Lymphedema Incidence After Axillary Lymph Node Dissection

Quantifying the Impact of Radiation and the Lymphatic Microsurgical Preventive Healing Approach

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Background: Axillary surgery and radiotherapy are important aspects of breast cancer treatment associated with development of lymphedema. Studies demonstrate that Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) may greatly reduce the incidence of lymphedema in high-risk groups. The objective of this study is to summarize the evidence relating lymphedema incidence to axillary lymph node dissection (ALND), regional lymph node radiation (RLNR) therapy, and LYMPHA.

Methods: We performed a literature search to identify studies involving breast cancer patients undergoing ALND with or without RLNR. Our primary outcome was the development of lymphedema. We analyzed the effect of LYMPHA on lymphedema incidence. We chose the DerSimonian and Laird random-effects meta-analytic model owing to the clinical, methodological, and statistical heterogeneity of studies.

Results: Our search strategy yielded 1476 articles. After screening, 19 studies were included. Data were extracted from 3035 patients, 711 of whom had lymphedema. The lymphedema rate was significantly higher when RLNR was administered with ALND compared with ALND alone ($P < 0.001$). The pooled cumulative incidence of lymphedema was 14.1% in patients undergoing ALND versus 2.1% in those undergoing LYMPHA and ALND ($P = 0.029$). The pooled cumulative incidence of lymphedema was 33.4% in those undergoing ALND and RLNR versus 10.3% in those undergoing ALND, RLNR, and LYMPHA ($P = 0.004$).

Conclusion: Axillary lymph node dissection and RLNR are important interventions to obtain regional control for many patients but were found to constitute an increased risk of development of lymphedema. Our findings support that LYMPHA, a preventive surgical technique, may reduce the risk of breast cancer–related lymphedema in high-risk patients.

Key Words: lymphedema, breast cancer, axillary lymph node dissection, regional lymph node radiation, immediate lymphatic reconstruction

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Upper extremity lymphedema (LE) is a feared complication of breast cancer treatment.[1] This disease can detrimentally affect patient quality of life and cause significant morbidity.[2] In one study, patients diagnosed as having breast cancer–related lymphedema (BCRL) were shown to experience higher levels of mood disorders such as anxiety and depression, higher risks of fatigue and chronic pain, and greater difficulty with sexual and social functioning when compared with patients with breast cancer without LE. Furthermore, BCRL can result in chronic infection, discomfort, and functional impairment.[3]

Axillary lymph node dissection (ALND) and regional lymph node radiation (RLNR) therapy are important for attaining regional control of breast cancer.[4,5] However, both therapies can result in LE.[6–8] Once LE develops, it is considered to be largely irreversible, although available therapies can often reduce its severity.

Microsurgical approaches including lymphovenous bypass and vascularized lymph node transplant are performed to ameliorate established LE.[9] More recent advances have led to attempts to prevent BCRL via the Lymphatic Microsurgical Preventive Healing Approach (LYMPHA).[10] In this technique, a dye injected into the upper arm at the time of ALND is used to identify divided arm lymphatics. These lymphatics, measuring 0.2 to 0.6 mm, are then bypassed into a vein using standard microsurgical technique. This bypass facilitates rerouting of arm lymph into the central venous system. This technique has demonstrated promising results in high-risk patients in several small institutional studies.[10–14] However, the potential impact of LYMPHA requires an understanding of the baseline risk of BRCL in the available literature.

With the aim of determining the influence of ALND with and without LYMPHA, and ALND and RLNR with or without LYMPHA on rates of LE, we analyzed and compared postoperative rates of LE after these surgical interventions and adjunct therapies. Our objective for this study is to summarize the evidence on how LE incidence after ALND is affected by RLNR and/or LYMPHA by conducting a systematic literature review and meta-analysis.

METHODS

Literature Search

A systematic literature search was performed on April 17, 2018, with a medical research librarian in accordance with PRISMA guidelines.[15] The PubMed, Embase, Web of Science, and Cochrane databases were searched from inception through April 17, 2018, for publications describing breast cancer patients who underwent ALND with or without RLNR. The search strategy is detailed in Table 1. The primary outcome of interest was the development of LE. In addition, the impact of a microsurgical technique, LYMPHA, on the development of LE in this patient population was assessed. The medical subject headings and text words were modified according to the results yielded in each database search as an iterative process. In addition, all included studies were subjected to a manual reference search. Published articles that met all the inclusion criteria and none of the exclusion criteria were included for analysis.

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TABLE 1. Search Strategy

Database	Search Strategy
PubMed	(((((LYMPHA[tw]) OR ("Lymphedema/prevention and control"[Mesh])) OR (("lymphedema"[tw] OR "lymphedemas"[tw] OR "lymphoedema"[tw] OR "lymphoedemas"[tw])))) AND (((("Breast Neoplasms/surgery"[Mesh]) OR "Breast Cancer Lymphedema/surgery"[Mesh]) OR ("Breast Cancer Surgery"[tw] OR "Breast Cancer excision"[tw]) OR (("Breast tumor"[tw] OR "Breast Cancer*") AND ("Surgery"[tw] OR "Excision"[tw]" OR "Extirpation"[tw]))))) AND (((("Lymph Nodes/surgery"[Mesh]) OR "Lymph Node Excision"[Mesh] OR "Lymph Node Excision*"[tw] OR "lymph node dissection"[tw] OR "lymph node dissections"[tw] OR "Axillary Lymph Node Dissection"[tw] OR "Axillary Lymph Node Dissect*"[tw] OR "alnd"[tw])))
EMBASE	("breast cancer'/exp AND "microsurgery"/exp OR "breast neoplasms surgery" OR "breast surgery"/exp OR "mastectomy"/exp) AND ("internal mammary lymph node"/exp OR "lymph node"/exp OR "lymphedema"/exp) AND (lympha OR slympha OR "microsurgery"/exp)
Web of Science	No. 1: (TS = breast cancer OR TS = breast neoplasms) AND (TS = surgery OR TS = microsurgery OR TS = mastectomy) No. 2: TS = (lympha) OR TS = (microsurgery) OR TS = (slympha) Nos. 1 and 2
Cochrane Library	Lymphedema AND (breast NEXT cancer OR breast NEXT neoplasms) (LYMPHA OR Slympha OR microsurgery)

Study Selection

All articles published describing the incidence of LE in breast cancer patients undergoing ALND with or without RLNR were included. If articles were written in a different language, all efforts were made to contact the authors to obtain an English-language version. There was no date limit imposed. Exclusion criteria included the following: non-ALND intervention (ie, axillary sampling or sentinel lymph node biopsy), unspecified modality of radiotherapy, studies that did not quantify the number of lymph nodes removed, and studies without any follow-up time. In addition, duplicate studies, review articles, editorials, abstracts, expert opinions, commentary articles, and descriptive studies detailing surgical technique were excluded.

Data Extraction

All identified citations yielded from the initial search were imported into EndNote X8.0.1 (Thomas Reuters, New York, New York). After removal of duplicates, all publications were subject to title and abstract screening by 2 reviewers (A.R.J. and S.E.). All remaining articles underwent a full-text screening using the inclusion and exclusion criteria. Data extraction was performed independently by 2 researchers (A.R.J. and S.E.), and disagreement was resolved by consensus. If consensus could not be reached, a third researcher (D.S.) served as the adjudicator. Data collected included the following: study design, sample size, definition of LE, description of LE measurement modality(ies), type of axillary surgery, radiotherapy administered, number of lymph nodes removed during ALND, incidence of LE, and follow-up period. Unadjusted event rates for development of LE were reported. The definition of LE used was that described by the study authors. When both subjective and objective definitions were reported, we reported on the quantitative assessment. All statistical analyses were performed using these definitions. Regional lymph node therapy was defined as radiotherapy involving a supraclavicular, supraclavicular-axillary, or axillary field—with or without a posterior axillary boost. If a study included a subset of patients undergoing ALND and radiotherapy, data for this specific subset of patients were extracted.

Statistical Analysis

Pearson χ^2 was used to assess the homogeneity of the proportion of patients developing LE in each intervention group. A P value of <0.05 was considered statistically significant for each pooled effect. The DerSimonian and Laird random-effects meta-analytic model was chosen a priori given the inherent clinical, methodological, and statistical heterogeneity associated with synthesizing data from observational studies, in addition to the specific methodologic heterogeneity discovered during review. A meta-analysis of single proportions was conducted because of a lack of sufficient numbers (n > 4) of studies with both an intervention group and a reference group of interest. Statistical heterogeneity was assessed using the Mantel-Haenszel method and I^2 statistic, defining low heterogeneity as an I^2 of less than 50%, moderate heterogeneity as an I^2 of 50% to 80%, and considerable heterogeneity as an I^2 of greater than 80%. Weighted proportions and their 95% confidence intervals (CIs) were summarized in forest plots. Meta-regression was not conducted because of the insufficient number of covariates reported for each included study. All analyses were conducted, and figures were generated in R v3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Selection and Characteristics

The initial search yielded 1374 unique results after removal of duplicates. The article selection process is detailed in Figure 1. After title and abstract screen, 62 articles were subjected to full-text review. Of these, 16 unique articles met all inclusion criteria and none of the specified exclusion criteria. Three additional articles were found after a manual reference screening. In total, 19 unique published articles were included in our meta-analysis. Of these, 3 were randomized clinical trials, 5 were prospective cohort studies, and 11 were retrospective reviews. Common reasons for exclusion included the following: missing or vague information regarding radiotherapy treatment; axillary surgeries, which were not ALND (ie, axillary sampling); and missing patient follow-up time. If a study described a patient cohort reported on in a previous study, the most recently published study was included to capture long-term outcomes. We extracted data on a total of 3035 patients, 711 of whom had LE. The median follow-up time was 25.7 months (range, 6.0–118.8 months). The definition of LE, its assessment method, and the follow-up period for each study are summarized in Table 2. Definitions of axillary node dissection according to each study are listed in Table 3.

Analysis of LE Rates Across Subgroups

The pooled cumulative incidence of LE was 14.1% in the ALND group versus 2.1% in the ALND with LYMPHA group, a difference of 12.0% ($P = 0.029$). Similarly, the incidence in the ALND with RLNR group was 33.4% versus 10.3% in the ALND with RLNR with LYMPHA group, a difference of 23.1% ($P = 0.004$). The incidence of LE was significantly higher when RLNR was administered with ALND

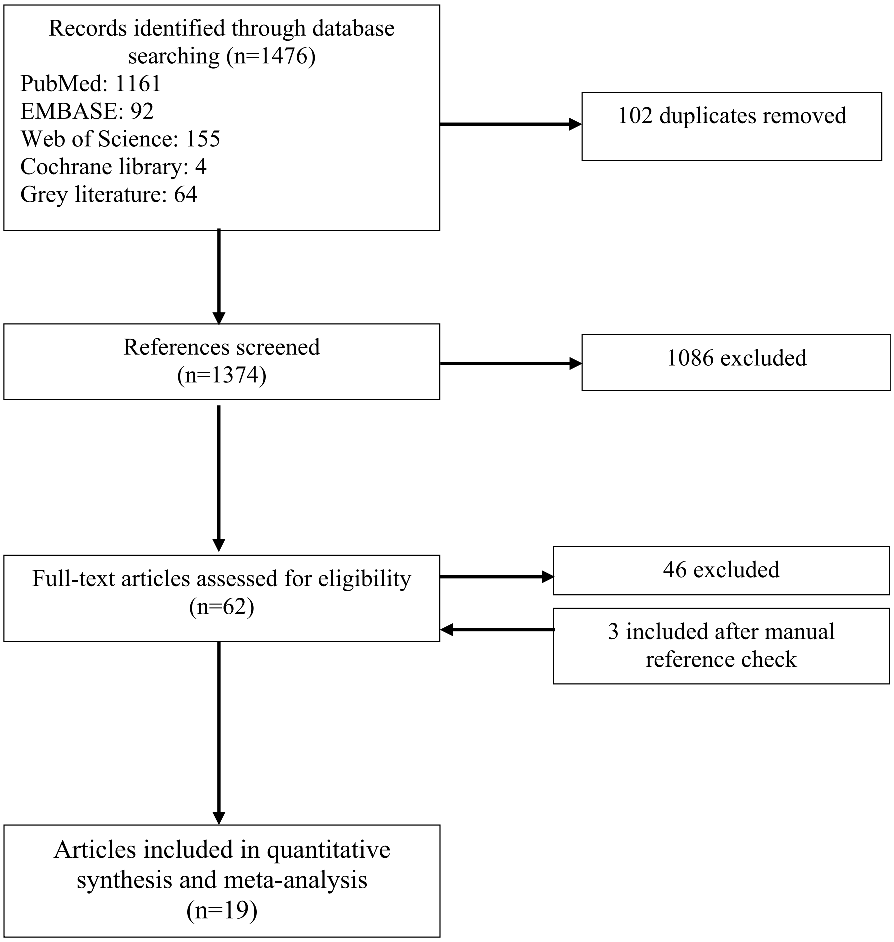

FIGURE 1. Flow diagram illustrating article selection.

(increase of 19.3%, $P < 0.001$) compared with when ALND was performed alone (Table 4).

On meta-analysis, statistical heterogeneity (I^2) ranged from low (0%) to considerable (97%). The weighted proportion of patients who developed LE in the ALND group was 15.58% (95% CI, 8.27%–27.41%; $I^2 = 94\%$) compared with 4.62% (95% CI, 0.53%–30.54%; $I^2 = 39.9\%$) for the ALND with LYMPHA group (Fig. 2). Similarly, the weighted proportion of patients who developed LE in the ALND with RLNR group was 26.49% (95% CI, 14.02%–44.34%; $I^2 = 97\%$) compared with 10.55% (95% CI, 4.81%–21.58%; $I^2 = 0\%$) for the ALND with RLNR and LYMPHA group (Fig. 3).

Publication Bias Assessment

Publication bias is unlikely for the ALND (Fig. 4) and ALND + RLNR groups (Fig. 5), as the funnel plots seem fairly symmetric grossly and on Egger test ($P = 0.404$ and $P = 0.122$, respectively).

DISCUSSION

In this systematic literature review and meta-analysis including more than 3000 patients, we highlight the lack of consensus on a standard method of measurement and diagnosis of BCRL, which has contributed to the variability in reported incidence. Despite this variability, our study is appropriately powered to report a significant increase in LE incidence when RLNR is administered after ALND. Moreover, our study demonstrates that LYMPHA significantly reduces the incidence of LE after ALND with or without RLNR.

The variability of method of assessment used to diagnose LE warrants further discussion. The National Lymphedema Network defines LE as an abnormal collection of high-protein fluid just beneath the skin.[31] This swelling, or *edema*, occurs most commonly in the arm or leg, but it also may occur in other parts of the body. Despite this pathophysiologic understanding of LE, to date, there has been no consensus on a standard method of measurement and diagnosis of BCRL. Studies included in our review used different types of assessment methods varying from self-report to the use of multiple modalities such as clinical measurements, volumetry, and bioimpedance spectroscopy. Self-reported measures of BCRL and arm circumference measurements lack specificity and sensitivity.[32] Notably, they were used as the sole objective outcome measurements for LE in one study.[26] Measurements of arm circumference have little sensitivity to detect preclinical BCRL and must take into account body weight changes over time using interlimb differences or equations to assess relative change.[33,34] However, arm circumference was used in 74% of studies included in this analysis. The most rigorous current standards for assessment of BCRL are bioimpedence spectroscopy[35–38] and volumetry (water displacement or perometry).[39–42] Bioimpedence spectroscopy is sensitive in the early detection of extracellular fluid changes. This technique was used in only 10.6% of studies included in this analysis. Moreover, of significant note, all 3 articles reporting on the results of LYMPHA used rigorous methods of measurement including bioimpedence and/or volumetry.[12–14] The composition of a low percentage of studies with the potential to "overdiagnose" LE (eg, bioimpedence spectroscopy) and the high percentage of studies with the potential to "underdiagnose"

TABLE 2. Study Characteristics

Reference	Study Design	LE Definition	LE Assessment Method	Median Follow-up Period, mo
Boccardo et al[12]	RR	Excess volume of ≥100 mL	Volumetry	48.0
Donker et al[16]	RCT	>10% increase in circumference in the lower arm or the upper arm, or both	Measurement of arm circumference 15 cm above the medial epicondyle and 15 cm below the medial epicondyle	73.2
Feldman et al[13]	PCS	>2 cm difference Abnormal L-Dex bioimpedance score	Measurement of arm circumference performed at 5 specified locations L-Dex bioimpedance spectroscopy	6
Francis et al[17]	PCS	>5% increase in limb volume by a LE nurse practitioner	Volume % change ([current volume − preoperative volume]/ preoperative volume) × 100	12
Golshan et al[18]	RR	>3-cm difference	Measurement of arm circumference 10 cm above and 10 cm below the olecranon process	12
Graham et al[19]	RR	>200-mL difference in calculated volume and >2-cm difference	Circumferential measurements every 10 cm from the extended fingertips	50.4
Hahamoff et al[14]	RR	Signs/symptoms of LE and either change in circumferential measurements or abnormal L-Dex value	Circumferential measurements at the ulnar styloid and every 8 cm proximal L-Dex bioimpedence spectroscopy Clinical signs and symptoms of LE	24
Kim et al[20]	RR	>5% difference in limb volume	Circumferential measurements 10 cm above and below the antecubital fold Patient assessment	61.2
Lucci et al[21]	RCT	≥2-cm difference	Patient assessment Measurement of the arm circumference 10 cm proximal to the medial epicondyle	36
Lumachi et al[22]	RR	≥2-cm difference	Arm circumference	22
Mathew et al[23]	RR	≥2-cm difference	Arm circumference: 10 cm above and below the olecranon, at the level of the wrist, at the level of the palmar crease	24
Ozcinar et al[24]	PCS	>2-cm difference in forearm circumference	Measurement of arm circumference 10 cm above and 10 cm below the olecranon process	64
Powell et al[25]	RR	>2-cm difference in forearm circumference >4-cm difference with concomitant movement restriction was defined as severe edema	Measurement of arm circumference 10 cm below the olecranon process	72
Schijven et al[26]	RR	Clinical signs	Patient assessment	—
Schrenk et al[27]	RR	Patient subjective assessment	Clinical signs Arm circumference measurements: 15 cm above and 10 cm below the lateral epicondyle	16
Tummel et al[28]	PCS	>20% in volume of the affected side	Volumetric changes by water displacement	26
Veronesi et al[29]	RCT	>2-cm difference	Arm circumference 15 cm above the lateral epicondyle	24
Wernicke et al[30]	RR	Arm circumference difference of ≥1 cm compared with the nonoperated extremity	Measurement of arm circumference 10 cm superior and 10 cm inferior to the antecubital fossa and at the wrists	118.8
Warren et al[8]	PCS	≥10% arm volume increase	Perometry	25.4

PCS, prospective cohort study; RCT, randomized control trial; RR, retrospective review.

LE (eg, clinical measurements) likely underestimates the overall incidence of LE in our study findings. In addition, LE can occur any time after surgery. A notable percentage of studies (25%) in our study reported a follow-up time of less than 24 months, which would further contribute to an underestimation of actual LE rates.

At our institution, patients are diagnosed as having LE if they fulfill 2 criteria: (1) the patient reports symptoms (eg, heaviness) consistent with LE as evaluated by a certified LE therapist and (2) the patient has at least one objective measure consistent with LE. High-risk patients at our institution are prospectively surveilled using multiple measurement modalities. Circumferential measurements of the arm at 4-cm intervals, These measurements are then converted to a volume using the truncated cone formula.[43] Additional objective measurements used for surveillance include bioimpedance spectroscopy (L-Dex) and perometry. Volume differences of 10% or more are considered positive if the affected extremity is the patient's dominant hand. Volume differences of 7% or more are considered positive if the affected extremity is the nondominant hand. We use standard L-Dex values of ±10 L-Dex units from the patient's baseline value as their reference range. In this manner, we diagnose only clinically significant LE, which we believe to be most relevant for patient care. Thus, we advocate for inclusion of both clinically relevant subjective and objective measures in future studies.

Our systematic review and meta-analysis concludes that the addition of RLNR after ALND significantly increases the risk of LE development. This finding is consistent with RLNR being considered one of the most significant independent risk factors for the development of LE. The LE incidence of RLNR alone, after a positive SLN biopsy, is 11%. This percentage is similar to our reported incidence of LE after ALND alone.[16] Presumably, with the addition

TABLE 3. Definition of ALND and Quantification of Nodes Removed

Study	Definition of ALND	No. Nodes Removed, Median (Range)
Boccardo et al[12]	Levels I–III	19 (12–21)
Donker et al[16]	Levels I and II and ≥10 nodes	15 (12–20)
Feldman et al[13]	Levels I and II	18 (3–37)
Francis et al[17]	—	11*
Golshan et al[18]	Levels I and II	14*
Graham et al[19]	—	17* (1–37)
Hahamoff et al[14]	Levels I and II	19*
Kim et al[20]	—	11 (5–41)
Lucci et al[21]	Levels I and II and ≥10 nodes	16 (1–56)
Lumachi et al[22]	Levels I and II	17*
Mathew et al[23]	Minimum of level II and >4 nodes	10 (4–27)
Ozcinar et al[24]	—	15 (7–42)
Powell et al[25]	Levels I–III per surgeon's discretion	12 (0–47)
Schijven et al[26]	—	10*
Schrenk et al[27]	Levels I and II	16 (10–26)
Tummel et al[28]	Levels I and II	13.5
Veronesi et al[29]	Levels I–III	24*
Wernicke et al[30]	Levels I and II and >5 nodes	18 (7–36)
Warren et al[8]	—	16 (3–43)

*Mean value reported.

of RLNR after ALND, additional potential drainage pathways from the upper extremity are damaged, which likely accounts for the incidence of LE development doubling.

The most significant finding from our study was that the addition of LYMPHA reduces the risk of LE in patients undergoing ALND with or without RLNR. This finding is particularly significant because prior reports on the efficacy of LYMPHA for LE prevention were single institutional studies that lacked the appropriate power. Our study was the first to aggregate data from available reports that specifically examined LYMPHA to quantitatively assess its impact in breast cancer patients with different risk factor profiles. Although axillary reverse mapping successfully preserved lymphatic pathways draining the arm and reduced rates of LE,[44] LYMPHA represents the first known attempt to actively reconstruct the lymphatic system at the time of lymphadenectomy. It not only prevents LE but also reduces early lymphatic complications (ie, lymphorrhea, lymphocele) due to decreased regional intralymphatic pressures.[10]

Our study has noteworthy limitations. Most studies assessed were retrospective reviews that introduce a greater risk of selection and reporting bias. In addition, RLNR included radiation to one or multiple included fields, with or without an axillary boost, compromising our ability to determine the number and type of fields that may be associated with a higher risk of LE. Further hindering our ability to interpret the radiation fields is the existing variation in contemporary practice regarding the width of fields. Moreover, despite a comprehensive literature search, we were only able to find 3 randomized studies that prospectively collected information on the number of nodes dissected and radiation field used. As we highlighted in our study, the variability of assessment measures and follow-up time is a significant limitation in the field of LE. In addition, ALND was operationalized differently across studies, thereby limiting our ability to comment on the number of nodes removed and their association with LE. These findings underscore why routine collection of these data is needed to better appraise study outcomes and facilitate comparisons across studies.

We were able to identify only 3 studies that reported on LYMPHA, pointing to the need for further research to determine the efficacy of this technique in patients with different risk factor profiles. Furthermore, although rates of LE decreased after ALND + LYMPHA, the wide CI underscores the need for more research to collect additional data to better evaluate its efficacy.

As the field of breast surgery continues to evolve and progress from the Halsted mastectomy to breast conservation therapy, a similar process is currently unfolding in the management of nodal disease. Although the standard of care for metastatic disease to the axilla, that is, an ALND, was once universally accepted, this concept is being challenged today by trials demonstrating a similar efficacy of local-regional control with radiation therapy alone.[16,31,44] The motivation for this shift away from surgery to radiation has most often been

TABLE 4. Differences in Pooled Incidence Rates of LE by Type of Intervention

Intervention *a*	Incidence of LE (*n*)	Intervention *b*	Incidence of LE (*n*)	$\|a_n - b_n\|$, %	*P*
ALND	14.1% (200/1419)	ALND with RLNR	33.4% (504/1510)	19.3	<0.001
ALND	14.1% (200/1419)	ALND with LYMPHA	2.1% (1/48)	12.0	0.029
ALND with RLNR	33.4% (504/1510)	ALND with RLNR and LYMPHA	10.3% (6/58)	23.1	0.004

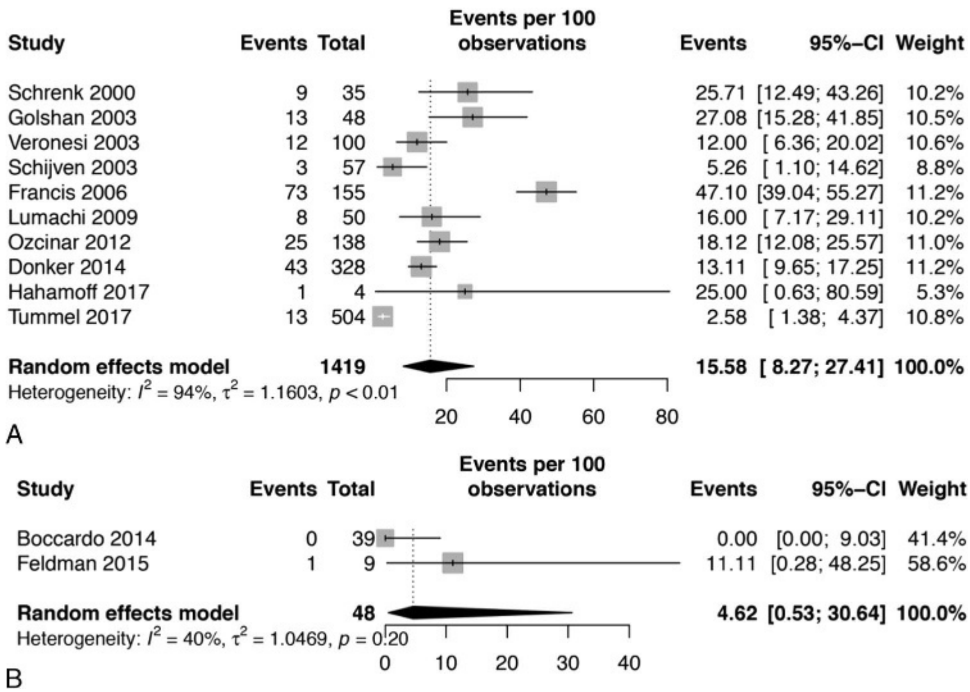

FIGURE 2. Incidence of LE in patients undergoing ALND with and without LYMPHA.

explained by the lower morbidity, for examplel, incidence of LE, with RLNR versus ALND.[8] Lymphatic Microsurgical Preventive Healing Approach has the potential to alter this paradigm. If further data support that LYMPHA reduces rates of LE more than RLNR alone, surgery may be poised to reemerge as the primary modality in the management of the node-positive axilla. Further studies will be needed to explore this potential paradigm shift.

CONCLUSIONS

Both ALND and RLNR are important interventions to obtain regional control for many patients but place them at higher risk of developing LE. Our findings suggest that LYMPHA may effectively reduce the risk of BCRL in patients who are at a high risk of BCRL from these interventions.

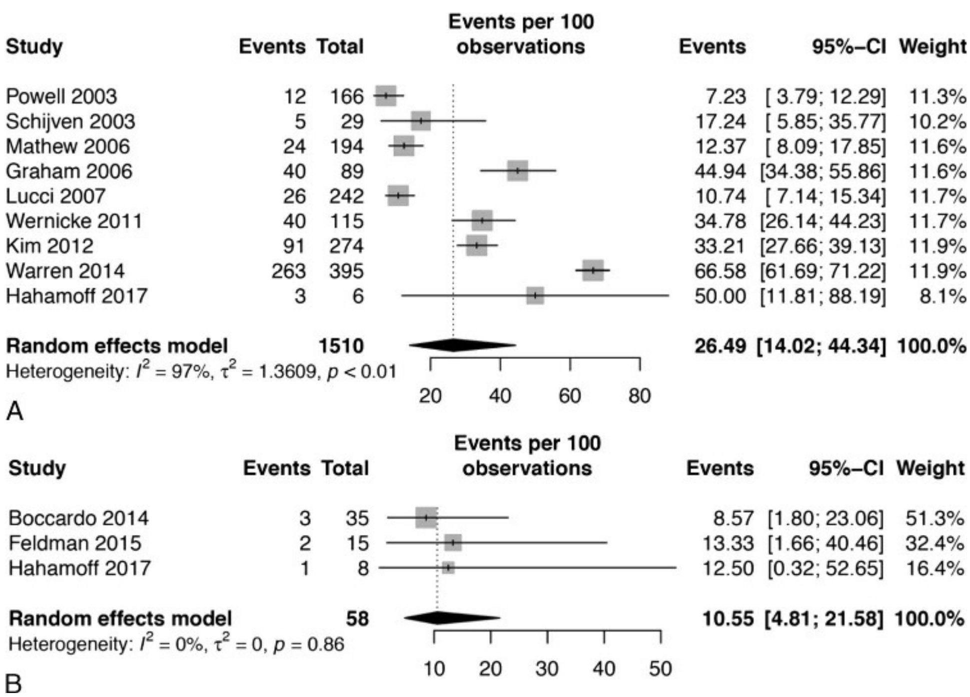

FIGURE 3. Incidence of LE in patients undergoing ALND and RLNR with and without LYMPHA.

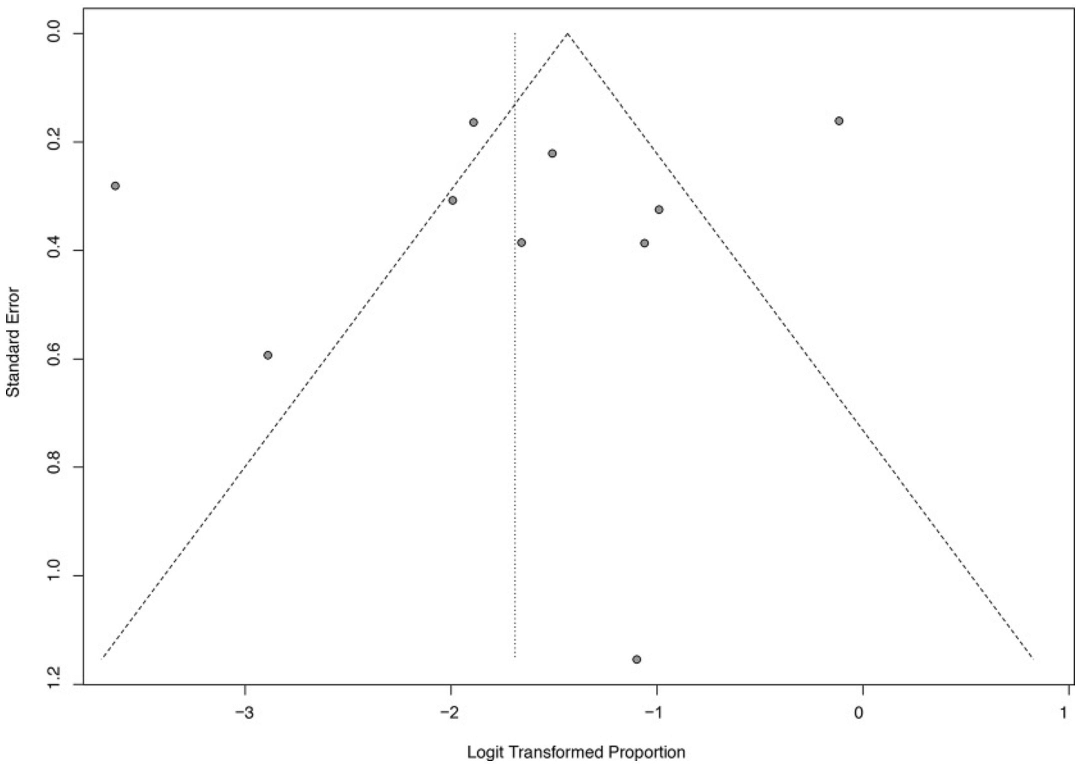

FIGURE 4. Funnel plot illustrating the incidence of LE among patients undergoing ALND.

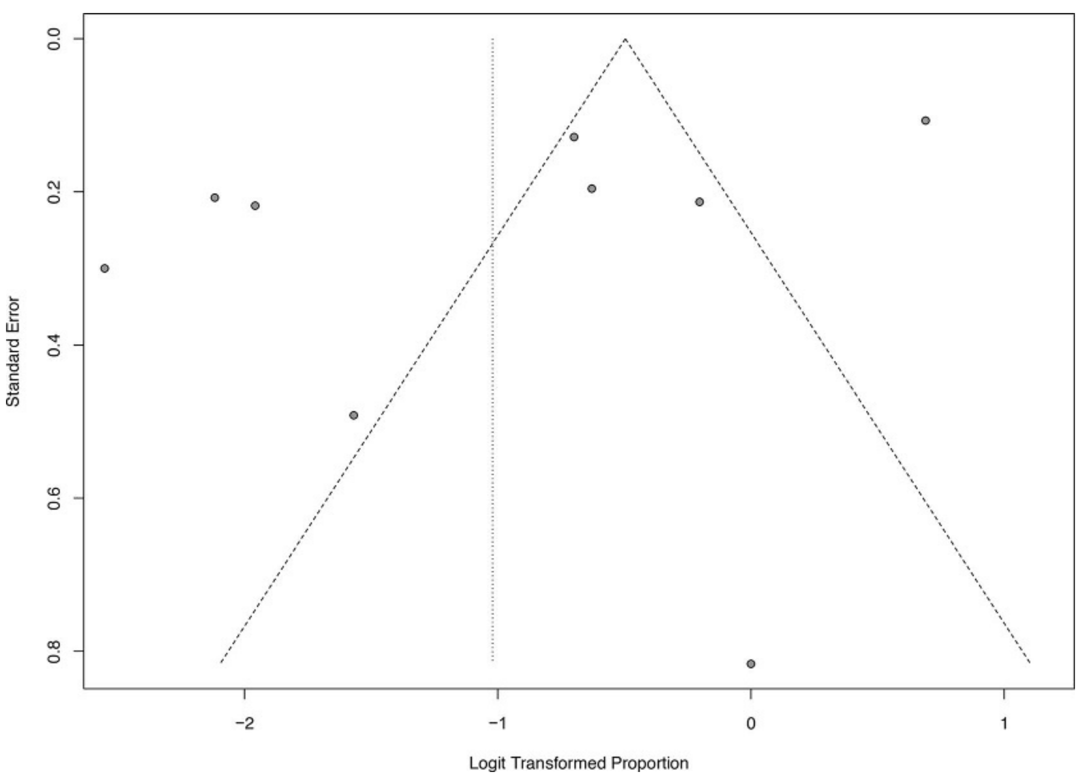

FIGURE 5. Funnel plot of the incidence of LE in patients undergoing ALND and RLNR.

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