the extent of pre- and post-operative CGT suggests that volumetric outcomes should be viewed cautiously. Furthermore, there was no of consensus on the optimal volumetric outcome with 5 reported (CRR, LI, PD, CD, EVR). As the most widely used measure, CRR was taken as the primary outcome of interest. Meta-analysis of other volumetric outcomes was only possible for LI due to the small number of studies available. Similarly, meta-analysis of lymphoedema-related quality of life was precluded by variability in interpretation and reporting. Donor site morbidity was also variably reported and assessed informally with 5 studies providing no data. We recommend that a core outcome set as advocated by the COMET initiative[64] be developed for appraising surgical lymphoedema interventions to address variability in outcome reporting and facilitate future meta-analysis. Furthermore, the development of RCTs incorporating the domains of our peri-operative ILS score would improve the literature.

Limitations

Limitations are the large number of studies of low methodological quality including 13 studies with ≤ 10 patients. Furthermore, follow-up was short with only 8 studies following patients for >24-months. The variability in pre-operative lymphoedema duration, stage and follow-up should be acknowledged when considering generalisability. In addition, due to dataset heterogeneity it was impossible to adjust for confounders such as body mass index or individual cancer treatments. Related to this, there is likely to be significant variation in cancer stage at diagnosis and oncological treatments received[65-67]. Hence, the management of regional lymph nodes in similar cases may be different impacting CTRL incidence and efficacy of VLNT. Similarly, some studies were published > 10 years ago and, more recently, there has been

a trend towards de-escalation of nodal surgery in favour of radiotherapy[68-71]. We are unable to adjust for these trends, which supports our recommendations for more robust methodological evaluations in new surgical interventions for lymphoedema.

Finally, it is important to interpret the findings in the broader context of lymphoedema management and resource utilization. Whilst our analysis suggests that VLNT can offer significant reductions in limb volume further economic analysis is required to link this to meaningful clinical outcomes and assess impact on resource utilization. For example, further work should interpret what a CRR of 40% equates to in terms of de-escalating CGT grade or daily duration and, in what proportion of patients, would VLNT make CGT obsolete? There is no published data that defines the relationship between volume reduction and downgrading CGT, or symptoms experienced. Furthermore, considering the design of RCTs, a high degree of patient engagement is essential to ensure quantified outcomes are meaningful clinically and are representative of physiological changes. Finally, it would be pertinent to integrate health economic analyses into trial designs to examine cost-effectiveness against pre-existing interventions.

Conclusions

VLNT effectively reduces limb volume and cellulitis episodes in UL and LL CTRL. However, the majority of studies were judged methodologically low quality. The appraisal of VLNT would benefit from standardized outcome reporting and more methodologically rigorous RCTs.

Conflict of Interest Disclosures

None declared

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Figure Legends

Figure 1. Search strategy. a) Study Inclusion and exclusion criteria, b) PRISMA diagram demonstrating articles identified, screened and included

Figure 2. Assessment of the methodological quality of studies. Studies were evaluated for methodological quality using either STROBE or CONSORT frameworks and compliance with ILS score

Figure 3. Meta-analysis on the effect of VLNT on circumferential reduction rate (CRR) in patients with CTRL affecting both upper and lower limbs. a) Above elbow, b) Below elbow **c)** Above knee c) Below knee

Figure 4. Meta-analysis of the effect of VLNT donor site on circumferential reduction rate (CRR) in patients with upper limb CTRL and episodes of infection in all patients with CTRL. a) Extra-abdominal VLNT, b) Abdominal VLNT c) VLNT with autologous breast reconstruction d) Standardised mean difference in cellulitis episodes (per annum) following VLNT.

Supplementary Figure 1. VLNT procedure. a) Potential donor and recipient sites for VLNT procedures, Image credit: https://www.hopkinsmedicine.org/plastic_reconstructive_surgery/services-appts/lymphedema.html b) i) Right groin VLNT flap being raised based upon the superficial circumflex iliac vessels following indocyanine green injection into the lower abdomen (white arrows) to localize regional lymph nodes. Reverse mapping, using patent blue dye injection in the foot, was utilized to minimise the risk of donor limb lymphoedema , ii) Indocyanine green (ICG) injection sites (white arrows) are visble under near infra-red light and ICG fluorescence is seen within draining lymph nodes within the flap (red arrow), iii) Vascular pedicle of the groin VLNT flap based on superficial circumflex iliac artery (SCIA) and vein (SCIV) (white arrow), iv) VLNT demonstrating presence of nodal ICG fluorescence after completion of raise.

Supplementary Figure 2. Meta-analysis of the effect of VLNT donor site on circumferential reduction rate (CRR) in patients with upper and lower limb CTRL. Includes CRR where reported as a mean of upper and lower limb measures. a) above elbow b) below elbow c) above knee d) below knee

Supplementary Figure 3. Meta-analysis of the effect of VLNT on Lymphatic Index (LI) in patients with upper and lower limb CTRL. a) upper limb and, b) lower limb.

Table 1. Characteristics of Study Sample

Authors	Country	Study type	No. of pts	Reported Volumetric Measure	VLNT procedure performed	Follow-Up
Akita et al., 2017	Japan	Cohort	27	LI	DIEP+SCIA VLNT (n=13) vs. SCIA VLNT only (n=14)	6 months
Visconti et al., 2018	Italy	Cohort	10		Supraclavicular VLNT	12 months
Coriddi et al., 2017	US	Cohort	10		Jejunal mesenteric VLNT	10.4m (SD: 6.2)
Dionyssiou et al., 2016	Greece	RCT	18	EVR	SCIA VLNT (n=10); SIEA VLNT (n=8)	18 months
Tan et al., 2016	Singapore	Case-series	2		Submandibular VLNT	12 months
Nguyen et al., 2015	US	Cohort	29		VLT + DIEP/MSTRAM	12 months
Maruccia et al., 2019	Italy	Cohort	16	CRR	Double Gastroepiploic VLT + physio	24 months
Ciudad et al., 2019	Taiwan	Cohort	83		VLNT (groin, supraclav, gastroepiplopic, apendicular, ileocaecal)	32.8m
Engel et al., 2017	Taiwan	Cohort	45		MBR-VLNT (n=11); VLNT (n=34). VLNT: Groin or Submental VLNT.	VLNT: 58.3 (SD: 19.1); MBR & VLNT: 15.4 (SD: 1.8)
Maruccia et al., 2019	Italy	Cohort	39		VLNT vs VLNT and scar release (VLNT: Groin (n=20); Gastroepiploic (n=19))	24m
Liu et al., 2018	China	Cohort	30		Groin VLNT	22.1m (SD: 7.8)
Ciudad et al., 2016	Taiwan	Case report	1		Appendicular VLNT	6m
Agko et al., 2017	Taiwan	Cohort	12		Extended gastroepiploic VLNT with subsequent suction assisted lipectomy	23.5m
Ciudad et al., 2017	Taiwan	Cohort	7		Double Gastroepiploic VLT	9.7m
Gratzon et al., 2016	US	Cohort	50		SIEA/SCIA VLNT	12m
Ciudad et al., 2015	Taiwan	Cohort	10		Right Gastroepiploic VLNT	14.7 (SD: 3)
Cheng et al., 2013	Taiwan	Cohort	10		SCIA VLNT	36.6 (SD: 17.8)
Cheng et al., 2012	Taiwan	Cohort	6		Submental VLNT	8.7 (SD: 4.2)

Lin et al., 2009	Taiwan	Cohort	13		SCIA VLNT	56.31 (SD: 27.12)
Aljaaly et al., 2019	Taiwan	Cohort	15		Submental VLNT	12m
Mousavi et al., 2019	Iran	Cohort	24	PD	Gastroepiploic VLNT	12m
Sapountzis et al., 2014	Taiwan	Case-series	2		Right Transverse Cervical Artery VLNT	6.5m
Viitanen et al., 2013	Finland	Cohort	19	Raw data converted to CRR	VLNT (SCIA) (n=6); VLNT (LN-msTRAM/LN-DIEP) (n=13)	27.4m
Chen et al., 2014	China	Cohort	9		VLNT (LN-msTRAM/LN-DIEP)	12m
Saaristo et al., 2012	Finland	Cohort	9		VLNT (LN-msTRAM (n=5) /LN-DIEP (n=4))	6m
Arrivé et al., 2017	France	Cohort	15		SCIA VLNT	16.9m
Patel et al., 2015	Taiwan	Cohort	20		Submental VLNT (n=11); Groin VLNT (n=9)	27.3m
Wong & Liu, 2015	China	Case report	1		SCIA VLNT	10m
Gharb et al., 2011	Taiwan	Cohort	21		Standard Groin VLNT; Hilar Perforator Groin VLNT	46m
Chen et al., 2016	US	Cohort	3	N/A - QOL data only	Groin & Supraclav VLNT	12m
De Brucker et al., 2016	Belgium	Cross-sectional patient survey	25		SCIA VLNT (n=3); SCIA VLNT and DIEP (n=22)	29m (SD: 14)

Table 2. Summative patient and procedure-level data for included studies.

Domain	Parameter	Number
Number of Studies	n=	31
Total No. of patients	n=	581
Patient-level Data		
Operative Site (Numbers)	UL LL	476 105
Pathology	Breast Cancer Gynaecological Cancer Urological Cancer Skin Cancer Cancer not otherwise specified (NOS) Other	462 69 6 14 3* 27** (unable to exclude)
Pre-operative Lymphoedema Duration	Mean (SD)	55.6 (SD: 38.2)
Post-operative Follow-Up	Mean (SD)	19.2 (SD: 12.3)
Intervention	VLNT (unable to define) VLNT (extra-abdominal, non-BR) VLNT (intra-abdominal) VLNT and BR	83 293 99 106
Study-level Data		
Pre-operative Investigations	Lymphoscintigraphy (LSG) Indocyanine Green (ICG) Magnetic Resonance Imaging (MRI) LSG and ICG LSG and MRI Not stated	12 4 1 2 1 11
Pre-operative compression garment grade and duration stated	Yes No	0 31
Post-operative compression garment grade and duration stated	Yes No	2 29
Documented Donor Site Complications	Yes No Not stated	7 19 5
Last Follow-up	< 6m 6-12m 13-18m 19-24 > 24m	0 16 3 4 8

* Refers to study 122 (Chen *et al.*)
** Refers to studies 6 (Marrucia *et al.* 2019; idiopathic aetiology, n=3), 9 (Ciudad *et al.* 2019; trauma aetiology, n=5, primary lymphoedema, n=11), 90 (Coriddi *et al.* 2017; defibrillation injury, n=1), 141 (Patel *et al.* 2015; post-surgical lower extremity lymphoedema, n=7) where we were unable to exclude these small number of patients without losing the co-reported cancer treatment-related lymphoedema cohorts from the meta-analysis.

Supplementary Table 1. International Society of Lymphology – Lymphoedema Classification. Taken from: *"The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the international society of lymphology"* published in Lymphology 2016; 46: 170-84

Stage	Descriptor
Stage 1	Early accumulation of fluid (relatively high in protein content) which subsides with limb elevation. Pitting may occur.
Stage 2a	Limb elevation alone rarely reduces the tissue swelling. Pitting is manifest.
Stage 2b	Limb that may or may not pit as excess subcutaneous fat and fibrosis develops
Stage 3	Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, alterations in skin character and thickness, further deposition of fat and fibrosis, and warty overgrowths have developed.

Supplementary Table 2. Peri-operative lymphatic care – a quality scoring system for methodological reporting in clinical lymphoedema studies. Based upon the International Lymphology Society Consensus Guidelines (2016)[13] we scored studies based on their adherence to recommendations for reporting clinical parameters in patients undergoing surgery for lymphoedema.

Criterion	Attributable points
1. Was reverse mapping employed to reduce the risk of donor site lymphoedema?	1
2. Were compression garment regimens described clearly (duration, frequency of use and compression grade)?	
Pre-operatively only	1
Post-operatively only	1
Pre- and post-operatively	3
3. Was volume excess quantified using water displacement, perometry or the truncated cone formula?	1
4. Was post-operative evidence of lymphatic flow through the vascularised lymph node transfer demonstrated?	1
5. Were adjunctive imaging or assessment of tissue composition (e.g. bioimpedance, MRI tissue dielectric constant) outcomes quantified and reported?	1
6. Was the LymQoL PROM, or another relevant validated PROMs reported?	1
7. Were volumetric outcomes reported with at least 12 months follow-up?	1
Total score (maximum 9)	**/9**

Supplementary Table 3. Lymphoedema characteristics for included studies

Authors	No. of pts	Pre-op Lymphoedema Duration (Mean)	Stage of lymphoedema	Site (UL, LL)
Akita et al., 2017	27	Not clear	ISL Stage 1; Early & Late Stage 2	UL
Visconti et al., 2018	10	64.7m (SD: 89.4)	ISL Stage 2b: 10	LL
Coriddi et al., 2017	10	121m (SD: 79.1)	Not clear	UL (6); LL (4)
Dionyssiou et al., 2016	18	Not stated	Stage 2	UL
Tan et al., 2016	2	13yr (UL); 20yrs (LL)	ISL Stage 2	UL (1); LL (1)
Nguyen et al., 2015	29	3.3yrs	Not clear	UL
Maruccia et al., 2019	16	Not clear	ISL Stage 2: 9; Stage 3: 7	LL
Ciudad et al., 2019	83	42m (SD: 14.5)	ISL Stage 2 & 3	UL(30); LL (53)
Engel et al., 2017	45	34.2, SD:10.4 (VLNT only), 101.7, SD: 38.1 (MBR + VLNT)	Cheng Stage 2: 22; Stage 3: 20; Stage 4: 3	UL
Maruccia et al., 2019	39	VLNT and SR (26+/-4), VLNT (25+/-3)	ISL Stage 2b: 24; Stage 3: 15	UL
Liu et al., 2018	30	6 yrs	ISL Stage 1: 1; Stage 2a: 25; Stage 2b: 4	UL
Ciudad et al., 2016	1	3 yrs	“Moderate”	LL
Agko et al., 2017	12	32m	ISL Stage 2b	UL (6); LL (6)
Ciudad et al., 2017	7	29.1m	ISL Stage 3: 7	UL (4); LL (3)
Gratzon et al., 2016	50	4.9 yrs	ISL Stage 1 or 2	UL
Ciudad et al., 2015	10	35.2m (SD: 11.8)	ISL Stage 2: 2; Stage 3: 8	UL (5); LL (5)
Cheng et al., 2013	10	33.2 (SD: 22.7)	ISL Stage 2	UL
Cheng et al., 2012	6	71 (SD: 42.2)	ISL Stage 2: 3; Stage 3: 3	LL
Lin et al., 2009	13	33.2 (SD: 28.9)	Not clear	UL
Aljaaly et al., 2019	15	28.8 (SD: 25.8)	Cheng Stage 2: 2; Stage 3: 9; Stage 4: 4	UL
Mousavi et al., 2019	24	5.6yr (n=18); 5m (n=6)	Not clear	UL
Sapountzis et al., 2014	2	6.5m	ISL Stage 1: 2	LL
Viitanen et al., 2013	19	55.1m	Not clear	UL
Chen et al., 2014	9	Not clear	Moderate: 2; Severe: 4	UL
Saaristo et al., 2012	9	42.6m (SD: 34.9)	Not clear	UL

Arrivé et al., 2017	15	Not clear	Absent, mild, moderate and severe	UL
Patel et al., 2015	20	51.2 (SD: 7.9)	Cheng Stage 1 & 2: 0; Stage 3: 4; Stage 4: 14	UL (13); LL (7)
Wong & Liu, 2015	1	8yrs	ISL Stage 2	UL
Gharb et al., 2011	21	Not clear	ISL Stage 2a	UL
Chen et al., 2016	3	Not clear	Campisi Stage 4	UL (2); LL (1)
De Brucker et al., 2016	25	42 (SD: 42)	ISL Stage 1 or 2	UL

Supplementary Table 4. Results of comparative intra-limb, cross-limb and cross-VLNT statistical testing.

Statistical Analysis	Result		Finding	P-Value
	CRR 1	CRR 2		
Intra-limb	Above elbow	Below Elbow	CRR greater above elbow	**
	Above knee	Below Knee	CRR greater below knee	ns
Cross-VLNT	Extra-Abdominal VLNT	Abdominal VLNT	No difference	ns
	Abdominal VLNT	BR-VLNT	No difference	ns
	Extra-abdominal VLNT	BR-VLNT	CRR greater for extra-abdominal VLNT	*

** $p<0.01$, * $p<0.05$, ns = not significant

Supplementary Table 5. Summary of pre- and post-operative LYMQOL score (overall domain only)

Study	Sample size	Pre-VLNT LymQoL (Overall Domain Mean Score)	SD	Post-VLNT Time-point	Post- VLNT LymQoL (Overall Domain Mean Score)	SD	Difference	
Maruccia *et al.*, 2019	16	2.5	0.4	12m	7.8	0.6	+5.3	Improvement
Visconti *et al.*, *2018*	10	4.375	NR	12m	6.65	NR	+2.275	Improvement
Gratzon *et al.*, 2016	50	5.72	NR	12m	7.79	NR	+2.07	Improvement
Ciudad *et al.*, 2015	10	3.1	NR	12m	8.2	NR	+5.1	Improvement
Cheng *et al.*, 2012	7	2.2	0.8	8.7m (Mean F/U)	7.5	0.5	+5.3	Improvement
Aljaaly *et al.*, 2019	15	2.5	0.6	12m	8	0.7	+5.5	Improvement
					Mean Difference:		**4.26 (SD: 1.48)**	

Figure 1

a)

Inclusion Criteria

(1) Any published full-length article
(2) VLNT performed as the sole therapeutic procedure for lymphoedema resulting from the therapeutic management of cancer
(3) Volumetric limb and or patient-reported lymphatic quality of life and or cellulitis-related outcome data reported

Exclusion criteria

(1) Non-English language article
(2) Article reporting VLNT following previous surgical management of lymphoedema
(3) Anatomical/cadaveric studies and/ or systematic reviews presenting no original data
(4) Conference proceedings, abstracts, letters

b)

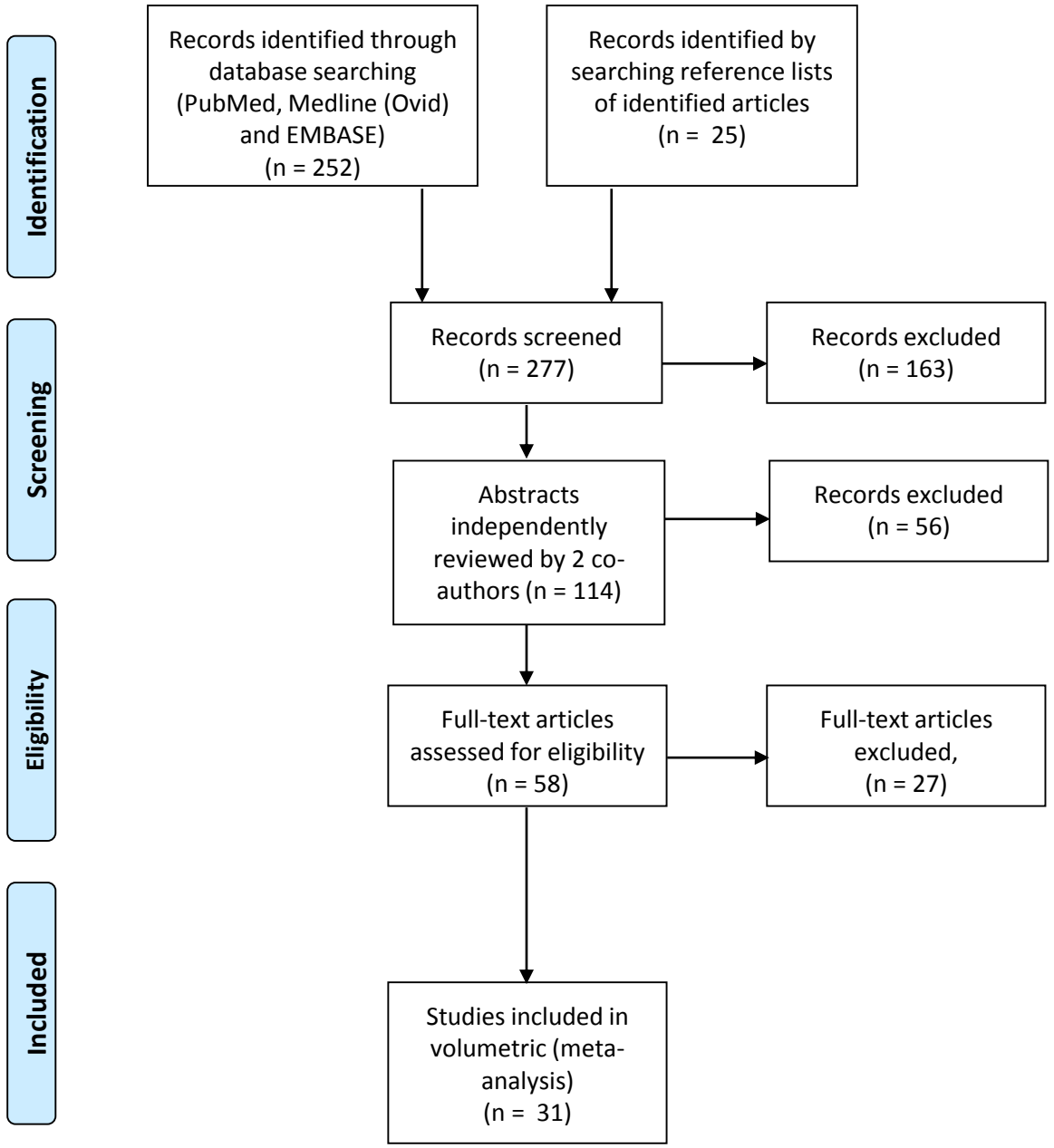


Figure 2

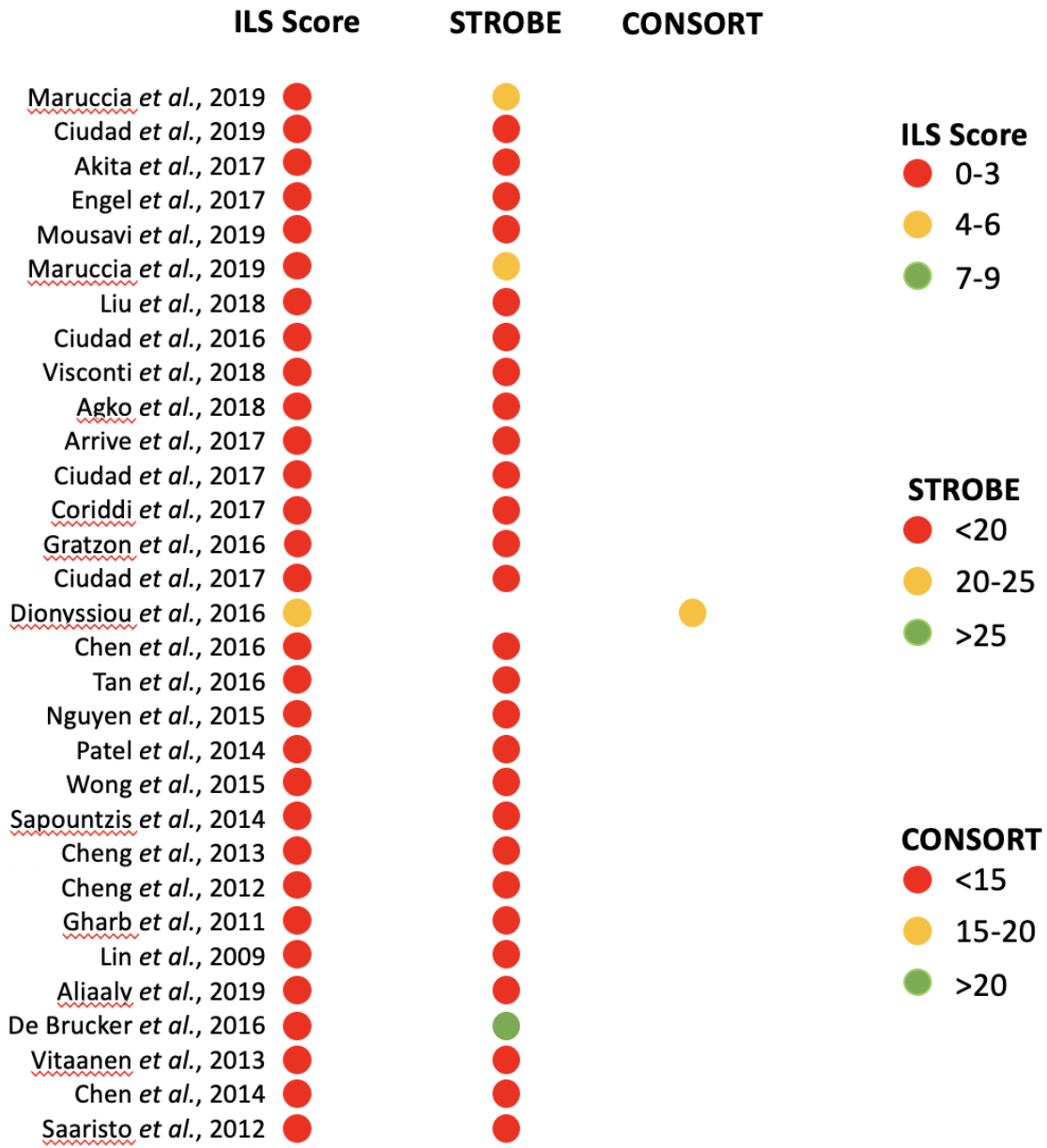
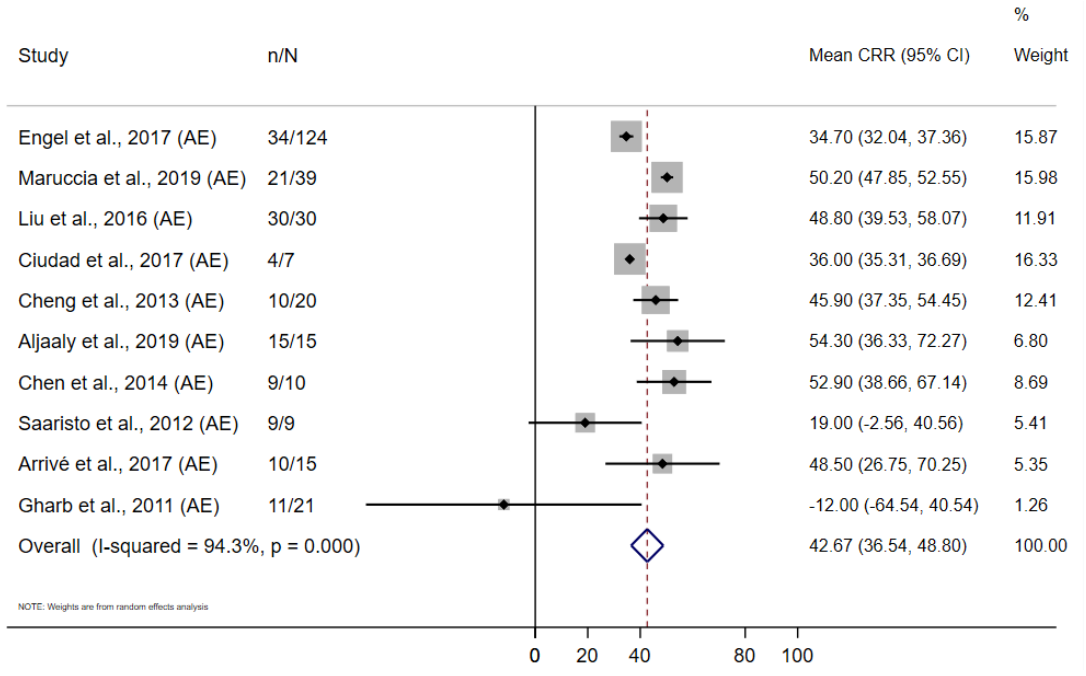

ILS Score
STROBE
CONSORT
Maruccia et al., 2019
Ciudad et al., 2019
Akita et al., 2017
Engel et al., 2017
Mousavi et al., 2019
Maruccia et al., 2019
Liu et al., 2018
Ciudad et al., 2016
Visconti et al., 2018
Agko et al., 2018
Arrive et al., 2017
Ciudad et al., 2017
Coriddi et al., 2017
Gratzon et al., 2016
Ciudad et al., 2017
Dionyssiou et al., 2016
Chen et al., 2016
Tan et al., 2016
Nguyen et al., 2015
Patel et al., 2014
Wong et al., 2015
Sapountzis et al., 2014
Cheng et al., 2013
Cheng et al., 2012
Gharb et al., 2011
Lin et al., 2009
Aliaalv et al., 2019
De Brucker et al., 2016
Vitaanen et al., 2013
Chen et al., 2014
Saaristo et al., 2012
ILS Score
0-3
4-6
7-9
STROBE
<20
20-25
>25
CONSORT
<15
15-20
>20

Figure 3

a)



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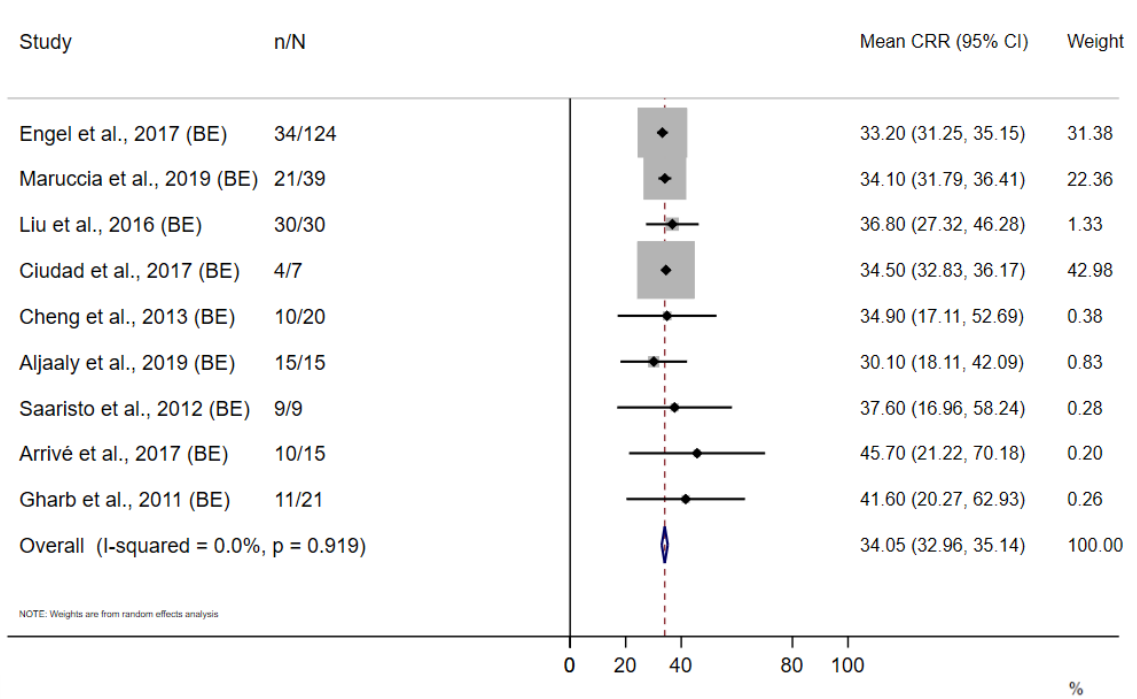

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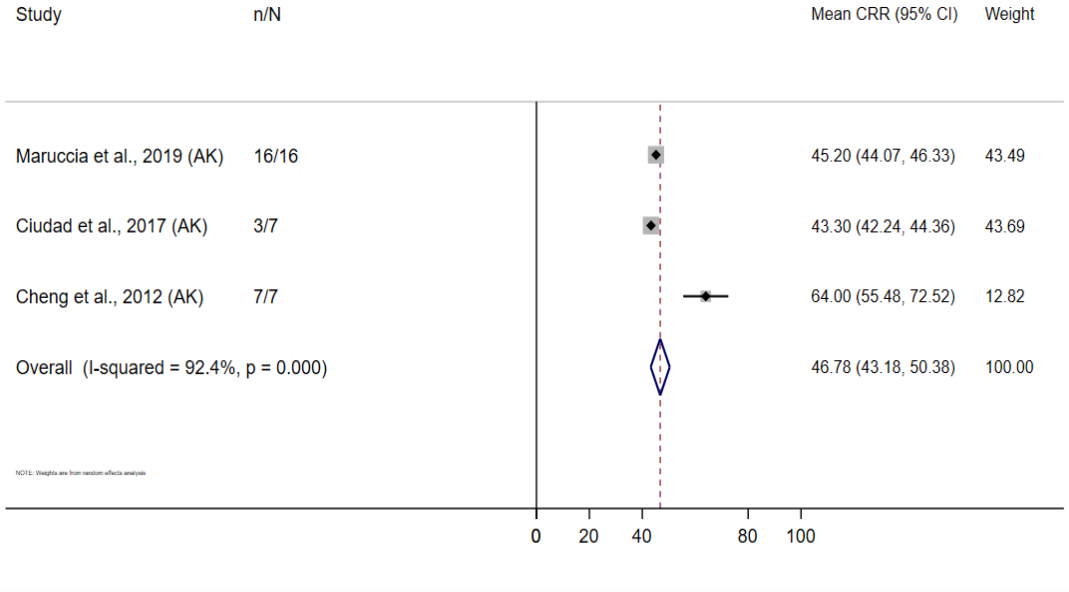

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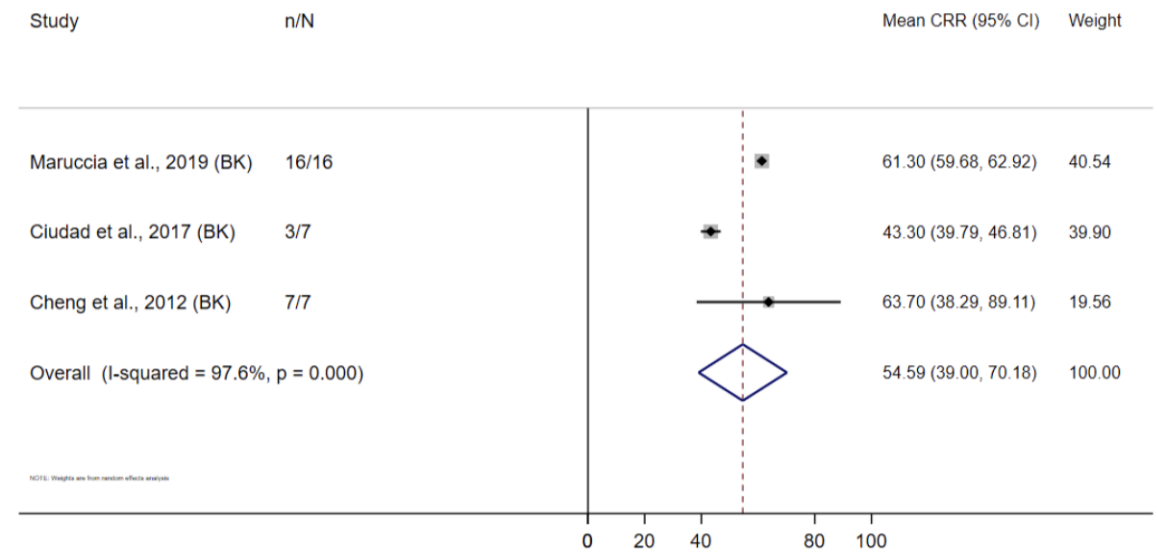
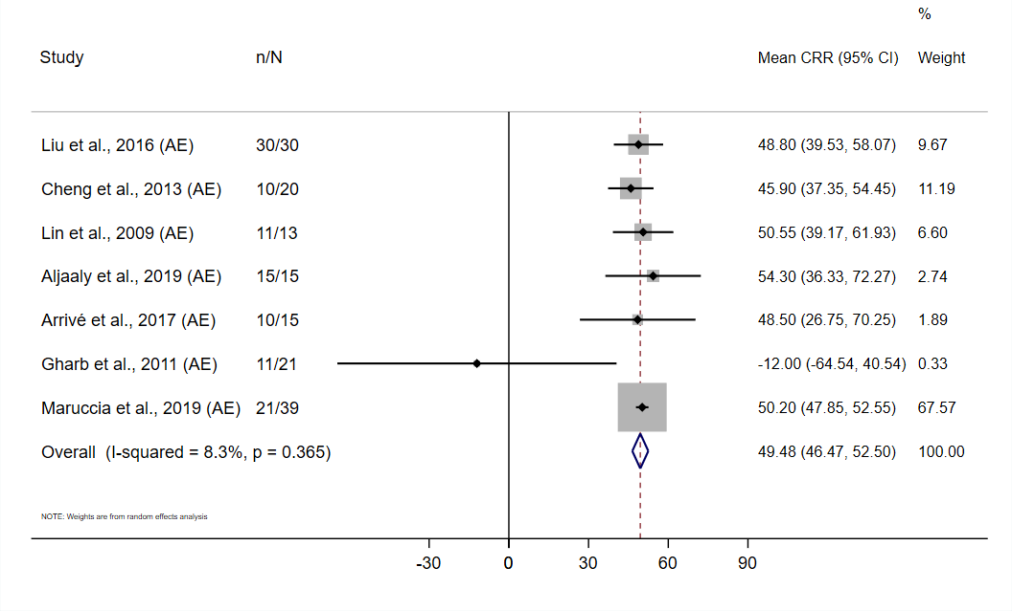
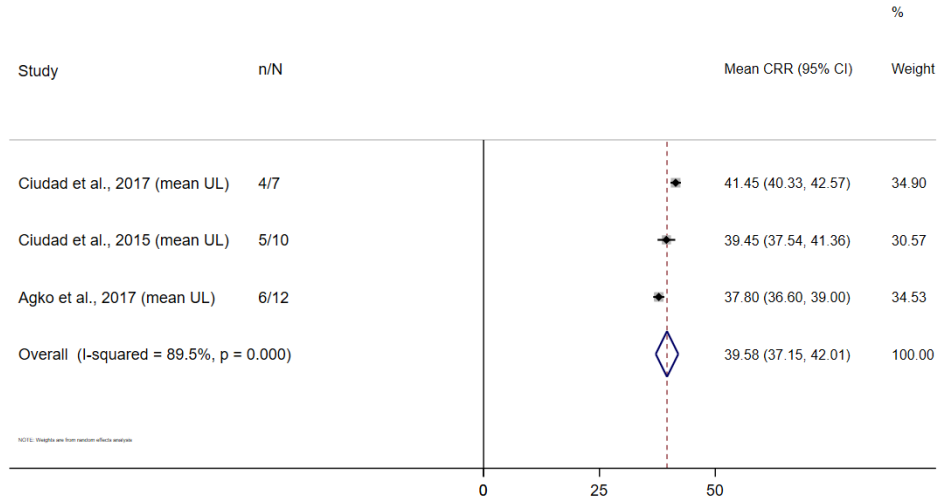


Figure 4

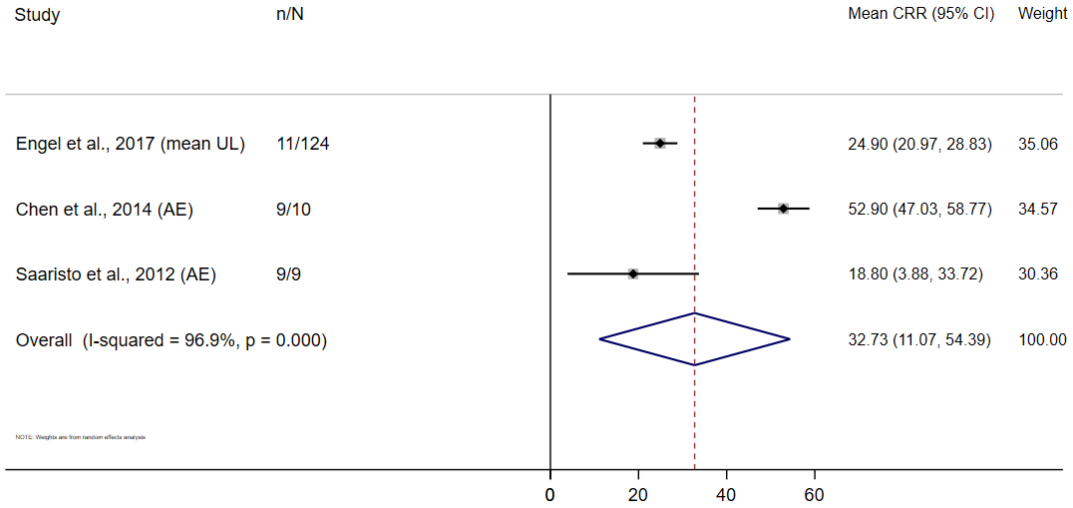
a) Extra-abdominal VLNT



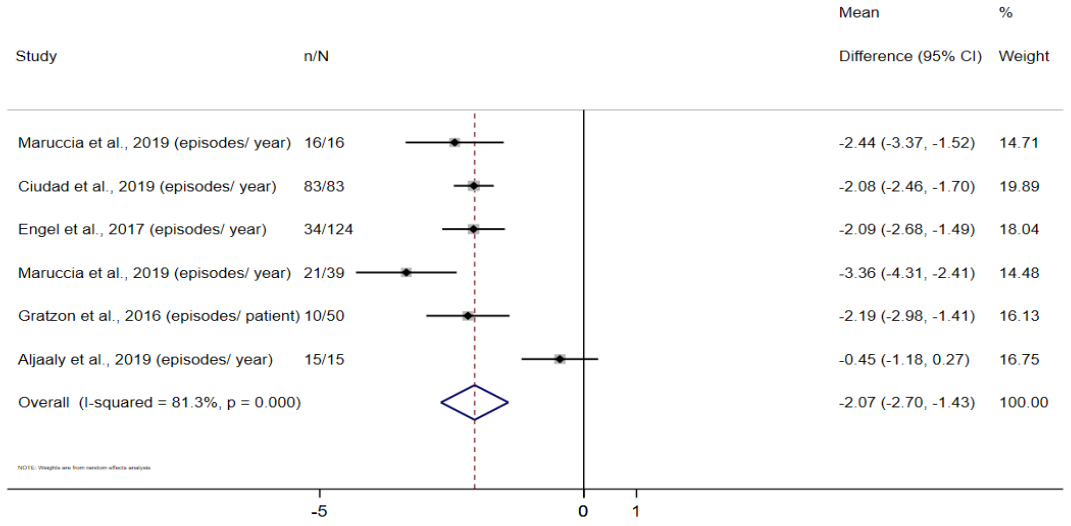
b) Abdominal VLNT



c) Autologous breast reconstruction with VLNT flap

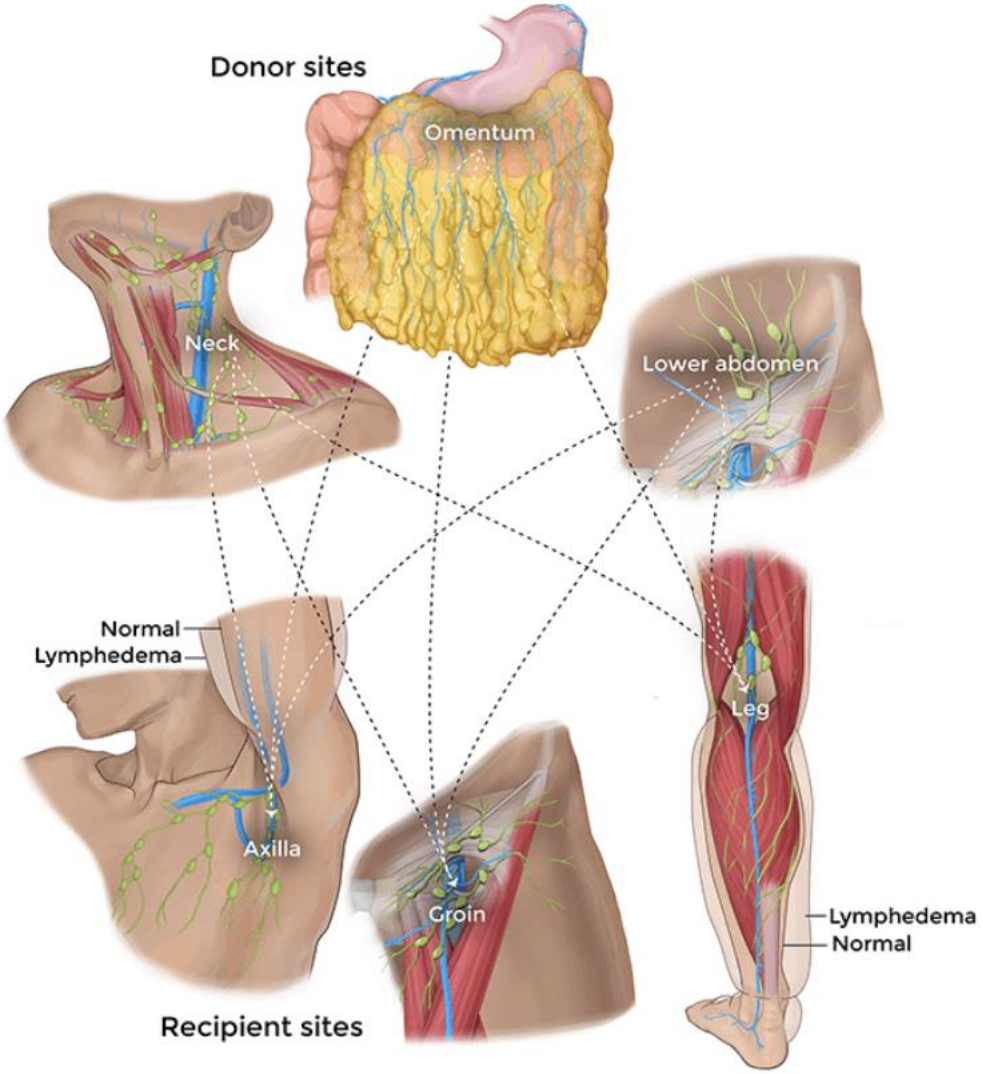


d) Cellulitis Episodes

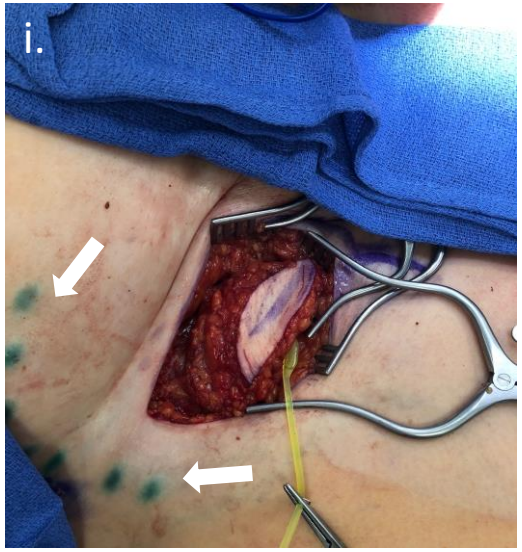


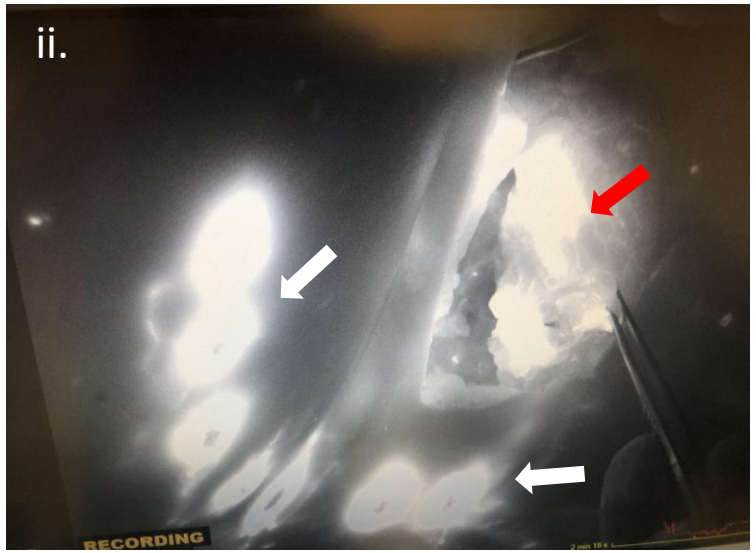
Supplementary Figure 1

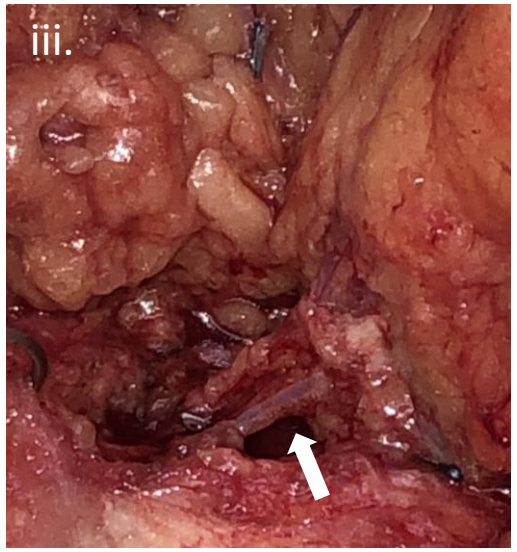
a)

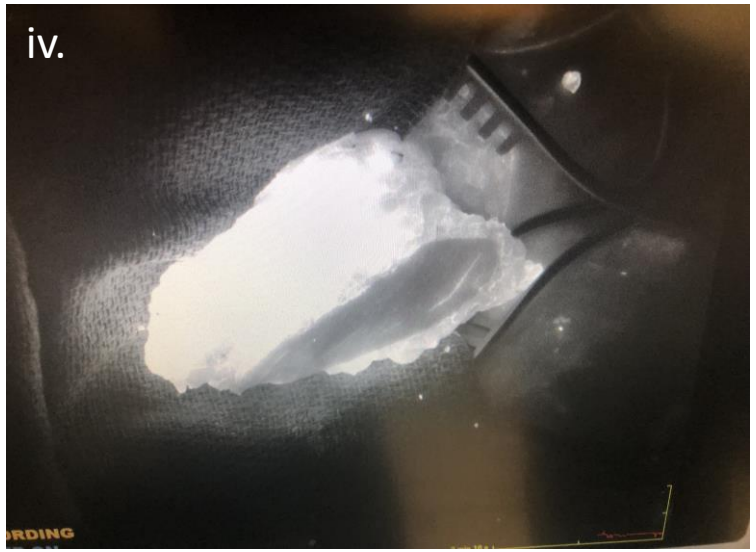


b)



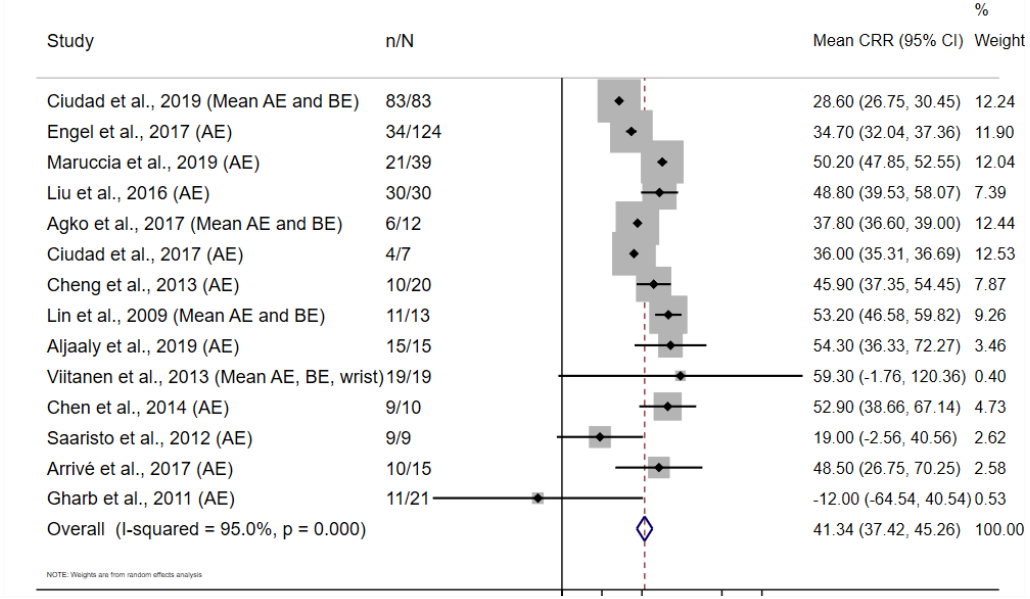






Supplementary Figure 2

a)



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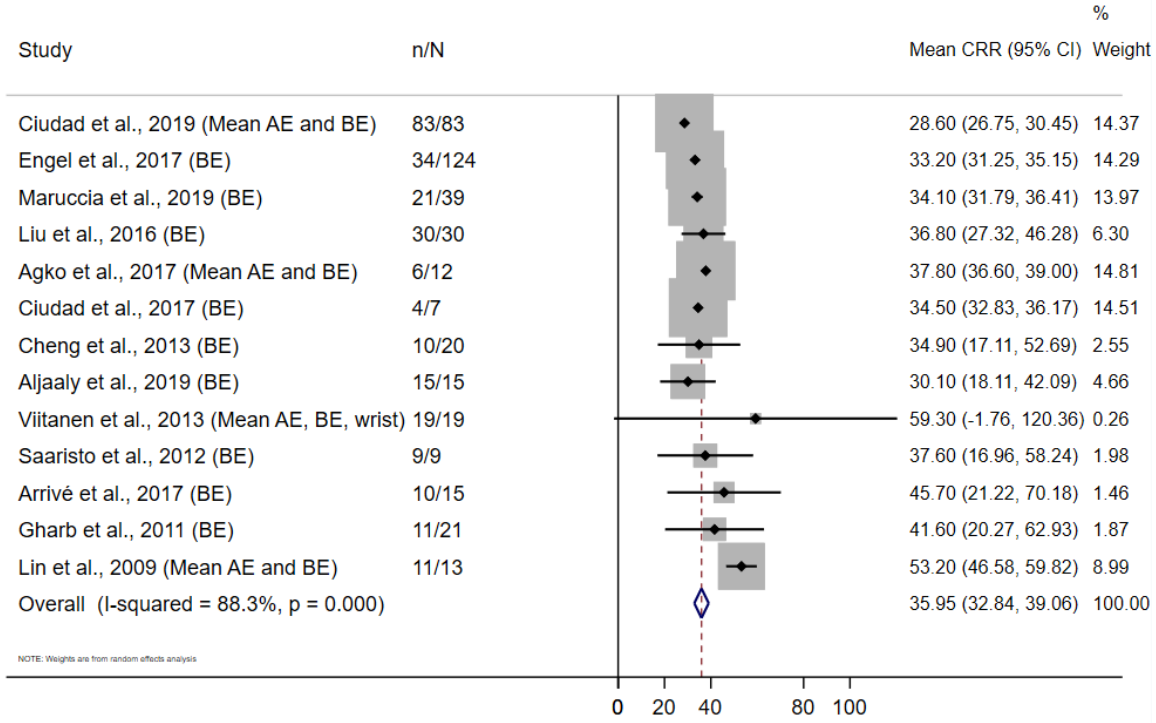

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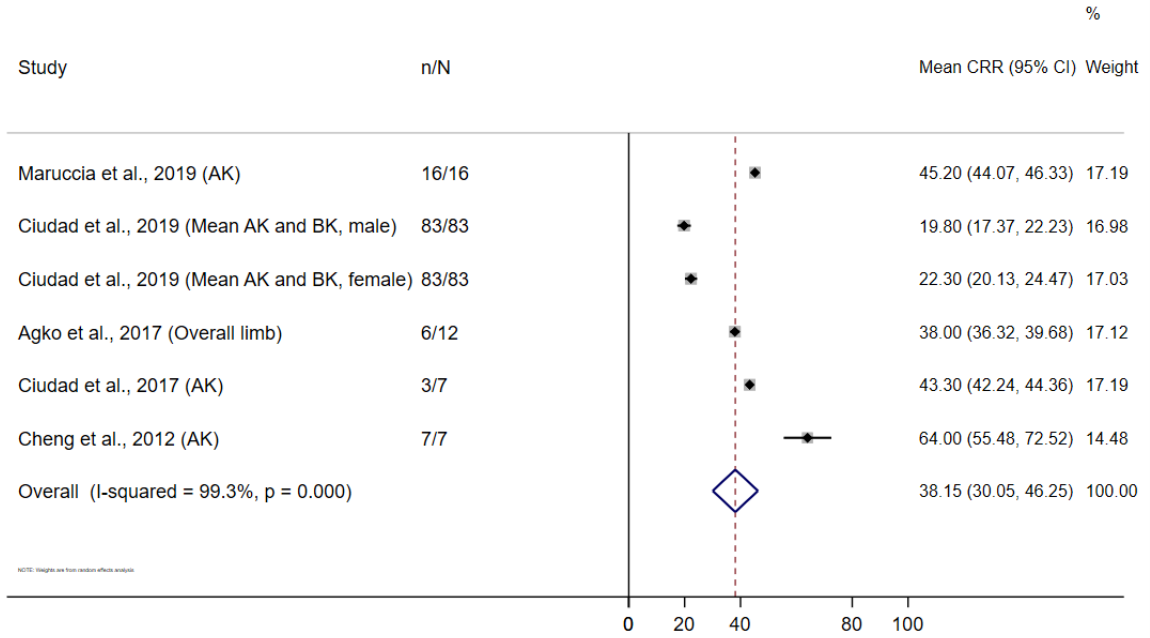

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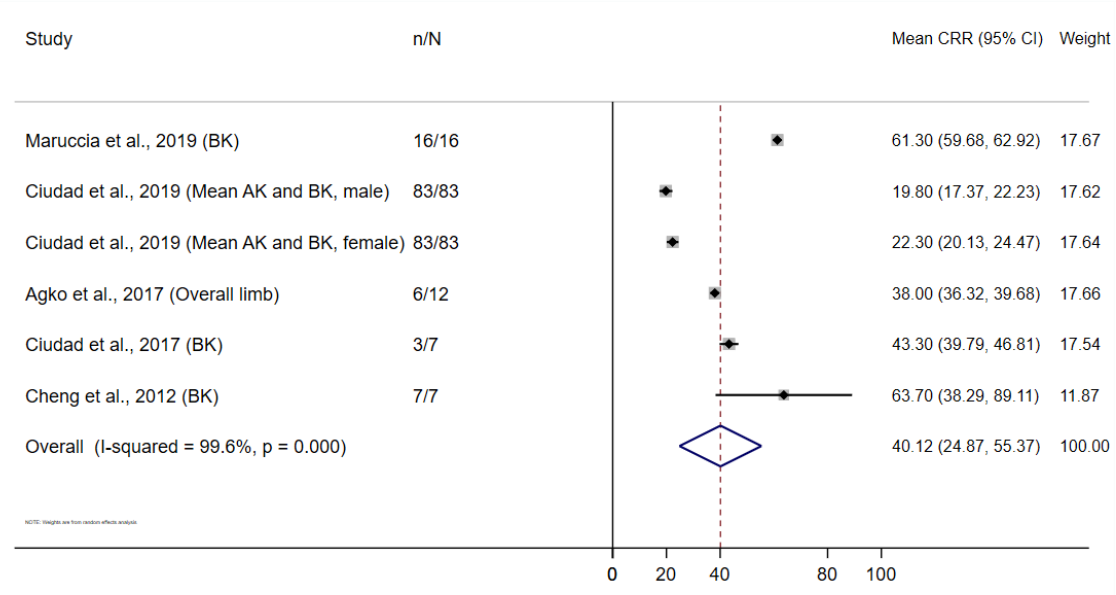
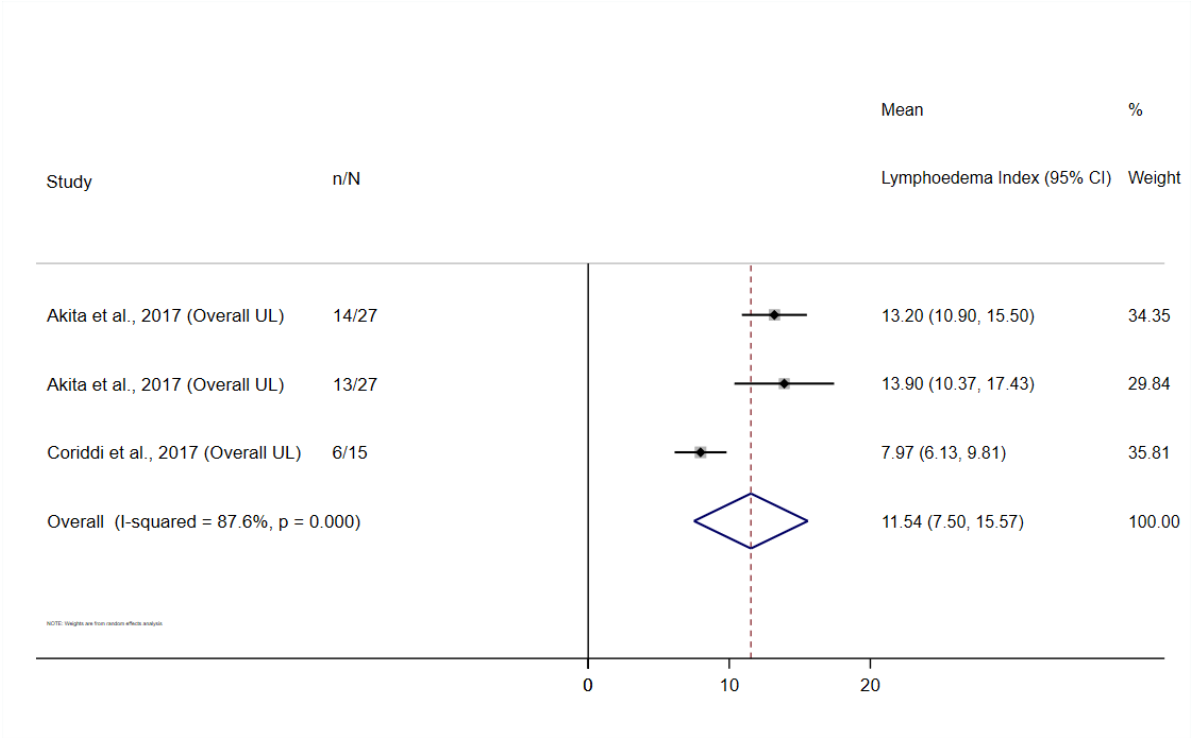
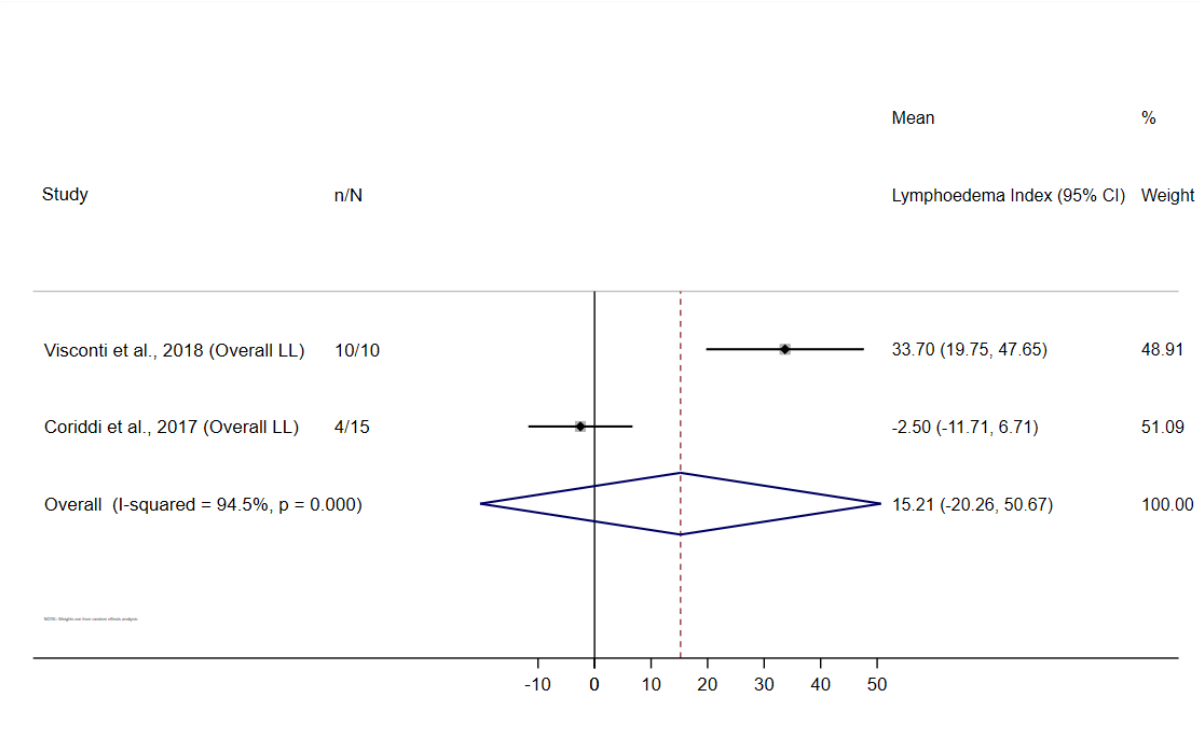


Supplementary Figure 3

a) Upper Limb



b) Lower Limb



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Contribution	Author(s)
Study concepts:	IK, AK, KR
Study design:	IK, AK, KR
Data acquisition:	JW, IK, NI
Quality control of data and algorithms:	JW, IK, AK
Data analysis and interpretation:	JW, IK, AK, KR, BA
Statistical analysis:	JW, AK, BA
Manuscript preparation:	JW, AK, KR, IK
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Possible Conflict of Interest: No / (Yes)
(Please ensure that a 'Conflict of Interest' statement is included in your manuscript)

Number of Tables: 7 (2 MAIN + 5 SUPPLEMENTARY) **Number of Figures:** 7 (4 MAIN + 3 SUPPLEMENTARY)

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"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *European Journal of Cancer*".

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Date: 12/21/2021