Is Immediate Lymphatic Reconstruction Cost-effective?

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Mini We conducted a cost-utility analysis to evaluate the cost and quality of life of patients undergoing axillary lymph node dissection (ALND) and ALND with regional lymph node radiation (RLNR), with and without lymphatic microsurgical preventive healing approach (LYMPHA), in a node-positive breast cancer population. We found that the addition of LYMPHA to both ALND or ALND with RLNR is more cost-effective.

Objective: This manuscript is the first to employ rigorous methodological criteria to critically appraise a surgical preventative technique for breast cancer-related lymphedema from a cost-utility standpoint.

Summary of Background Data: Breast cancer-related lymphedema is a well-documented complication of breast cancer survivors in the US. In this study, we conduct a cost-utility analysis to evaluate the cost-effectiveness of the LYMPHA.

Methods: Lymphedema rates after each of the following surgical options: (1) ALND, (2) ALND + LYMPHA, (3) ALND + RLNR, (4) ALND + RLNR + LYMPHA were extracted from a recently published meta-analysis. Procedural costs were calculated using Medicare reimbursement rates. Average utility scores were obtained for each health state using a visual analog scale, then converted to quality-adjusted life years (QALYs). A decision tree was generated and incremental cost-utility ratios (ICUR) were calculated. Multiple sensitivity analyses were performed to evaluate our findings.

Results: ALND with LYMPHA was more cost-effective with an ICUR of \$1587.73/QALY. In the decision tree rollback analysis, a clinical effectiveness gain of 1.35 QALY justified an increased incremental cost of \$2140. Similarly, the addition of LYMPHA to ALND with RLNR was more cost-effective with an ICUR of \$699.84/QALY. In the decision tree rollback analysis, a clinical effectiveness gain of 2.98 QALY justified a higher incremental cost of \$2085.00.

Conclusions: Our study supports that the addition of LYMPHA to both ALND or ALND with RLNR is the more cost-effective treatment option.

Keywords: breast cancer-related lymphedema, cost-effectiveness, costutility, LYMPHA, lymphatic surgery

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B reast cancer is the most common malignancy facing women living in the United States.¹ Advancements in early detection and treatment of this disease have led to increased life-expectancies for cancer survivors. Breast cancer-related lymphedema (BCRL) is a

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complication that occurs in 20% of women after breast cancer treatment, and by definition, the prevalence of this condition will continue to increase in tandem with the number of survivors living with a treatment complication.² Independent risk factors for its development include axillary lymph node dissection (ALND), regional lymph node radiation (RLNR), and elevated body mass index.3-6 BCRL has significant physical, psychosocial, and economic ramifications.⁷ In fact, a study by Shih et al. found that the health care costs of patients living with BCRL is double those of their non-BCRL counterparts.⁸ Immediate lymphatic reconstruction or the lymphatic microsurgical preventive healing approach (LYMPHA) is a microsurgical technique performed at time of ALND and can prevent the development of lymphedema.^{9,10} In studies of patients undergoing this procedure, lymphedema rates dropped from 30% to 10% in high-risk patient cohorts.¹¹ Despite these promising results, insurance companies do not currently provide coverage for this procedure. This underscores the need to evaluate the cost-effectiveness of this procedure.

Prior studies have attempted to estimate lymphedema-associated costs and evaluate potential cost-savings associated with therapeutic interventions for BCRL.^{8,12–16} Existing cost-analyses have evaluated the efficacy of different conservative management strategies, including pneumatic compression devices, 12,13,16 complex decongestive therapy,^{14,15} and compression bandaging^{13–15} for patients with chronic lymphedema. These studies have identified efficacious and cost-effective strategies to prevent symptom progression and disease exacerbation. A study by Brayton et al. found that use of a pneumatic compression device not only decreased health care expenditure by \$11,833/patient, but also decreased rates of hospitalization, outpatient health costs, and incidence of cellulitis.¹² A study by Stout et al. analyzed the efficacy of a prospective surveillance model for patients at high risk for BCRL and found an annual cost savings of \$2488.73 per patient.¹⁵ Multiple studies have shown that the ability to detect and manage early-stage BCRL has been associated with improved patient outcomes.^{17–19} Still, the economic impact of immediate lymphatic reconstruction remains unknown.

Despite the promise of immediate lymphatic reconstruction for BCRL prevention, there remains no study to date that has analyzed its cost-effectiveness nor utility. In our current healthcare environment, treatments must not only be efficacious, but also costeffective. There is an exigent need to appraise the life-long costs associated with lymphedema and the potential cost-benefit of a surgical technique that can prevent the onset of the most common breast cancer survivorship burden.

In this study, we conduct a cost-utility analysis to evaluate and compare the cost and quality of life of patients undergoing ALND and ALND with RLNR, with and without LYMPHA, in a nodepositive breast cancer patient population.

METHODS

Case Reference

We defined our case reference as a 45-year old female patient who has node-positive breast cancer and undergoes an ALND

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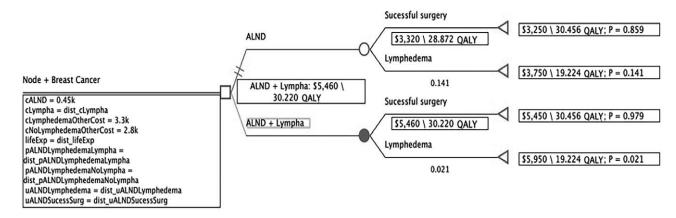


FIGURE 1. Decision tree analysis comparing ALND, with and without LYMPHA (Model 1): the green line and green circle in the ALND and LYMPHA arm demonstrate the more cost-effective strategy. ALND indicates axillary lymph node dissection; LYMPHA, lymphatic microsurgical preventive healing approach.

without RLNR (Model 1) or with RLNR (Model 2). Our case reference has no previous breast or axillary surgery, or any previous radiation to the breast and/or axilla. All patients with node-positive breast cancer undergoing ALND were eligible for LYMPHA. Complications of breast surgery, ALND, and RLNR, other than lymphedema, were not tracked nor accounted for in this study. The duration of follow up of this patient was assumed to be 12 months postoperatively.

Decision Analysis Model and Probabilities

To compare the cost-effectiveness of LYMPHA after ALND, with or without RLNR, 2 decision trees were constructed using TreeAge Software Pro Version 2015 (TreeAge Software, Inc., Williamstown, MA) (Figs. 1 and 2). In Model 1, a patient undergoes ALND alone or ALND with LYMPHA. LYMPHA is a procedure performed at the time of ALND in which divided lymphatics are identified and anastomosed to a tributary of the axillary vein. At our institution, the senior author (DS) performed all LYMPHA procedures ($x \ge 100$) in a standard fashion.

In this model and for this cost-effectiveness analysis, we assume that a patient undergoing ALND with LYMPHA has the

same perioperative recovery as a patient undergoing ALND alone. For each health state, the probabilities of lymphedema after ALND with or without RLNR were obtained from pooled data from a metaanalysis. Base-case values were also obtained by pooling the results of all included studies.¹¹ The means of values from the strongest available evidence were used. The probabilities of lymphedema after ALND without LYMPHA was 14.1% and with LYMPHA was 2.1%. Further, the probabilities of BCRL after ALND and RLNR without LYMPHA was 33.4% and 10.3% with LYMPHA (Supplemental Digital Content 1, http://links.lww.com/SLA/B879).

Cost Data

In these 2 models, costs were obtained from the national Medicare and Medicaid physician fee schedule reimbursement for the 2018 calendar year.²⁰ Current Procedural Terminology (CPT) codes used and their respective costs are summarized in Supplemental Digital Content 2, http://links.lww.com/SLA/B880. To estimate the cost of lymphedema, annual health-care related costs (both cancer and noncancer related) for patients who underwent surgery with a diagnosis of BCRL and those without BCRL were sourced from a study by Dean et al.²¹ All estimates were based on health care

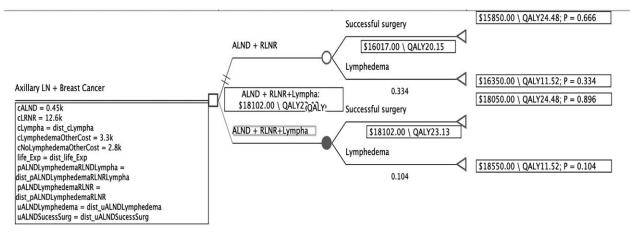


FIGURE 2. Decision tree analysis comparing ALND and RLNR, with and without LYMPHA (Model 2): the green line and green circle in the ALND and LYMPHA arm demonstrate the more cost-effective strategy. ALND indicates axillary lymph node dissection; LYMPHA, lymphatic microsurgical preventive healing approach; RLNR, regional lymph node radiation.

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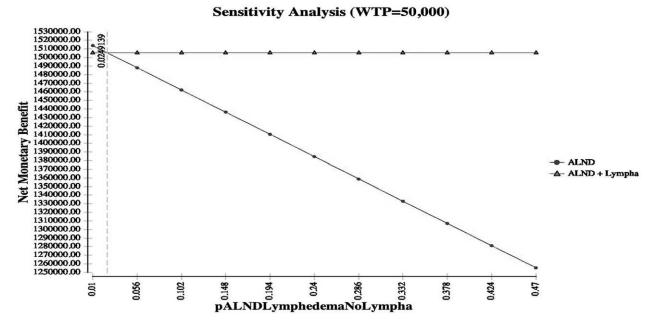


FIGURE 3. One-way sensitivity analysis of ALND with and without LYMPHA. When baseline rates of postoperative incidence of BCRL are varied, ALND with LYMPHA becomes the more cost-effective strategy when the baseline rate of BCRL is greater than 2.5% at a WTP of \$50,000. ALND indicates axillary lymph node dissection; BCRL, breast cancer-related lymphedema; LYMPHA, lymphatic microsurgical preventive healing approach; WTP, willingness to pay.

delivery costs incurred over a 1-year time period for patients that underwent breast cancer surgery who developed and did not develop lymphedema.⁸

As LYMPHA has not been adopted by the Medicare reimbursement system, institutional CPT codes were used. Similar codes for this procedure are also recommended for use at outside institutions.²² CPT codes for a routine course of RLNR at our institution were also used. In our institutional experience, there have been no complications that occurred that could be linked specifically to LYMPHA. This is consistent with findings from a 2018 meta-analysis by Jørgenson et al which found a 0% complication rate after prophylactic lymphovenous bypass for BCRL.²³ Thus, complication rates (other than lymphedema) in patients undergoing ALND and ALND with LYM-PHA were assumed to be equal. A similar assumption was made for complications secondary to RLNR. All costs were estimated over a 1year span and reported as the value of the U.S. dollar during the given year with respect to the source of data.

Utility Data

To obtain the utilities for each health outcome, 25 surgical and medical oncologists familiar with LYMPHA at our institution were surveyed. The health outcomes included ALND with and without the surgical sequelae of BCRL, and ALND with RLNR, with and without the surgical sequalae of BCRL. Institutional Review Board approval was obtained (2018-P-000779). Participants were queried using a visual analog scale, a validated assessment tool for cost-analysis research.²⁴ Experts were provided with similar clinical scenarios for each of the 4 health outcomes and were asked to mark a value on a "feeling thermometer," that ranged from 0 (death) to 100 (perfect health) (Supplemental Digital Content 3, http://link-s.lww.com/SLA/B881). Of note, a successful surgery was defined as 1 without the postoperative outcome of lymphedema.

The overall utility of each health state was obtained by averaging the utility scores for each health state. These were then

converted to quality-adjusted life years (QALYs) which was used to measure the effectiveness in both models. This was multiplied by the time each patient spent in this health state (1 year). The respective costs for each health state were also incorporated into this model and an incremental cost-utility ratio (ICUR) was calculated.

- 1. ICUR = (expected cost of ALND and LYMPHA-expected cost of ALND)/(expected QALY of ALND and LYMPHA-expected QALY of ALND)
- 2. ICUR = (expected cost of ALND and LYMPHA with RLNR expected cost of ALND with RLNR) / (expected QALY of ALND and LYMPHA with RLNR expected QALY of ALND with RLNR)

The ICUR represents the additional cost to prolong a patient's life by 1 year of perfect health.²⁵ An intervention was defined as cost-effective if the ICUR is less than the willingness to pay (WTP) for an added year of perfect health, which we defined as less than \$50,000.²⁶

Sensitivity Analysis

We conducted 1-way and 2-way sensitivity analyses to evaluate the robustness of our model and identify points at which the preferred surgical modality would change. Specifically, parameters including the probability of postoperative lymphedema and the utility of the absence and presence of lymphedema were varied. Both probabilities were sourced from published values available in the literature (Supplemental Digital Content 1, http://links.lww.com/ SLA/B879). This was performed to capture a threshold value at which the ICUR exceeds WTP. The threshold value is the cut-off value at which LYMPHA is not the cost-effective approach. A 1-way sensitivity analysis was performed for both decision trees (ALND + LYMPHA, ALND + RLNR + LYMPHA) (Figs. 3 and 4).

Two-way sensitivity analyses were also conducted to appraise the effectiveness of successful surgery with or without lymphedema

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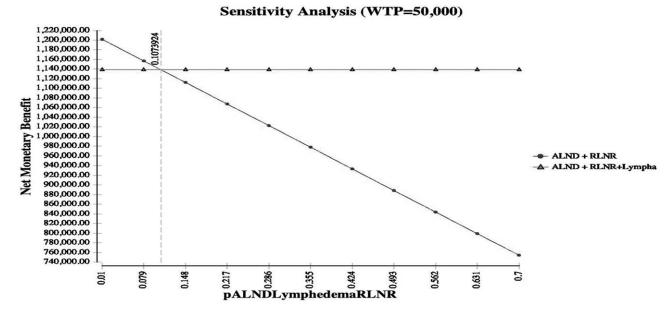


FIGURE 4. One-way sensitivity analysis of ALND and RLNR, with and without LYMPHA. When baseline rates of postoperative incidence of BCRL are varied, ALND and RLNR with LYMPHA is the more cost-effective strategy over ALND with RLNR when the baseline rate of BCRL is greater than 10.7% at a WTP of \$50,000. ALND indicates axillary lymph node dissection; BCRL, breast cancer-related lymphedema; LYMPHA, lymphatic microsurgical preventive healing approach; RLNR, regional lymph node radiation; WTP, willingness to pay.

		Costs	Effectiveness		Incremental Cost/QAL	
Procedure	Annual Cost (\$USD)	Incremental Cost (\$USD)	Effectiveness (QALY)	Incremental Effectiveness	ICUR	
ALND	3320		28.87			
ALND + LYMPHA	5460	2140	30.22	1.35	\$1587.73	
ALND + RLNR	16,017		20.15			
ALND + LYMPHA + RLNR	18,102	2085	23.13	2.98	\$699.48	

ALND indicates axillary lymph node dissection; ICUR, incremental cost-utility ratio; LYMPHA, lymphatic microsurgical preventive healing approach; QALY, quality-adjusted life years; RLNR, regional lymph node radiation.

by varying assigned utility scores (Supplemental Digital Content 4, http://links.lww.com/SLA/B882 and 5, http://links.lww.com/SLA/B883). The highest and lowest utility values (and intervening range) obtained from the expert surveys were used. In the 2-way sensitivity analysis, results were determined for every combination from the highest to lowest utilities to determine the point at which the other strategy becomes more cost-effective, where all other variables in the analysis are held constant.

Further, we also conducted probabilistic sensitivity analyses (PSA) using a Monte Carlo Simulation to assess how uncertainty around model parameters could affect our results. The following variables were varied: cost of LYMPHA, utility scores for lymphedema and successful surgery, probability of BCRL with and without LYMPHA, and life expectancy (number of health years remaining). The number of health years remaining was calculated by subtracting the average age of the patient from the average life expectancy.

Number of health years remaining = 81.1 years - 45 years = 36.1 years.²⁵

RESULTS

The decision tree for Model 1 favored ALND with LYMPHA, with an ICUR of \$1587.73 per QALY (Fig. 1 and Table 1). There was a net clinical benefit of 1.35 QALYs of ALND with LYMPHA (30.22 QALY) over ALND (28.87 QALY). There was an incremental cost of \$2140.00 associated with ALND with LYMPHA. Similarly, the results of the decision tree for Model 2 favored ALND and RLNR with LYMPHA, with an ICUR of \$699.48/QALY (Fig. 2, Table 1). There was a net clinical benefit of 2.98 QALYs associated with ALND and RLNR with LYMPHA. The addition of LYMPHA was associated with an incremental cost of \$2085.00. In both models, the addition of LYMPHA was the more cost-effective strategy, meaning that the total annual cost of ALND with LYMPHA (\$3320) and ALND and RLNR with LYMPHA (\$18,102) were below the WTP (\$50,000) value with associated increment in effectiveness. This underscores that our results favoring LYMPHA were robust. The values and the associated annual health care costs for each health state are listed in Table 2. The utility scores for the 4 health states

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TABLE 2.	Utilities	and	Annual	Health	Care	Costs	Incurred
Post-surge	ry						

Health State	VAS Mean (Range)	Annual Post-surgery Health Care Cost (\$USD)*
ALND, successful surgery	84 (65-95)	
ALND and RLNR, successful surgery	67 (50-90)	3324.90
ALND, with lymphedema	54 (65-95)	
ALND and RLNR, with lymphedema	32 (10-55)	2792.17

*Data extracted from Dean et al.21

ALND indicates axillary lymph node dissection; RLNR, regional lymph node radiation; VAS, visual analog scale.

were: (1) ALND with no BCRL 84 ± 7 , (2) ALND with BCRL 53 ± 12 , (3) ALND and RLNR without BCRL 67 ± 9 , and (4) ALND and RLNR with BCRL 32 ± 12 (Table 2). The survey response rate was 100%.

One and 2-way Sensitivity Analyses

One-way sensitivity analysis revealed that ALND alone was only more cost-effective than ALND with LYMPHA when the baseline rate of lymphedema was assumed to be 2.5% or lower (Fig. 3). Further, ALND and RLNR alone were only more cost-effective if the assumed baseline rate of lymphedema was 10.7% or lower (Fig. 4).

A 2-way sensitivity analysis demonstrated the window in which ALND without LYMPHA becomes more cost-effective. This occurs if the utility of a successful surgery falls below 0.71, and the utility of this procedure with lymphedema is above 0.49 (Supplemental Digital Content 4, http://links.lww.com/SLA/B882). It compares the utility of ALND's success in patients both with and without lymphedema. The red-shaded region in this figure represents ALND patients without BCRL where LYMPHA was successful. The blue shaded area represents patients who underwent LYMPHA that developed BCRL.

These findings were similar in Model 2 (ALND + RLNR). ALND and RLNR without LYMPHA only becomes the more costeffective strategy if the utility of successful surgery with no lymphedema falls below 0.72 and the utility of ALND + RLNR with lymphedema is above 0.50 (Supplemental Digital Content 5, http:// links.lww.com/SLA/B883). The baseline utility value for ALND + RLNR and successful surgery was 0.67 (X-axis value, ranged from 0.50 to 0.90) and 0.32 (Y-axis value, ranged from 0.10 to 0.70) for ALND + RLNR with lymphedema. The red-shaded portion represents ALND + RLNR patients without BCRL who had a successful surgery with LYMPHA. The blue-shaded region represents patients with BCRL who did not have a successful surgery with LYMPHA.

PSA

Using Monte Carlo simulation, we performed PSA that included and varied all variables which have the highest impact on Model 1 and Model 2. Our analyses demonstrated that ALND with LYMPHA had a higher probability to be cost-effective compared to ALND alone, with a confidence of 98% and a WTP of 50,000 (Fig. 5A). These findings remained even when the WTP was dropped to \$5000 (Fig. 5B). Similarly, the acceptability curve for ALND and RLNR with LYMPHA had a higher probability to be cost-effective compared to ALND and RLNR alone, with a confidence of 99% and WTP of \$50,000 (Fig. 6A). Similar to Model 1, these findings remained when the WTP was lowered to \$5000 (Fig. 6B). Supplemental Digital Content 6, http://links.lww.com/SLA/B884 and 7, http://links.lww.com/SLA/B885 illustrate the distributions of gamma, log-normal, and beta for Model 1 and Model 2, respectively.

DISCUSSION

The goal of this study was to evaluate the cost-utility of a surgical procedure performed for the prevention of lymphedema in a patient population undergoing ALND or ALND with RLNR. Our findings demonstrated that the addition of LYMPHA to ALND and ALND with RLNR is more cost-effective than ALND and ALND with RLNR alone, with favorable ICURs of \$1587.73/QALY and \$699.48/ QALY, respectively. The substantial clinical benefit of LYMPHA easily overcomes the cost-disadvantage, which is why our ICUR in both scenarios had a relatively low dollar amount per QALY. Although publications on the potential of LYMPHA have been met with positive reviews, they have also been met with skepticism on the cost incurred of an additional procedure that requires microsurgical expertise. However, our findings show that it is a cost-effective procedure that has the potential to prevent lymphedema, a costly outcome, which has been described as the largest cancer-survivorship burden.²⁷ This is an important addition to the existing literature, which has mainly focused on the cost-savings of therapeutic devices for chronic lymphedema.¹²⁻¹⁶ Overall, These findings align with previous studies, as we found an annual cost-savings associated with LYMPHA in a nodepositive breast cancer population.

In support of our findings, the 1-way sensitivity analyses revealed that LYMPHA was no longer cost-effective when lymphedema rates (without the use of LYMPHA) dropped below 2.5% after ALND and below 10.7% after ALND and RLNR. In a recent metaanalysis, the incidence of BCRL in patients who underwent ALND is 14.1%, and in patients who underwent ALND with RLNR 33.4%.11 Our results support the use of LYMPHA in a patient population requiring ALND, with or without adjuvant radiation.^{4,28} Additionally, our 2-way sensitivity analysis also supports our final conclusion that the addition of LYMPHA is the more cost-effective approach. It revealed that there was a narrow window in which the addition of LYMPHA in both models would no longer be beneficial. Further, when we varied all critical parameters in the decision tree, our Monte Carlo PSA found that the addition of LYMPHA to both ALND and ALND with RLNR was the dominant strategy, in 98% and 99% of all microsimulations run in each respective decision tree.

Lymphedema has been described as the largest cancer survivorship burden in breast cancer survivors. Using multiple, validated quality of life metrics, cancer survivors with lymphedema score lower than their nonlymphedema counterparts.²⁹⁻³³ There is a paucity of literature evaluating the efficacy of an increasingly popular surgical procedure for the prevention of lymphedema. As our health care system continues to strive to contain costs, we must critically and ethically evaluate procedures that may be associated with both economic savings and improved surgical outcomes.^{34,35} This study has noteworthy limitations including the utilization of cost data from heterogenous sources. The majority of costs used for analysis was extracted directly from the national Medicare and Medicaid physician fee schedule reimbursement for the 2018 calendar year (Table 2). However, LYMPHA is not currently reimbursed by Medicare and Medicaid (or any commercial payers as of 2019). Therefore, to estimate costs for this procedure, we utilized the corresponding CPT codes as they are billed for LYMPHA at our institution and according to existing guidelines for billing of lymphovenous bypass.⁵ Although hospital costs such as operating room time could have been reported, this would have been incongruent with the remainder of our data as we aimed to report costs from a third party-payor perspective for all 4 procedures evaluated. Additionally, 2 of the CPT codes used for RLNR had no corresponding cost data available in the 2018 Medicare and Medicaid physician fee schedule reimbursement database. Thus, to best estimate this cost we used institutional reimbursement data for these CPT codes from

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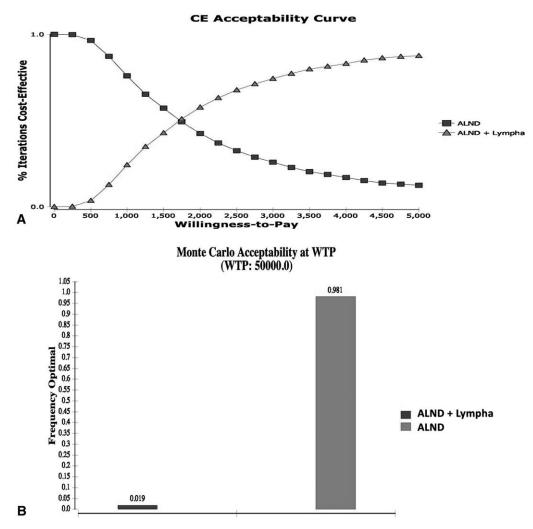


FIGURE 5. A, Cost-effectiveness acceptability curve for Model 1. The probabilistic sensitivity analysis acceptability curve is shown here. ALND with LYMPHA (red line) becomes more cost-effective than ALND alone (blue line) only when the WTP approaches \$1750 (intersection point). B, Monte Carlo probabilistic sensitivity analysis for ALND with and without LYMPHA. When all key decision tree parameters were varied within their ranges. ALND with LYMPHA was the dominant strategy in 98.1% of all microsimulations. ALND indicates axillary lymph node dissection; LYMPHA, lymphatic microsurgical preventive healing approach; WTP, willingness to pay.

Medicare beneficiaries. In addition, annual costs associated with lymphedema were extracted from another source. To capture the lymphedema-related costs that patients incur in excess of normal health-related costs after breast cancer surgery, we used data from Dean et al's 2019 study, which reported on a cohort of patients with BCRL and a matched control group to directly compare costs, including productivity and disability-related losses attributable to this condition.²¹ The variety of sources needed to adequately capture the costs associated with ALND, RLNR, LYMPHA, and lymphedema speaks to the lack of attention and analysis to lymphedema in the literature.

Despite limitations inherent in culling data from heterogenous cost sources, our cost-analysis approach was conservative in nature with best efforts to represent a third-party payer perspective. Our case reference is a 45-year-old female, who is more likely to be covered by a private payer compared to Medicare. Therefore, costs used in our analysis are likely to underestimate the reimbursements available to physicians for the majority of these procedures. Additionally, we have attempted to overcome the limitations in our model input parameters by performing extensive PSA. Even when the most critical input-parameters were varied within their respective ranges, strategies which included LYMPHA remained the most cost-effective.

The substantial clinical benefit of LYMPHA easily overcomes the cost-disadvantage, which is why our ICUR in both scenarios had a relatively low dollar amount per QALY. Another limitation of our analysis is the use of physician surveys for utility scores rather than patient surveys. Physician data has been adequately used in previous cost-utility analyses.^{25,36,37} Additionally, patients may bias and weigh their own negative experiences lower than other general outcomes that they have never seen nor experienced. Another limitation includes the costs of complications specific to the procedures studied that were not incorporated because complication rates between the 2 groups were assumed equivalent, supported by the negligible complication rate associated with the addition of LYM-PHA in the literature.^{38,39}

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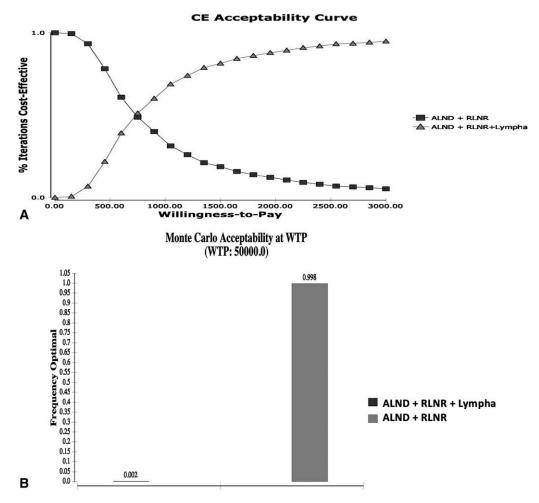


FIGURE 6. A, Cost-effectiveness acceptability curve for Model 2. The probabilistic sensitivity analysis acceptability curve is shown here. ALND and RLNR with LYMPHA (red line) becomes more cost-effective than ALND alone (blue line) only when the WTP approaches \$750 (intersection point). B, Monte Carlo probabilistic sensitivity analysis for ALND and RLNR with and without LYMPHA. When all key decision tree parameters were varied within their ranges. ALND and RLNR with LYMPHA was the dominant strategy in 99.8% of all microsimulations. ALND indicates axillary lymph node dissection; LYMPHA, lymphatic microsurgical preventive healing approach; RLNR, regional lymph node radiation; WTP, willingness to pay.

Finally, this analysis reports on patients as a homogenous population, with presumed equivalent risk factors for the development of lymphedema. Although established, independent, risk factors such as obesity and other contentious risk factors including taxane-based chemotherapy may contribute to higher rates of lymphedema development in certain patients, our analysis did not directly account for these factors. However, the effect of these risk factors in the aggregate group is minimized by the fact that lymphedema rates were sourced from a meta-analysis which included groups of patients with varying risk factor profiles.¹¹

CONCLUSIONS

LYMPHA has demonstrated decreases in rates of BCRL, the largest cancer survivorship burden for breast cancer survivors in the US. It has shown particular efficacy in high-risk patient populations undergoing ALND with adjuvant RLNR. Our study finds that the additional costs of this microsurgical procedure can be justified from a cost-utility perspective. This is the first study to demonstrate that the addition of LYMPHA to both ALND and ALND with RLNR is the more cost-effective treatment option for node-positive breast cancer.

REFERENCES

- U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, Based on November 2017 Submission Data (1999–2015): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. 2018. Available at: www.cdc.gov/ cancer/dataviz. [Accessed March 18, 2019]
- Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66:271–289.
- Fu MR. Breast cancer-related lymphedema: symptoms, diagnosis, risk reduction, and management. World J Clin Oncol. 2014;5:241–247.
- DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol.* 2013;14:500–515.
- Basta MN, Wu LC, Kanchwala SK, et al. Reliable prediction of postmastectomy lymphedema: the risk assessment tool evaluating lymphedema. *Am J Surg.* 2017;213:1125–1133.e1.

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- Gillespie TC, Sayegh HE, Brunelle CL, et al. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. *Gland Surg.* 2018;7:379–403.
- Taghian NR, Miller CL, Jammallo LS, et al. Lymphedema following breast cancer treatment and impact on quality of life: a review. *Crit Rev Oncol Hematol.* 2014;92:227–234.
- Shih Y-CT, Xu Y, Cormier JN, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2year follow-up study. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27:2007– 2014.
- Johnson AR, Singhal D. Immediate lymphatic reconstruction. J Surg Oncol. 2018;118:750–757.
- Boccardo F, Casabona F, De Cian F, et al. Lymphedema microsurgical preventive healing approach: a new technique for primary prevention of arm lymphedema after mastectomy. *Ann Surg Oncol.* 2009;16:703–708.
- Johnson AR, Kimball S, Epstein S, et al. Lymphedema incidence after axillary lymph node dissection: quantifying the impact of radiation and the lymphatic microsurgical preventive healing approach. *Ann Plast Surg.* 2019;82:S234– S241.
- Brayton KM, Hirsch AT, O Brien PJ, et al. Lymphedema prevalence and treatment benefits in cancer: impact of a therapeutic intervention on health outcomes and costs. *PloS One*. 2014;9:e114597.
- Boyages J, Xu Y, Kalfa S, et al. Financial cost of lymphedema borne by women with breast cancer. *Psychooncology*. 2017;26:849–855.
- Zasadzka E, Trzmiel T, Kleczewska M, et al. Comparison of the effectiveness of complex decongestive therapy and compression bandaging as a method of treatment of lymphedema in the elderly. *Clin Interv Aging*. 2018;13:929–934.
- Stout NL, Pfalzer LA, Springer B, et al. Breast cancer-related lymphedema: comparing direct costs of a prospective surveillance model and a traditional model of care. *Phys Ther.* 2012;92:152–163.
- Karaca-Mandic P, Hirsch AT, Rockson SG, et al. The cutaneous, net clinical, and health economic benefits of advanced pneumatic compression devices in patients with lymphedema. *JAMA Dermatol.* 2015;151:1187–1193.
- Kilgore LJ, Korentager SS, Hangge AN, et al. Reducing breast cancer-related lymphedema (BCRL) through prospective surveillance monitoring using bioimpedance spectroscopy (BIS) and patient directed self-interventions. *Ann Surg Oncol.* 2018;25:2948–2952.
- Whitworth PW, Cooper A. Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpedance spectroscopy. *Breast J.* 2018;24:62–65.
- Shah C, Arthur DW, Wazer D, et al. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. *Cancer Med.* 2016;5:1154–1162.
- Physician Fee Schedule Search. Available at: https://www.cms.gov/apps/ physician-fee-schedule/search/search-criteria.aspx. Accessed April 22, 2019.
- Dean LT, Moss SL, Ransome Y, et al. It still affects our economic situation": long-term economic burden of breast cancer and lymphedema. *Support Care Cancer*. 2019;27:1697–1708.
- Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. *Plast Reconstr Surg.* 2014;133:905–913.

- Jørgensen MG, Toyserkani NM, Sørensen JA. The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: a systematic review and meta-analysis. *Microsurgery*. 2018;38:576–585.
- Brazier J, Green C, McCabe C, et al. Use of visual analog scales in economic evaluation. *Expert Rev Pharmacoecon Outcomes Res*. 2003;3:293–302.
- Chatterjee A, Asban A, Jonczyk M, et al. A cost-utility analysis comparing large volume displacement oncoplastic surgery to mastectomy with free flap reconstruction in the treatment of breast cancer. *Am J Surg.* 2019;218:597– 604.
- Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res.* 2008;8:165– 178.
- Cormier JN, Askew RL, Mungovan KS, et al. Lymphedema beyond breast cancer. *Cancer*. 2010;116:5138–5149.
- Golshan M, Smith B. Prevention and management of arm lymphedema in the patient with breast cancer. J Support Oncol. 2006;4:381–386.
- Kwan W, Jackson J, Weir LM, et al. Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life. J Clin Oncol Off J Am Soc Clin Oncol. 2002;20:4242–4248.
- Pyszel A, Malyszczak K, Pyszel K, et al. Disability, psychological distress and quality of life in breast cancer survivors with arm lymphedema. *Lymphology*. 2006;39:185–192.
- Chachaj A, Małyszczak K, Pyszel K, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. *Psychooncology*. 2010;19:299–305.
- Pusic AL, Cemal Y, Albornoz C, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. J Cancer Surviv Res Pract. 2013;7:83–92.
- Beaulac SM, McNair LA, Scott TE, et al. Lymphedema and quality of life in survivors of early-stage breast cancer. Arch Surg. 2002;137:1253–1257.
- Blank MM, Chen L, Papageorge M, et al. The underreporting of cost perspective in cost-analysis research: a systematic review of the plastic surgery literature. J Plast Reconstr Aesthet Surg. 2018;71:366–376.
- Blank MM, Papageorge M, Chen L, et al. Hidden bias in cost-analysis research: what is the prevalence of under-reporting cost perspective in the general surgical literature? J Am Coll Surg. 2017;225:823–828.e12.
- 36. Chatterjee A, Krishnan NM, Van Vliet MM, et al. A comparison of free autologous breast reconstruction with and without the use of laser-assisted indocyanine green angiography: a cost-effectiveness analysis. *Plast Reconstr* Surg. 2013;131:693e-701e.
- Asban A, Homsy C, Chen L, et al. A cost-utility analysis comparing large volume displacement oncoplastic surgery to mastectomy with single stage implant reconstruction in the treatment of breast cancer. *Breast Edinb Scotl.* 2018;41:159–164.
- Boccardo F, Casabona F, De Cian F, et al. Lymphatic microsurgical preventing healing approach (LYMPHA) for primary surgical prevention of breast cancerrelated lymphedema: over 4 years follow-up. *Microsurgery*. 2014;34:421– 424.
- Feldman S, Bansil H, Ascherman J, et al. Single institution experience with lymphatic microsurgical preventive healing approach (LYMPHA) for the primary prevention of lymphedema. *Ann Surg Oncol.* 2015;22:3296–3301.