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Breast

Immediate Lymphatic Reconstruction during Axillary Node Dissection for Breast Cancer: A Systematic Review and Meta-analysis

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Background: The objective of this study is to summarize the current body of evidence detailing the impact of immediate lymphatic reconstruction (ILR) on the incidence of breast cancer-related lymphedema (BCRL) following axillary node dissection (ALND).
Methods: Medline and Embase databases were queried for publications, where ILR was performed at the time of ALND for breast cancer. Exclusion criteria included lymphaticovenous anastomosis for established BCRL, animal studies, non-breast cancer patient population studies, and descriptive studies detailing surgical technique. Meta-analysis was performed with a forest plot generated using a Mantel -Haenszel statistical method, with a random-effect analysis model. Effect measure was reported as risk ratios with associated 95% confidence intervals. The risk of bias within studies was assessed by the Cochrane Collaboration tool.
Results: This systematic review yielded data from 11 studies and 417 breast cancer patients who underwent ILR surgery at the time of ALND. There were 24 of 417 (5.7%) patients who developed BCRL following ILR. Meta-analysis revealed that in the ILR group, 6 of 90 patients (6.7%) developed lymphedema, whereas in the control group, 17 of 50 patients (34%) developed lymphedema. Patients in the ILR group had a risk ratio of 0.22 (CI, 0.09 -0.52) of lymphedema with a number needed to treat of four.
Conclusions: There is a clear signal indicating the benefit of ILR in preventing BCRL. Randomized control trials are underway to validate these findings. ILR may prove to be a beneficial intervention for improving the quality of life of breast cancer survivors. *(Plast Reconstr Surg Glob Open 2022;10:e4291; doi: 10.1097/GOX.0000000000004291; Published online 9 May 2022.)*

INTRODUCTION

Women undergoing axillary lymph node dissection (ALND) following breast cancer are at risk of significant challenges associated with upper extremity lymphedema.[1–3] This condition imparts functional and psychosocial morbidities, predisposing to recurrent cellulitis, and impairment of the affected limb.[4–6] A recent systematic review highlights the impact of lymphedema on the breast cancer patient population, which impacts one-third of patients undergoing ALND and postoperative radiation.[2]

Currently, breast cancer-related lymphedema (BCRL) is considered an incurable condition, and treatment is largely focused on nonoperative management with aggressive physiotherapeutic interventions.[6] Lymphaticovenous anastomosis (LVA) is an established method, when indicated, to treat pre-existing lymphedema and is reported to improve both objective- and patient-reported outcomes.[7] Extrapolating this, similar microsurgical techniques to reduce the incidence of lymphedema following ALND have been trialed. This

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is known as immediate lymphatic reconstruction (ILR), and with this technique, LVA is performed at the time of axillary node dissection to bypass the impasse of lymph from the arm caused by the node dissection. Several registered randomized control trials are underway to evaluate the efficacy of this intervention.

The objective of this study was to summarize the current body of evidence on how ILR impacts the incidence of BCRL following axillary node dissection.

Takeaways

Question: What is the impact of ILR on postoperative lymphedema in women with breast cancer undergoing ALND?

Findings: Performing ILR reduced the incidence of BCRL. The number needed to treat for this intervention is four.

Meaning: The current body of evidence suggests promising and durable results of ILR. Randomized control trials are underway to confirm these results.

METHODS

A systematic literature query was run on January 9, 2021 with the guidance of an institutional librarian in accordance with the PRISMA guidelines.[8] Medline and Embase databases were searched for English language publications. Neither study authors nor grey literature was sought. Studies identified were exported and stored on Microsoft Excel (version 16.48). The search strategy utilized for the Medline database, including field alias and logic statements, is described in Supplemental Digital Content 1. (**See appendix, Supplemental Digital Content 1,** which shows the search strategy. **http://links.lww.com/PRSGO/C17**.)

STUDY ELIGIBILITY

All studies identified from this search, where ILR was performed in breast cancer patients undergoing ALND, were included. A priori exclusion criteria included LVA for established BCRL, animal studies, nonbreast cancer patient population studies, conference abstracts, studies without follow-up, expert opinion, commentary articles, case reports, and descriptive studies detailing surgical technique. In situations of multiple publications where there were overlapping patient populations, the more recent study encompassing the entire patient population was used.

DATA EXTRACTION

After removal of duplicates, studies underwent title and abstract screening by two independent reviewers (WKFH and AP). Cases of disagreement were settled by verbal consensus. Relevant data extracted included adjuvant therapy, ILR technique (end-to-side, primary anastomosis, and multiple end-to-end), ILR feasibility number of recipient veins, number of LVAs, ILR operative time, follow-up length, diagnostic criteria, and incidence of lymphedema. In patients with bilateral ILR, each side was considered as one case (Table 1).

STATISTICAL ANALYSIS

Data were entered to the Cochrane Review Manager 5.4 (2021) for statistical analysis. A forest plot was generated using a Mantel–Haenszel statistical method with a random-effect analysis model. Effect measure was reported as risk ratios with associated 95% confidence intervals. The risk of bias within studies was assessed by the Cochrane Collaboration tool, and publication bias was assessed using a funnel plot.

RESULTS

Study Selection and Characteristics

The initial systematic review yielded 271 unique articles after removal of duplicates. The PRISMA flow diagram is outlined in Figure 1. After title and abstract reviews, a total of 130 studies were identified for full-text review. Eleven articles met inclusion criteria. These articles consisted of one randomized control trial, seven prospective cohort studies, and three retrospective reviews. Four of the 11 studies with control groups could be included in a meta-analysis.

Analysis of BCRL

This systematic review yielded data from 11 studies and 417 breast cancer patients who underwent ILR surgery at the time of ALND.[1,9–18] There were 277 patients who underwent ILR with postoperative radiation (66.4%). The pooled incidence revealed that 24 of 417 (5.7%) patients subsequently developed BCRL following ILR (Table 1). The follow-up period and method of lymphedema diagnosis showed notable variability among study groups. The pooled median length of follow-up, when reported, was 12 months (range 6–48 months).

Common methods to detect lymphedema included clinical examination, limb circumference measurements, volumetry, bioimpedance spectroscopy, and lymphoscintigraphy. There was heterogeneity in the technique and criteria for lymphedema diagnosis within the studies analyzed. For circumferential arm measurements, Schwarz et al[13] identified patients with symptoms, abnormalities in circumferential measurements or abnormal bioimpedance spectroscopy, and referred to a lymphedema therapist to confirm the diagnosis. Cook et al[1] diagnosed lymphedema if patients had limb circumference measurements that increased by 2 cm following ALND or clinically by the plastic surgeon. A discrepancy of greater than 1 cm was used by Boccardo et al[11] to detect lymphedema with limb circumference measurements. Feldman et al[16] used arm measurements that increased by more than 2 cm compared with either presurgical measurements or the contralateral unaffected arm and lymphoscintigrams with a transit index greater than 10. Volumetry was another technique used to detect lymphedema in three studies. Johnson et al[18] identified lymphedema if there was a 10% volume increase in the dominant arm or 7% increase in the nondominant arm. Boccardo et al[15] identified

Table 1. Qualitative Analysis of Studies Meeting Inclusion Criteria

Article	No.	Study Design	Radiation Therapy	LVA Technique	No. Veins	No. Lymphatics	LVA Feasibility	LVA Time (Min)	Follow-up (Mo)	Lymphedema Diagnosis	Lymphedema with ILR	Lymphedema in Controls
Boccardo et al[11]	19	Prospective cohort study	7/19	End-to-side	1	2–4	18/19 (95%)	15	12	CM, LS	0/18 (0%)	—
Casabona et al[9]	9	Prospective cohort study	9/9	End-to-side	NR	NR	8/9 (89%)	17	9	CE, LS	0/8 (0%)	—
Boccardo et al[12]	74	Prospective cohort study	35/74	End-to-side	1	2–4	74/78 (95%)	20	48	V, LS	3/74 (4.1%)	—
Agrawal et al[10]	35	Prospective cohort study	10/35	End-to-side	1	1–5	NR	53.28	NR	CE, LS	2/35 (5.7%)	—
Schwarz et al[13]	58	Prospective cohort study	52/58	Primary anastomosis and end-to-side	NR	1–4	58/60 (97%)	85	11.8	CE, CM, BIS	2/58 (3.4%)	—
Cook et al[1]	33	Retrospective review	22/33	Multiple end-to-end	1	1–3	NR	NR	12	CE, CM	3/33 (9.1%)	—
Le et al[14]	100	Prospective cohort	80/100	Primary anastomosis and multiple end-to-end	1.44	1–2	NR	NR	12.9	CE, BIS	8/100 (8%)	—
Boccardo et al[15]	46	Randomized control trial	ILR: 11/23 Control: 12/23	End-to-side	1–2	2–4	23/23 (100%)	15-20	18	V, LS	1/23 (4.3%)	7/23 (30%)
Feldman et al[16]	37*	Prospective cohort study	ILR: 15/24 Control: 6/8	End-to-side	1	1–3	27/37 (73%)	45	6 (3–24)	CE, CM, BIS, LS	3/27 (11.1%)	4/8 (50%)
Hahamoff et al[17]	18	Retrospective review	ILR: 8/8 Control: 8/10	NR	NR	NR	NR	NR	15	CE, CM, BIS	1/8 (12.5%)	4/10 (40%)
Johnson et al[18]	41	Retrospective review	ILR: 28/32	End-to-side	NR	1–3	32/41 (78%)	85	11.4	V, BIS	1/32 (3.1%)	1/9 (11%)

*Five patients excluded due to preoperative lymphedema or follow-up <3 months.

BIS, bioimpedance spectroscopy; CE, clinical evaluation; CM, circumference measurement; LS: lymphoscintigraphy; NR, not reported; V, volumetry.

lymphedema if there was greater than 100-mL discrepancy compared with preoperative volume measurements by 18 months postoperatively.

Analysis of Surgical Technique

In all studies, ILR was performed prophylactically at the time of ALND, rather than therapeutically for established BCRL. The feasibility of performing LVA was reported in seven of the 11 studies with an average of 83%. The most common technique was end-to-side (9/11). Six of the 11 studies reported the number of recipient veins. Most commonly, a single recipient vein was used (range 1–2). The number of anastomosed lymphatics varied within and between studies but ranged from one to five. The average operative time to complete anastomosis for LVA as reported in eight of the 11 studies was 48 minutes (15–85 minutes) (Table 1).

Meta-analysis

There were four studies with a control group included in the meta-analysis.[14–17] Demographics such as patient age (58 versus 60), body mass index (28 versus 28), or nodes involved (4 versus 2.3) were similar in the control and ILR groups, respectively. In the pooled ILR group, six of 90 patients (6.7%) developed lymphedema, whereas in the pooled control group, 17 of 50 patients (34%) developed lymphedema. Patients in the ILR group had a risk ratio of 0.22 (CI, 0.09–0.52) of developing lymphedema (Fig. 2). This yields a number needed to treat (NNT) of four.

Lymphedema was measured with variable and multiple techniques, including clinical examination (2/4), circumferential measurements (2/4), volumetry (2/4) bioimpedance spectroscopy (3/4), and lymphoscintigraphy (2/4) (Table 1). Funnel plot analysis was not suggestive of publication bias. However, the limited number of studies did not allow for any definitive conclusion. Risk of bias assessment was performed (Fig. 3). Only one study[15] mentioned randomized study arms, and in no study was the assessor blinded nor was there allocation concealment. One study had selection bias in that their control group was composed of patients who found unfeasible to successfully undergo ILR intraoperatively, potentially introducing a confounding influence such as bulkier disease requiring a more radical resection, leaving veins and lymphatics too sparse to anastomose.[16] A meta-regression was not feasible because all studies were identified to be at high risk of bias.

DISCUSSION

An evolving entity within the realm of plastic surgery oncology is the primary risk reduction of lymphedema following lymphadenectomy. Patients with breast cancer undergoing axillary node dissection are particularly at high risk of developing lymphedema in the affected arm. A recent systematic review by Johnson et al showed that in patients undergoing ALND and postoperative radiation, there is an incidence of lymphedema of 33%. The impact of lymphedema on patients' quality of life is considerable. Patients experience recurrent cellulitis, economic stress,

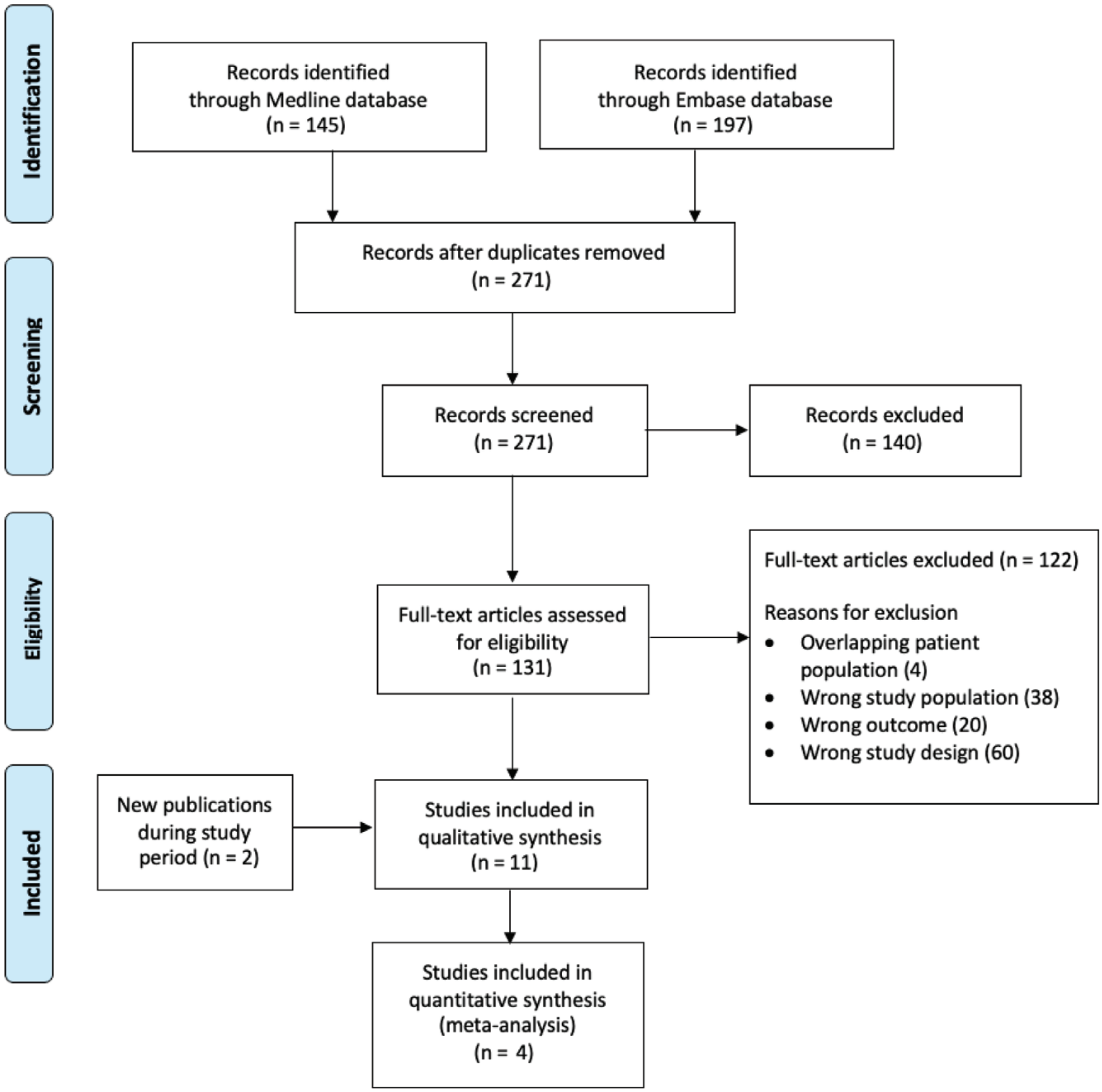

Fig. 1. PRISMA flow diagram of systematic review and study screening.

functional impairment of the arm, fatigue, anxiety, frustration, and increased self-consciousness.[19,21] Given the refinement of supermicrosurgical instruments and technique,[21,24] the growing literature and experience gained in the treatment of established lymphedema with LVA,[7] and the increasing focus on survivorship and quality of life, the time is ripe for ILR to be considered at the time of node dissection.

ILR was first introduced by Boccardo et al[11] with their initial series including 19 patients; in 18 patients, lymphatic channels were successfully identified. None of these 18 patients had experienced lymphedema at 1 year of follow-up. Our systematic review and meta-analysis was undertaken to better understand the impact of ILR following ALND for breast cancer patients. With an average time of 48 minutes to perform ILR and a pooled feasibility of 83%,[9,11–16] this is a viable technique with acceptable added time to the ALND, with all being performed during the same general anesthetic.

Studies included in this systematic review and meta-analysis were one randomized control trial, seven prospective cohort studies, and three retrospective reviews. Other authors have reviewed the ILR literature, but none have focused on breast cancer and the axilla specifically.[13] Axillary and inguinal lymph node dissections are distinct entities with different rates of lymphedema.

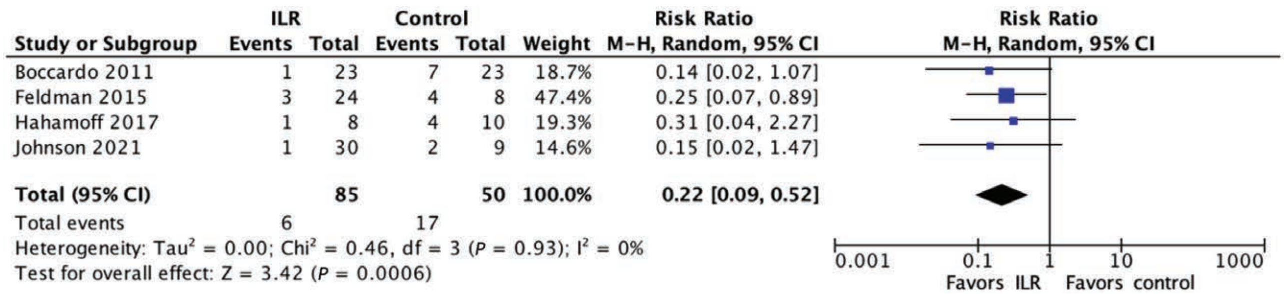

Fig. 2. Meta-analysis of eligible studies.

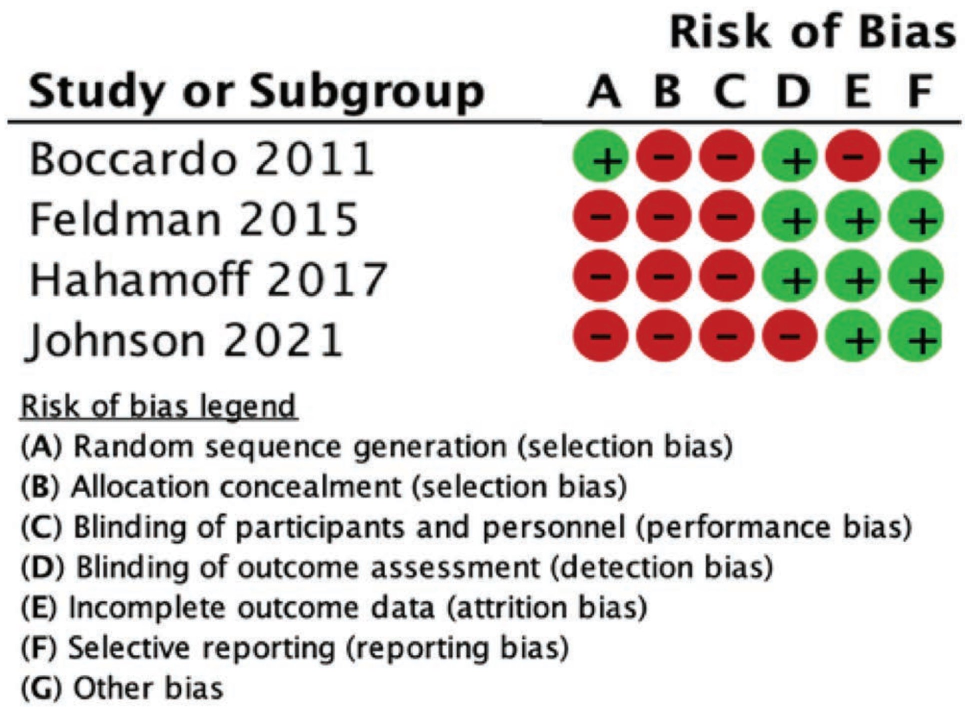

Fig. 3. Risk of bias assessment.

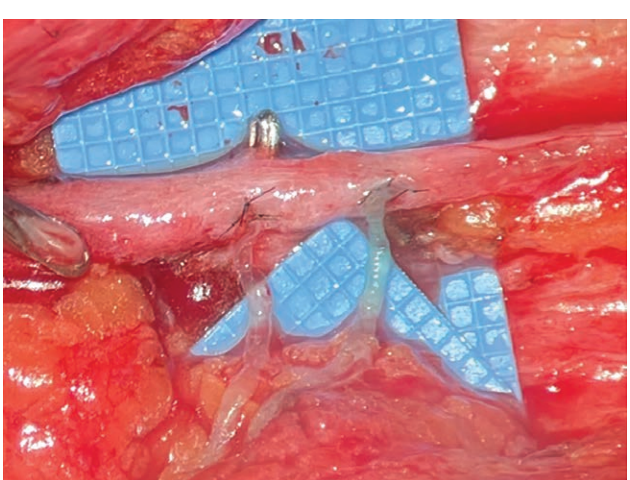

Fig. 4. ILR following axillary node dissection with two lymphatic channels anastomosed end-to-side to vein within the surgical field.

Similarly, compared with other tumor types such as cutaneous and gynecologic malignancies, breast cancer should be analyzed separately, as adjuvant therapies and radiotherapy are applied differently. By focusing the literature search on ALND in the context of breast cancer, the included patient population allowed comparison of groups with similar patient characteristics, indication for lymphadenectomy, oncologic therapy, and pathophysiology for lymphedema. A recent meta-analysis by Johnson et al explored the incidence of lymphedema in various scenarios pertaining to breast cancer surgery and highlighted the impact of ILR at the time of ALND.[2] The focus on lymphatic reconstruction and the pertinent technical details in our article provides accurate context to interpret and understand the true impact of ILR in the context of BRCL.

Since the introduction of ILR, no consensus on technique or number of anastomoses has been reached. All studies used axillary reverse mapping to identify lymphatic

Table 2. Characteristics of Registered Controlled Trials to Determine the Protective Benefit of Immediate LVA after ALND

Research Group	Trial Number	No. Patients	Condition	LE Measurement	LE Diagnosis (% between Measurements)	Study Start Date	Estimated Study Completion Date	Follow-up (Mo)
Mayo Clinic	NCT03428581	264	Breast cancer Melanoma	BLVM	>5%	April 2018	February 2023	36
MD Anderson Cancer Center	NCT03941756	50	Breast cancer	BLVM	>5%	August 2018	December 2020	18
Memorial Sloan Kettering Center	NCT04241341	174	Breast cancer	BLVM with the truncated cone formula	>10%	January 2020	January 2022	24
Pusan National University Hospital	NCT04328610	34	Breast cancer	BLVM and lymphoscintigraphy	Not specified	March 2020	February 2022	12

BLVM, bilateral limb volume measurements; LE, lymphedema.

channels. This technique utilizes the injection of patent blue dye and/or indocyanine green into the subcutaneous tissue of the upper arm at the time of surgery to allow visualization and preservation of upper extremity lymphatic channels during ALND.[23] In the majority of studies, end-to-side ILR was performed, with some authors opting for primary anastomosis with an appropriate size match[11,12] or multiple end-to-end with a cut vein.[1,12] The number of anastomoses varied, namely between one and five. Lack of technique uniformity may influence lymphedema rates. An example of end-to-side technique is shown in Figure 4.

One of the challenges of outcome reporting with ILR is the definition of lymphedema. There is inconsistency in the definition of lymphedema throughout the studies identified. Most studies looked at composite measures taking into account clinical examination and limb volumetry[1,11,13,15,17] with or without other measurement modalities, including bioimpedance spectroscopy[13,14,16–18] and lymphoscintigraphy.[9–12,15,16] The lack of a standardized objective definition and evaluation of lymphedema remains a barrier in research and limits the interpretation of pooled results. The 2020 consensus document of the international society of lymphology suggests that in each patient undergoing therapy, an assessment of limb volumes should be made before, during, and after treatment. Additionally, health-related quality of life and patient perceptions of self-efficacy, assessed with disease-specific instruments and visual analog scales, should be used in conjunction with objective measurements to evaluate the effects of treatment.[24] This meta-analysis revealed that volumetry was used in a minority of cases, and patient-reported outcomes were measured only in one study by Johnson et al. The time to develop lymphedema after ALND is an important consideration when studying the impact of ILR. The median follow-up for the studies included was 12 months. The risk of developing lymphedema has been shown to peak between 6–12 months postoperatively in patients undergoing ALND without radiation and 18–24 months in patients undergoing ALND with radiation.[25]

Despite these challenges in study quality, design, and differences in measurement outcome, there remains a signal that ILR reduces BCRL. This contrasts with the overall incidence of BCRL in all patients who underwent ALND with an ILR of 5.8%. The results proved to be durable with a median follow-up of 12 months.

Our pooled analysis revealed a 32% of incidence of BCRL following ALND in the control groups. This is in keeping with the published rate of 34% by Johnson et al[2] in patients undergoing ALND and radiation. Of the studies included in the meta-analysis, an incidence of 6.7% was found in patients undergoing ALND and ILR. This yields a statistically different risk reduction of developing BRCL following ALND of 0.22, and a calculated NNT is four with ILR compared with standard of care. If this is substantiated by the currently enrolling randomized control trials (Table 2), the number of patients needed to treat is four in order to prevent one instance of BCRL.

Four randomized controlled trials are currently accruing to determine the protective benefit of performing ILR following ALND. Teams from the Mayo Clinic, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, and Pusan National University Hospital are recruiting and randomizing adult female cancer patients undergoing ALND to ILR or standard care. After a follow-up period between 12 and 36 months, the presence of lymphedema will be determined by comparing preoperative and postoperative bilateral limb volume measurements. Additionally, questionnaires assessing quality of life will be used. These trials are expected to be completed by the end of 2022, with results published around the beginning of 2023 (Table 2).

CONCLUSIONS

This systematic review and meta-analysis shows promising and durable results for ILR in reducing the rate of lymphedema for breast cancer patients undergoing ALND. The current body of evidence demonstrates an NNT of four. Randomized control trials are underway to validate these findings. ILR may prove to be a feasible, relatively short, and beneficial intervention to improve the quality of life of breast cancer survivors.

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