Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Association for Academic Surgery

A lymphedema surveillance program for breast cancer patients reveals the promise of surgical prevention

Mandee Hahamoff, BS,[a] *Nachi Gupta, MD, PhD,*[b] *Derly Munoz, PT,*[c] *Bernard T. Lee, MD,*[d] *Pamela Clevenger, RN,*[e] *Christiana Shaw, MD,*[e] *Lisa Spiguel, MD,*[e] *and Dhruv Singhal, MD*[a,d,*]

[a] *Department of Surgery, Division of Plastic and Reconstructive Surgery, University of Florida School of Medicine, Gainesville, Florida*

[b] *Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, New York*

[c] *Department of Physical Therapy, University of Florida College of Public Health and Health Professions, Gainesville, Florida*

[d] *Division of Plastic and Reconstructive Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts*

[e] *Section of Surgical Oncology, Department of Surgery, UF Health, University of Florida School of Medicine, Gainesville, Florida*

ARTICLE INFO

Article history:
Received 10 March 2017
Received in revised form
9 October 2017
Accepted 12 October 2017
Available online xxx

Keywords:
LYMPHA
Lymphedema surveillance
Lymphatic surgery

ABSTRACT

Background: Breast cancer–related lymphedema (BCRL) is one of the most significant survivorship issues in breast cancer management. Presently, there is no cure for BCRL. The single greatest risk factor for developing BCRL is an axillary lymph node dissection (ALND). Lymphatic Microsurgical Preventative Healing Approach (LYMPHA) is a surgical procedure to reduce the risk of lymphedema in patients undergoing an ALND. We present our single institution results after offering LYMPHA in the context of an established lymphedema surveillance program.

Materials and methods: A retrospective review of our lymphedema surveillance program at the University of Florida was performed over a 2-year period (March 2014-March 2016). LYMPHA was offered to patients undergoing ALND beginning in March 2015. Patients who developed lymphedema were compared with those who did not. Demographics and potential risk factors for development of lymphedema such as age, body mass index, clinical stage, radiotherapy, and chemotherapy were reviewed.

Results: Eighty-seven patients participated in the surveillance program over the study period with an average age of 60 y (range 32-83) and body mass index of 30 kg/m^2 (range 17-46). The single most significant risk factor for the development for lymphedema was an ALND ($P < 0.001$). One of 67 patients undergoing a sentinel lymph node biopsy developed lymphedema (1.5%). Four of 10 patients who underwent an ALND alone developed

* *Corresponding author*. Division of Plastic and Reconstructive Surgery Beth Israel Deaconess Department of Surgery, 110 Francis Street, Suite 5A, Boston, MA 02215. Tel.: +617 632-7855; fax: +617 632-7840.
E-mail address: dsinghal@bidmc.harvard.edu (D. Singhal).

0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2017.10.008

lymphedema (40%). One of 8 patients in the ALND + LYMPHA group developed transient lymphedema (12.5%).
Conclusions: Offering LYMPHA with ALND decreased our institutional rate of lymphedema from 40% to 12.5%. Long-term follow-up and randomized control trials are necessary to further elucidate the promise of this surgical technique to reduce the incidence of BCRL.

Introduction

Breast cancer–related lymphedema (BCRL) is one of the most significant survivorship issues in breast cancer management.[1] Of 2.8 million breast cancer survivors in the United States, it is estimated that one in five suffers from BCRL.[2] Patients presenting with BCRL often complain of tightness, heaviness, fatigue, and inability to fit into clothing secondary to swelling. In select cases, patients present with repeated episodes of rapidly spreading cellulitis of the affected extremity that can be life threatening if not treated expeditiously. The signs and symptoms of BCRL have been associated with a predilection toward anxiety, depression, and overall reduced quality of life.[3] The most common risk factors for the development of BCRL are an axillary lymph node dissection (ALND), regional lymph node radiation (RLNR), and/or an elevated body mass index (BMI) (>30).[4] The standard treatment for BCRL has been physical therapy with manual lymphatic drainage, compression, local skin care, exercises, and pneumatic devices. More recent advances in the surgical management of chronic lymphedema including lymphovenous bypass and lymph node transfer have offered new hope for improving the quality of life of patients with BCRL. Unfortunately, neither therapy nor surgery provides a definitive cure.

Consequently, a focus on limiting progression of disease with early physical therapy intervention has emerged in the form of lymphedema surveillance programs.[4-9] In these programs, patients with newly diagnosed breast cancers are evaluated preoperatively to obtain critical baseline objective measures of the at-risk extremity followed by close postoperative surveillance. Early diagnosis of lymphedema and implementation of therapy has been correlated with improved long-term outcomes in randomized control trials.[8]

In parallel, an innovative approach to surgically prevent lymphedema in high-risk patients, such as those undergoing ALND, has been developed. In 2009, the Lymphatic Microsurgical Preventative Healing Approach (LYMPHA) was first described.[10] Divided arm lymphatics are identified at the time of ALND, and lymphovenous bypasses are performed to an axillary vein tributary. More recently, the authors reported a lymphedema rate of 4.05% after ALND + LYMPHA with a 4-year follow-up compared to 20-40% by historical controls.[11-15] This study was replicated by Feldman *et al.*[16] who confirmed a significant reduction in lymphedema rates after ALND + LYMPHA to 12.5%.

In validating a reduction in lymphedema rates, following LYMPHA, it is important to compare results against institutional controls as differences in surgical technique and delivery of radiation are likely to differ between centers thereby limiting the value of historical controls. One year after initiating a lymphedema surveillance protocol at our institution, we made an institutional decision to begin offering the LYMPHA procedure to any patient undergoing an ALND. We, therefore, had a control group of patients not being offered LYMPHA in the early part of the surveillance program to compare against those undergoing LYMPHA later in the program. Of significant note, both groups of patients were followed utilizing the same protocol for both diagnosis and follow-up.

Our present study aims to compare lymphedema rates of patients at a single institution before and after the implementation of the LYMPHA technique.

Materials and methods

A retrospective review of our lymphedema surveillance program at the University of Florida was performed. This retrospective review was approved by our internal review board with a waiver of documentation of informed consent. In March 2014, we initiated a lymphedema surveillance program where all newly diagnosed breast cancer patients were offered a lymphedema evaluation preoperatively and were followed by standard protocol postoperatively. Each evaluation, preoperatively and postoperatively, consisted of three components: (1) evaluation by a certified lymphedema therapist for signs and symptoms of BCRL, (2) circumferential measurements, and (3) bioimpedance spectroscopy. Lymphedema was defined as having signs/symptoms of BCRL and one positive objective measure. If a patient's lymphedema was diagnosed within 6 mo of their final oncologic treatment (chemotherapy, radiotherapy, and surgery), the lymphedema was defined as transient. If the lymphedema was diagnosed or continued beyond 6 mo after their final cancer treatment, it was defined as lymphedema.

Newly diagnosed breast cancer patients with unilateral disease participating in our surveillance program over a 2-year period (March 2014-March 2016) were included in the study. Participation in the program was defined as presenting for a preoperative lymphedema assessment and a minimum of one postoperative assessment. Baseline demographics (age, BMI, prior radiation, or chemotherapy), cancer treatment characteristics (chemotherapy, type of radiation treatment, and surgical management), and physical therapy evaluations (circumferential measurements, bioimpedance spectroscopy data, and follow-up) were included in the analysis.

Surgical technique

From March 2014 to February 2015, all patients undergoing an ALND underwent the procedure in standard fashion,

including resection of axillary level I and II nodes. From March 2015 to February 2016, all patients undergoing an ALND were offered a modified LYMPHA procedure. As previously described, 2 cc of 2% fluorescein isothiocyanate is injected intradermally in the ipsilateral upper arm prior to the initiation of the ALND.[17] During the ALND, the accessory vein or medial/lateral thoracic veins are preserved. Following completion of the ALND, a Pentero 900D microscope (Carl Zeiss Inc, Oberkochen, Germany) equipped with the YELLOW560 package was utilized to visualize arm lymphatics divided during the ALND. These lymphatics were then rerouted into the preserved axillary vein tributary (Fig. 1).

Data analysis

Patients who developed lymphedema were compared to those who did not. Demographics and potential risk factors for development of lymphedema such as age, BMI, clinical stage, radiotherapy, and chemotherapy were reviewed. Similarly, patients who underwent the LYMPHA technique were compared to those who had only ALND. Here again, demographics and potential risk factors were compared. All *P* values were computed using the Fisher's exact test or two-tailed *t*-test, as appropriate. Computations were done in the R language for statistical computing, version 3.3.2.

A power analysis was performed using SAS with the Fischer's exact conditional test. We utilized a set control percentage of 0.40 based on our institutional data. As previously reported in the single study from Italy{Boccardo:2014jh}, the incidence of lymphedema after simultaneous lymphovenous bypass was 0.04. Conservatively, we have set our study value at 0.05 and power at 0.8. Using these parameters for sample size calculation, we would have ideally recruited 50 patients.

Results

A total of 177 patients presented for a preoperative lymphedema evaluation, and 87 patients (49%) participated in the surveillance program over the study period. Sixty-seven of 145 patients (45%) undergoing sentinel lymph node (SLN) biopsy and 64% (18/28) of patients undergoing ALND participated in the program and had an average age of 60 y (range 32-83) and BMI 30 kg/m^2 (range 17-46); 40% of patients underwent mastectomy and 21% ALND. Eighteen percent of patients received neoadjuvant chemotherapy and 24% received RLNR. Most patients did not undergo any reconstruction (62%).

The single most significant risk factor for the development of lymphedema was an ALND ($P < 0.001$). Undergoing mastectomy ($P = 0.02$), adjuvant chemotherapy ($P = 0.03$), and RLNR ($P = 0.05$) were also associated with lymphedema development. A trend toward lymphedema development and clinical stage III disease ($P = 0.10$) was also noted (Table 1).

All patients in our cohort who developed lymphedema were initially diagnosed either during treatment or within 6 mo of the completion of their cancer therapy. Therefore, all patients were initially diagnosed with transient lymphedema. The average time to diagnosis after the surgical procedure was 4.7 mo. One patient in the SLN biopsy group developed transient and then persistent lymphedema (1/67 or 1.5%). Of five patients who developed transient lymphedema after undergoing an ALND without the LYMPHA procedure, one patient's symptoms and objective measures completely resolved, and four patients' symptoms persisted and they developed lymphedema (4/10 or 40%). Of these four patients, three were diagnosed with lymphedema based on changes in symptoms with associated changes in circumferential measurements and bioimpedance spectroscopy. The fourth patient was diagnosed based on symptoms and changes in

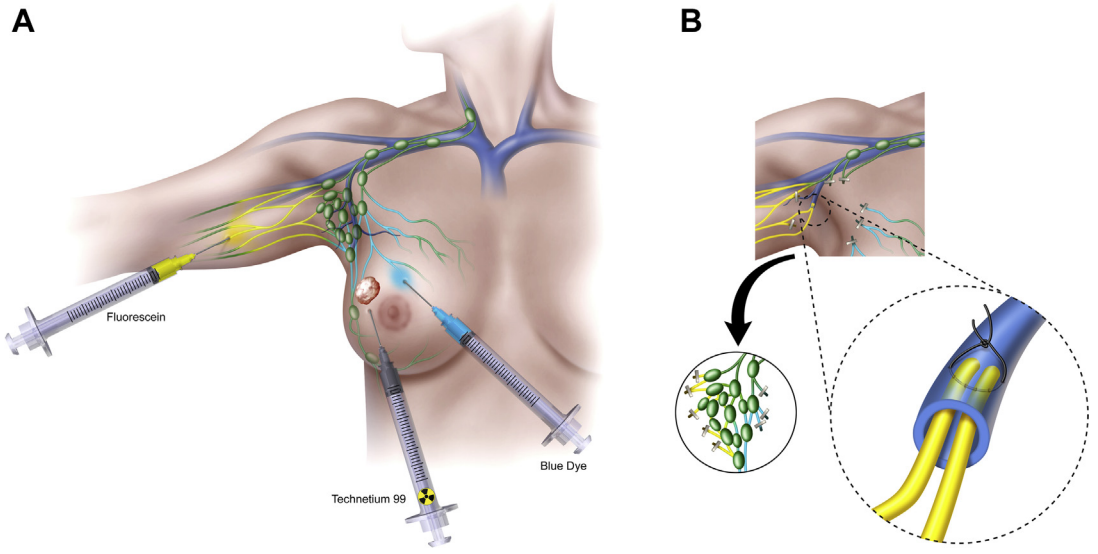

Fig. 1 – Schematic of the modified LYMPHA technique utilizing FITC. (A) Both blue and nuclear dyes are reserved for breast sentinel lymph node identification. FITC is injected in the proximal upper inner arm. (B) Following completion of the axillary dissection and removal of level 1 and 2 lymph nodes, arm lymphatic channels, now "glowing" from the FITC injection, are identified and rerouted into an axillary vein tributary. FITC = fluorescein isothiocyanate. (Reproduced with permission from the Annals of Plastic Surgery: from the study by Spiguel *et al.*).[17] (Color version of figure is available online.)

Table 1 – Patient demographics and treatment by incidence of lymphedema.

	No lymphedema	Lymphedema	P value[†]
	$n = 80$	$n = 7$[*]	
Age	60 (32-83)	60 (47-73)	0.87
BMI	30 (17-46)	31 (22-43)	0.81
Affected side (right)	42 (53%)	1 (14%)	0.11
Dominant hand (right)	73 (91%)	6 (86%)	0.50
Clinical stage (%)			
0	11 (14%)	0 (0%)	0.59
I	47 (59%)	4 (57%)	1.00
II	17 (21%)	1 (14%)	1.00
III	5 (6%)	2 (29%)	0.10
Surgery			
Breast			
Mastectomy	29 (36%)	6 (86%)	0.02
Lumpectomy	51 (64%)	1 (14%)	0.02
Axilla			
Sentinel lymph node biopsy	66 (83%)	1 (14%)	0.0005
Axillary lymph node dissection	12 (15%)	6 (86%)	0.0002
Adjuvant radiotherapy	61 (76%)	5 (71%)	0.67
Chest wall, breast, or intrabeam (no RLNR)	44 (55%)	1 (14%)	0.05
RLNR ± chest wall, breast, or intrabeam	17 (21%)	4 (57%)	0.05
Chemotherapy			
Neoadjuvant	14 (18%)	2 (29%)	0.61
Adjuvant	13 (16%)	4 (57%)	0.03
Reconstruction	30 (38%)	3 (43%)	1.00
None	50 (63%)	4 (57%)	1.00
Implant based	13 (16%)	0 (0%)	0.59
Autologous	7 (9%)	2 (29%)	0.15
Autologous and implant based	1 (1%)	0 (0%)	1.00
Oncoplastic	9 (11%)	1 (14%)	0.59

[*] Five of 7 patients have lymphedema, while 2 of 7 have transient lymphedema.
[†] P value calculated by t-test or Fisher's exact test.

circumferential measurements alone. Of the 17 patients who underwent the LYMPHA procedure at our institution during the study period, only eight participated in our surveillance program. One patient in the ALND + LYMPHA group developed transient lymphedema which is currently persistent but still within 6 mo of the completion of adjuvant radiation therapy (1/8 or 12.5%) (Fig. 2). This patient's diagnosis was based on changes in symptoms and bioimpedance without change in circumferential measurements. The only significant difference between the two groups undergoing ALND with or without LYMPHA was the follow-up period of 15 mo versus 20 mo ($P < 0.03$), respectively (Table 2).

As this study is a retrospective review and our patients were therefore not randomized into treatment arms, we compared demographics and cancer treatments for all patients undergoing ALND with or without LYMPHA who participated in our program versus those lost to follow-up in order to identify any potential confounding factors or bias (Table 3). The only difference between the groups noted is that participants who underwent LYMPHA were 10 y older than those patients lost to follow-up (59 versus 49, $P = 0.04$).

Discussion

With no cure to date for BCRL, recognition and potential prophylactic treatment for high-risk patients is an important consideration. With a limited sample size, we were able to reduce our institutional rate of lymphedema after ALND from 40% to 12.5% after introduction of the LYMPHA approach. Similarly, with the institution of a surveillance program, we were able to identify lymphedema in patients undergoing ALND within 5 mo of their procedure. ALND, mastectomy, adjuvant chemotherapy, and RLNR were associated with the development of lymphedema.

By far, our most notable finding was the reduction in rate of lymphedema development from 40% to 12.5% in patients undergoing an ALND after the introduction of the LYMPHA technique (Fig. 3). Evaluating lymphedema through the lens of our prospective surveillance program is revealing as our comparative groups were of similar demographics, underwent care of their cancer at a single institution, and were followed utilizing identical

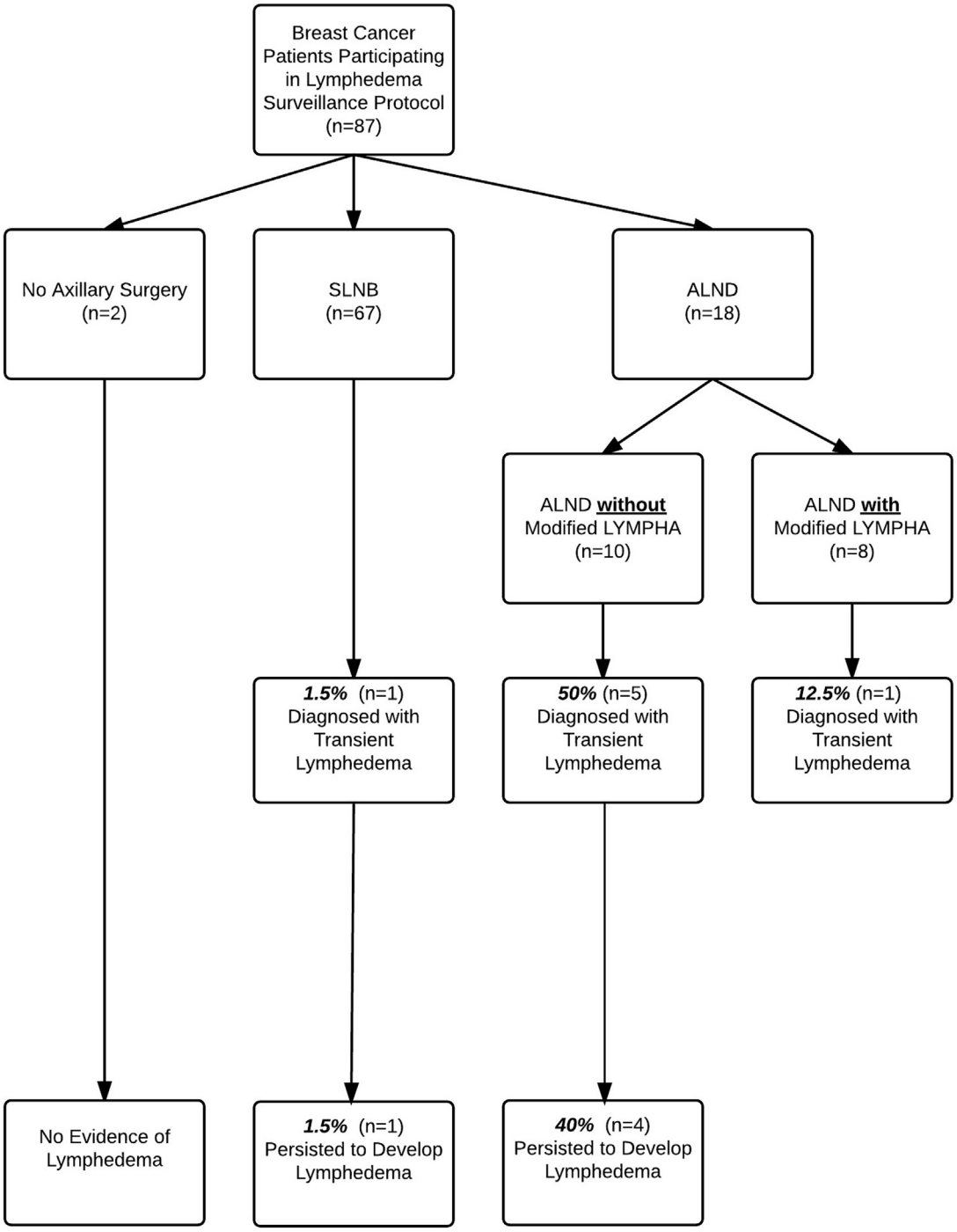

Fig. 2 – Flowchart of patients by type of axillary surgery and lymphedema incidence. SLNB = sentinel lymph node biopsy.

protocols for the evaluation, definition, and treatment of lymphedema.

Initiating a surveillance program was critical as it allowed us to define institutional rates of lymphedema and the scope of disease. All patients in our cohort to date who developed lymphedema presented initially with signs and symptoms either during treatment or within 6 mo of the end of their cancer therapy. Of these seven patients, one patient's condition completely resolved. No patient, to date, has presented with lymphedema more than 6 mo after the completion of cancer therapy. This finding underscores the value of surveillance programs in being able to detect early lymphedema which is especially important for high-risk patients as prompt detection and treatment can potentially slow the progression of disease.[8]

Our study confirmed multiple prior reports demonstrating ALND and RLNR as important risk factors for the development of lymphedema. While we noted an increased rate of

Table 2 – Comparison of demographics and treatment between patients undergoing ALND with or without LYMPHA.

	LYMPHA ($n = 8$)	Non-LYMPHA ($n = 10$)	P value*
Age	59 (48-73)	55 (34-72)	0.35
BMI	28 (19-40)	28 (22-36)	0.81
Average lymph nodes removed	18	19	0.98
Average positive lymph nodes	5	2	0.09
Type of breast surgery (mastectomy)	7 (88%)	9 (90%)	1.00
Adjuvant radiotherapy	8 (100%)	8 (80%)	0.48
Chest wall, breast, or intrabeam (no RLNR)	0 (0%)	2 (20%)	0.48
RLNR ± chest wall, breast, or intrabeam	8 (100%)	6 (60%)	0.09
Chemotherapy			
Neoadjuvant	5 (63%)	4 (40%)	0.63
Adjuvant	4 (50%)	4 (40%)	1.00
Follow-up (months)	15	20	0.03

*P value calculated by t-test or Fisher's exact test.

lymphedema in patients undergoing mastectomy, we believe this can be explained by our current indications for ALND. Specifically, patients with limited nodal involvement undergoing lumpectomy do not require an ALND[18], whereas those undergoing mastectomy will undergo an ALND for the same extent of nodal involvement. Therefore, patients undergoing mastectomy receive more aggressive axillary management than those undergoing lumpectomy. Our findings also reveal increased rates of lymphedema for patients who underwent adjuvant chemotherapy, which again, may be biased as those undergoing chemotherapy are more likely to have presented with more advanced disease initially. However, prior studies have linked specific chemotherapy regimens[19] to the development of lymphedema. Finally, as patients presenting for ALND have more advanced disease, it is not surprising that increased rates of lymphedema development were noted in those with clinical stage III disease.

While we believe in the promise of surgical prevention in improving the quality of life in breast cancer survivors, development of our program did have its challenges. If the institutional policy is to send all SLNs for permanent section and return to the operating room for an ALND at a later date, scheduling combination procedures between a breast and plastic surgeon will be more easily facilitated. However, for institutions where SLNs are sent for frozen section, the scheduling can be more erratic as a larger percentage of patients will never progress to ALND especially in light of recent trials challenging the need for ALND.[20,21] In this latter case, developing preoperative clinical and radiographic criteria for patients who are high-risk for undergoing an ALND can help minimize the lymphatic surgeon's downtime.

Ultimately, investment into a surgical program for lymphedema prevention has the potential to change the face of

Table 3 – Comparison of participants versus patients lost to follow-up.

	ALND participants ($n = 10$)	ALND lost to follow-up ($n = 10$)	P value*	ALND + LYMPHA participants ($n = 8$)	ALND + LYMPHA lost to follow-up ($n = 9$)	P value*
Age	55 (34-72)	52 (41-64)	0.49	59 (48-73)	49 (35-69)	0.04
BMI	28 (22-36)	27 (17-36)	0.56	28 (19-40)	28 (14-38)	0.96
Average lymph nodes removed	19	22	0.51	18	22	0.14
Average positive lymph nodes	2	2	0.64	5	2	0.27
Type of breast surgery (mastectomy)	9 (90%)	8 (80%)	1.00	7 (88%)	6 (67%)	0.58
Adjuvant radiotherapy	8 (80%)	10 (100%)	0.47	8 (100%)	5 (56%)	0.08
Chest wall, breast, or intrabeam (no RLNR)	2 (20%)	0 (0%)	0.47	0 (0%)	0 (0%)	1.00
RLNR ± chest wall, breast, or intrabeam	6 (60%)	10 (100%)	0.09	8 (100%)	5 (56%)	0.08
Chemotherapy						
Neoadjuvant	4 (40%)	7 (70%)	0.37	5 (63%)	5 (56%)	1.00
Adjuvant	4 (40%)	1 (10%)	0.30	4 (50%)	3 (33%)	0.64

*P value calculated by t-test or Fisher's exact test.

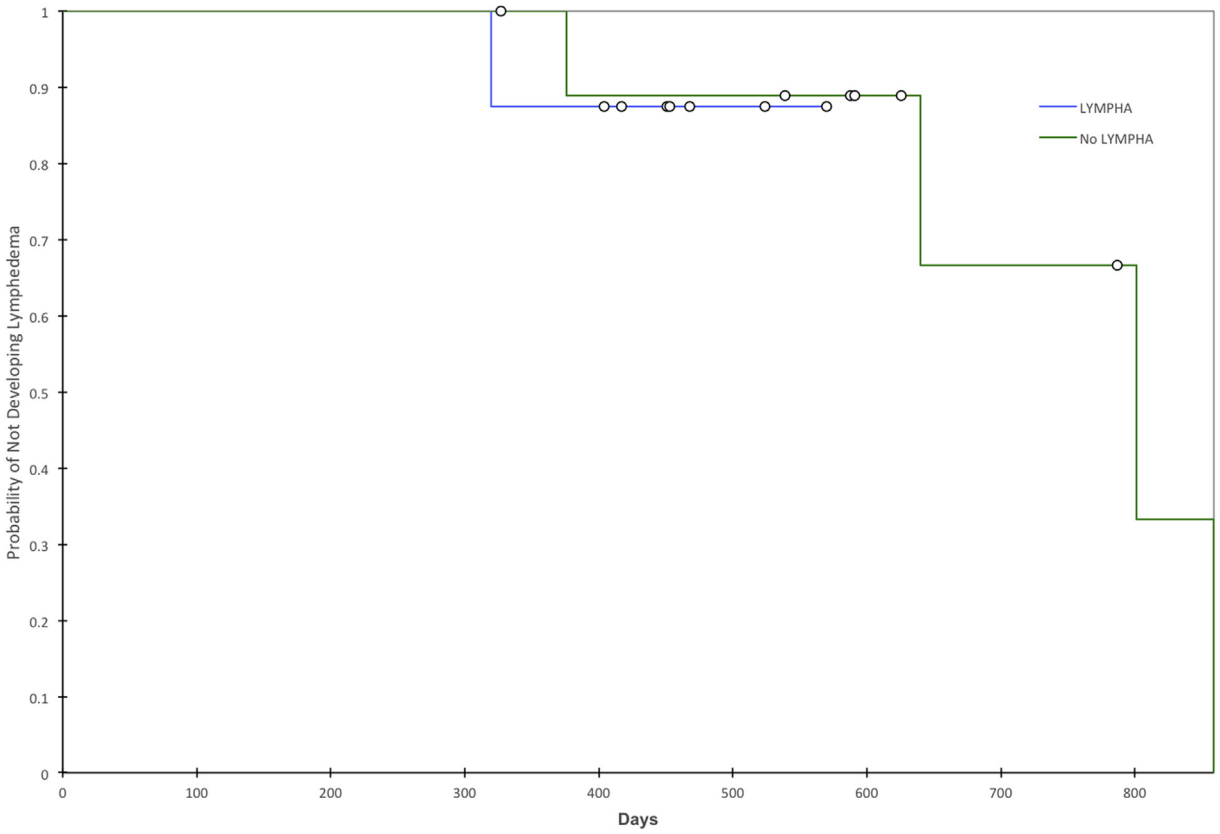

Fig. 3 – Kaplan–Meier curves for lymphedema development (ALND only).

how metastatic disease to the axilla is treated. Given the significant morbidity of ALND, namely lymphedema, there is a distinct push away from ALND in early stage breast cancer in place of RLNR.[22] However, with LYMPHA and the promise of lower rates of lymphedema, the role of ALND in providing the optimal method of loco-regional control may be preserved.

Similarly, while a lymphedema surveillance program has the potential to positively impact long-term cancer survivorship, implementation of this program revealed its own challenges. Understandably, when a patient is diagnosed with cancer, lymphedema may be the least of their concerns. A concerted and unified effort from the entire team including the breast surgeon, plastic surgeon, medical oncologist, radiation oncologist, and physical therapist will help increase patient participation in these programs. The remaining challenge of coordinating visits for surveillance can be offset by multidisciplinary clinics.

The most significant limitation of this study is the participation rate. We believe our participation rate was low because our surgical clinics were across town from our therapists who performed our evaluations. Despite this limitation, we chose to be rigorous in our inclusion criteria in order to present objective preoperative and postoperative data for comparison. While our participation rate is low, we do believe our most significant finding of a decrease in lymphedema rates after the advent of LYMPHA are notable as our average time to diagnosis of lymphedema was 4.7 mo following the surgical intervention, and our follow-up in the ALND versus ALND + LYMPHA groups was 20 mo and 15 mo, respectively. Ultimately, it will be important to follow these patients long term.

Conclusion

With a limited sample size, we found that offering LYMPHA with ALND decreased our institutional rate of lymphedema from 40% to 12.5%. Similarly, surveillance programs allow for early diagnosis and intervention by physical therapy. The significant risk factors for lymphedema development included ALND, RLNR, adjuvant chemotherapy, and mastectomy. Larger studies will need to be performed to confirm the pilot data presented. Moreover, long-term follow-up and randomized control trials are necessary to further elucidate the promise of this surgical technique for reducing the risk of BCRL.

Acknowledgment

Authors' contributions: M.H. contributed for concept design, acquisition of data, and manuscript preparation. N.G. contributed for acquisition of data, statistical analysis, and

manuscript preparation. D.M. contributed for acquisition of data, data analysis, and manuscript preparation.

B.T.L. contributed for manuscript preparation and manuscript editing. P.C. was responsible for concept design and acquisition of data. C.S. was responsible for concept design and manuscript editing. L.S. contributed for concept design, manuscript preparation, and editing manuscript. D.S. contributed for concept design, acquisition of data, manuscript preparation, and editing manuscript.

IRB information: Approved by the University of Florida Internal Review Board (IRB201300619).

Disclosure

The authors did not receive any funding for this study. They have no financial disclosures and report no conflicts of interest.

REFERENCES

1. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol*. 2016;34:611–635.
2. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14:500–515.
3. Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. *Int Wound J*. 2005;2:47–62.
4. Brunelle C, Skolny M, Ferguson C, Swaroop M, O'Toole J, Taghian A. Establishing and sustaining a prospective screening program for breast cancer-related lymphedema at the Massachusetts General Hospital: lessons learned. *JPM*. 2015;5:153–164.
5. Soran A, Ozmen T, McGuire KP, et al. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. *Lymphatic Res Biol*. 2014;12:289–294.
6. Liao S-F, Li S-H, Huang H-Y, et al. The efficacy of complex decongestive physiotherapy (CDP) and predictive factors of lymphedema severity and response to CDP in breast cancer-related lymphedema (BCRL). *The Breast*. 2013;22:703–706.
7. Miller CL, Specht MC, Horick N, et al. A novel, validated method to quantify breast cancer-related lymphedema (BCRL) following bilateral breast surgery. *Lymphology*. 2013;46:64–74.
8. Torres Lacomba M, Yuste Sanchez MJ, Zapico Goni A, et al. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. *BMJ*. 2010;340:b5396.
9. Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer*. 2008;112:2809–2819.
10. 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.
11. Boccardo F, Casabona F, DeCian F, et al. Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphedema: over 4 years follow-up. *Microsurgery*. 2014;34:421–424.
12. Warren LEG, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys*. 2014;88:565–571.
13. Ozcinar B, Guler SA, Kocaman N, Ozkan M, Gulluoglu BM, Ozmen V. Breast cancer related lymphedema in patients with different loco-regional treatments. *Breast*. 2012;21:361–365.
14. Armer J, Fu MR, Wainstock JM, Zagar E, Jacobs LK. Lymphedema following breast cancer treatment, including sentinel lymph node biopsy. *Lymphology*. 2004;37:73–91.
15. Golshan M, Martin WJ, Dowlatshahi K. Sentinel lymph node biopsy lowers the rate of lymphedema when compared with standard axillary lymph node dissection. *Am Surg*. 2003;69:209–211. discussion 212.
16. 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.
17. Spiguel L, Shaw C, Katz AJ, et al. Fluorescein isothiocyanate: a novel application for lymphatic surgery. *Ann Plast Surg*. 2017:1–5. In Press.
18. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases. *Trans Meet Am Surg Assoc*. 2010;128:12–21.
19. Jung S-Y, Shin KH, Kim M, et al. Treatment factors affecting breast cancer-related lymphedema after systemic chemotherapy and radiotherapy in stage II/III breast cancer patients. *Breast Cancer Res Treat*. 2014;148:91–98.
20. Giuliano AE, Ballman K, McCall L, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases. *Ann Surg*. 2016;264:413–420.
21. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303–1310.
22. Ahmed M, Douek M. What is the future of axillary surgery for breast cancer? *Ecancermedicalscience*. 2013;7:319.