OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Breast

Is Immediate Lymphatic Reconstruction on Breast Cancer Patients Oncologically Safe? A Preliminary Study

Ying-Sheng Lin, MD, MPH*
Chen-Hsiang Kuan, MD, PhD†
Chiao Lo, MD‡§
Li-Wei Tsai, MD‡¶
Chien-Hui Wu, MD‡
Chieh-Huei Huang, MD†
Eng-Kean Yeong, MD†
Hao-Chih Tai, MD, PhD†*
Chiun-Sheng Huang, MD, PhD, MPH‡*

Background: In breast cancer patients receiving axillary lymph node dissection (ALND), immediate lymphatic reconstruction (ILR) with lymphovenous anastomosis is an emerging technique for reducing the risk of arm lymphedema. However, the oncologic safety of surgically diverting lymphatic ducts directly into venules in a node-positive axilla is still a concern of inadvertently inducing metastasis of remaining cancer cells. This study aimed to assess the oncologic safety of ILR.
Methods: From January 2020 to January 2022, 95 breast cancer patients received ALND, and 45 of them also received ILR. Patients with recurrent cancer, with follow-up less than 12 months, and with missed data were excluded. Variables were compared between ILR and non-ILR groups, and the outcome of interest was the rate of distant recurrence after follow-up for at least 1 year.
Results: Thirty-four patients in the ILR group and 32 patients in the non-ILR group fulfilled the inclusion criteria for analysis. No statistically significant difference was noted between groups in terms of age, body mass index, type of breast surgery, pathologic cancer staging, histologic type and grade of breast cancer, molecular subtypes, frequency of axillary lymph node metastasis, or adjuvant therapy. For the patients receiving follow-up for at least 1 year, no statistically significant difference was found in terms of distant recurrence rates between ILR and non-ILR groups ($P = 0.44$).
Conclusion: For breast cancer patients receiving ALND, ILR with lymphovenous anastomosis is oncologically safe, within an average follow-up period of 21 months.
(Plast Reconstr Surg Glob Open 2023; 11:e5385; doi: 10.1097/GOX.0000000000005385; Published online 7 November 2023.)

INTRODUCTION

For breast cancer patients undergoing axillary lymph node dissection (ALND), one-fifth of the patients are likely to experience arm lymphedema.[1] Immediate lymphatic reconstruction (ILR), or lymphatic microsurgical preventing healing approach (LYMPHA), has been proposed to reduce the risk of breast cancer-related lymphedema (BCRL) after ALND.[2–4] In 2009, Boccardo et al first proposed the LYMPHA concept.[2] The procedure consists of identifying arm-draining lymphatic ducts in the axillary wound and anastomosing those lymphatic ducts to nearby venules under a surgical microscope. The authors reported their 4-year follow-up results in 2014 to support the efficacy of this procedure.[3] In 2018, Johnson and Singhal proposed using "immediate lymphatic reconstruction (ILR)" to describe the same procedure.[4] Accumulating evidence has suggested the efficacy of lymphedema risk reduction from this procedure.[5,6] In a meta-analysis by Hill et al in 2022, 6.7% of patients in the ILR (LYMPHA) group developed lymphedema. In the control group, 34% of patients developed lymphedema.[5] In a randomized controlled trial by Coriddi et al, the preliminary results show that ILR decreases BCRL

*From the *Division of Plastic Surgery, Department of Surgery, National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan; †Division of Plastic Surgery, Department of Surgery, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; ‡Division of General Surgery, Department of Surgery, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; §Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; and ¶Department of Surgical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan.*

Received for publication August 1, 2023; accepted September 20, 2023.

DOI: 10.1097/GOX.0000000000005385

Disclosure statements are at the end of this article, following the correspondence information.

incidences, which are 9.5% in the ILR group, and 32% in the control group.[6] However, understanding of the oncologic safety of ILR after ALND is still lacking. This concern comes from that this procedure involves surgically diverting lymphatic ducts directly into nearby venules in an axillary wound that was node-positive before ALND, and some breast cancer cells might be still present after ALND. According to a retrospective cohort study by Kaplan et al including a total of 6603 patients, the time to distant recurrence for stage II breast cancer patients was 5 years, and 3.83 years for stage III patients.[7] This study aimed to preliminarily assess the oncologic safety of ILR from the perspective of distant recurrence in a clinical setting.

Takeaways

Question: When performing immediate lymphatic reconstruction (ILR) with lymphovenous anastomosis in breast cancer patients receiving axillary lymph node dissection (ALND), the oncologic safety is a concern of inadvertently inducing metastasis of remaining cancer cells.

Findings: In a retrospective comparative study with 34 patients in the ILR group and 32 patients in the non-ILR group, no statistically significant difference was found in terms of distant recurrence rates between groups.

Meaning: For breast cancer patients receiving ALND, ILR with lymphovenous anastomosis is oncologically safe within an average follow-up period of 21 months.

PATIENTS AND METHODS

This retrospective study was conducted in a tertiary medical center and approved by an institutional review board (202302104RINB). Between January 2020 and January 2022, a total of 95 unilateral breast cancer patients received axillary lymph node dissection (level I and II). Among them, 45 patients also received ILR. Those patients were recruited from the division of breast surgery in our hospital. The allocation of ILR was nonrandom, primarily based on patients' willingness and plastic surgeons' availability. All the patients were asymptomatic of lymphedema preoperatively. Only patients with follow-ups of more than 1 year were included. Patients with recurrent cancer at the time of ALND were excluded because those patients might already have undetectable distant metastasis.

Operative Techniques

In the present study, ALND was performed by breast surgeons, who clipped or ligated the cut ends of the venules (instead of performing electrocautery) to preserve them for further lymphovenous anastomosis. Immediately after this, plastic surgeons performed ILR at the wound site created by ALND. Axillary reverse lymphatic mapping was used to identify arm-draining lymphatic vessels. In total, 2 mL of blue dye (Patent Blue V; Guerbet, France) and 2 mL of indocyanine green (ICG) (Diagnogreen; Daiichi Sankyo Propharma, Tokyo, Japan) were subcutaneously injected at multiple points over the volar aspect of the upper arm at 5 cm distal to the axillary wound. This injection is usually administered after ALND because the preparation of microsurgical equipment and personnel for ILR allows sufficient time for the injected dyes to fill the lymphatic vessels. With a surgical microscope coupled with a near-infrared camera (Leica M525 F50 with FL800 fluorescence system, Leica Microsystems, Germany), ICG-enhanced lymphatic vessels were easily visualized in the axillary wound; otherwise, blue dye-enhanced lymphatic vessels were identified using a regular surgical microscope without a specialized light filter (Leica M525 F50, Leica Microsystems, Germany). Venules with matched sizes and appropriate lengths were also identified in the axillary wound. These venules were usually the branches of the thoracoepigastric or thoracodorsal vein.[8] If the identified venules could not reach the transected end of the lymphatic vessels, further proximal dissection of the venules (to increase the available length) or slight adduction of the ipsilateral arm was performed. For size-matched lymphatic vessels and venules, end-to-end anastomosis was performed. When a size discrepancy of more than 0.5 mm or the presence of multiple lymphatic vessels was noted, end-to-side anastomosis or intussusception was performed.[2] For anastomosis, interrupted suture was performed using 11-0 (Ethicon, United States) or 12-0 nylon (Keisei Medical Industrial Co., Ltd., Japan) sutures. Because the operating field for anastomosis is close to the chest cavity, a patient's respiratory movement may be amplified under the high magnification of the surgical microscope, causing it to interfere with the passing of the suture through the vessel wall. A safe and helpful solution is coordinating with anesthesiologists to hold the patient's mechanical ventilation for several seconds. Placing a piece of loose sponge over the floor of the axillary wound is also helpful in mitigating the interference due to the patient's ventilation movement and reducing the depth of the surgical field to facilitate anastomosis. In the present study, the patency of anastomosis was intraoperatively evaluated using a surgical microscope coupled with an ICG camera (Figs. 1 and 2); alternatively, the Acland test was performed if the lymphatic vessels were not enhanced by ICG, or if an ICG camera-coupled microscope was unavailable (Fig. 3). Finally, surgical drains were carefully placed to avoid disrupting the anastomosis. Breast surgeons placed the drains before performing ILR; before closing the axillary wound, the plastic surgeons rechecked the locations of the drains to prevent them from interfering with the anastomosis.

Statistical Analysis

Statistical analysis was performed with Stata 17.0 (StataCorp, Inc., College Station, Tex.). Unpaired *t* test and Fisher exact test were used to compare the difference between groups in terms of various numerical variables [age, body mass index (BMI), number of lymphovenous anastomoses, frequency of axillary lymph

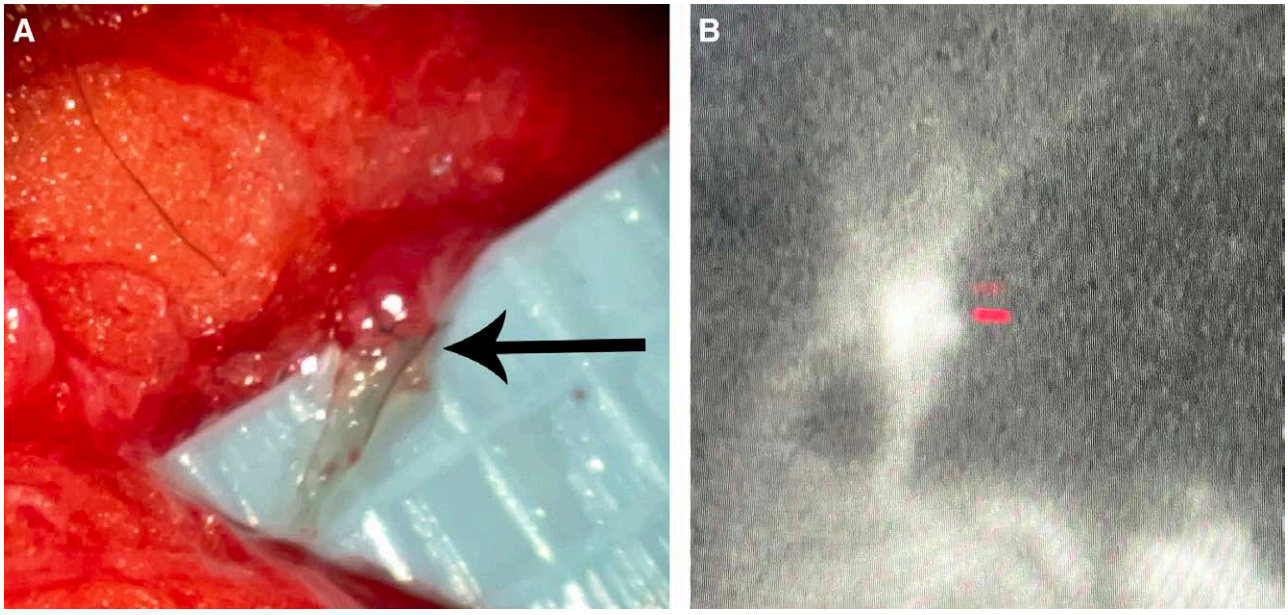

Fig. 1. A, An end-to-end lymphovenous anastomosis. B, The patency was confirmed by ICG.

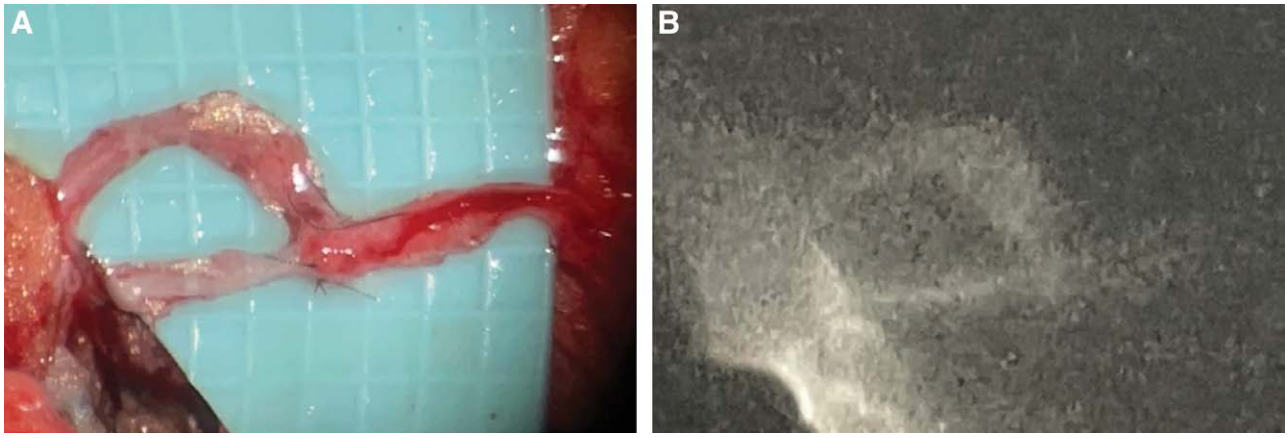

Fig. 2. A, One end-to-end and one end-to-side lymphovenous anastomosis. B, The patency was confirmed by ICG.

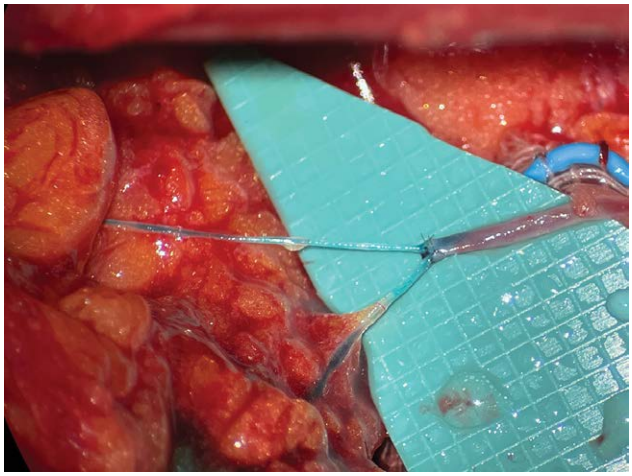

Fig. 3. Two-to-one lymphovenous anastomosis with intussusception technique. The blood in the venule was diluted by lymphatic fluid dyed by blue dye.

node metastasis, distant recurrence] and categorical variables (ethnicity, type of breast surgery, pathologic cancer staging, histologic type, histologic grade, molecular subtypes, adjuvant therapy), respectively. Those variables were chosen based on the understanding of possible risk factors of tumor recurrence.[9–22] Cox proportional hazards regression was used to evaluate if ILR or not would be the contributor to the time to tumor recurrence. A P value less than 0.05 was considered statistically significant.

RESULTS

The additional operation time for ILR was 1–1.5 hours. A total of 66 eligible patients (34 in the ILR group and 32 in the non-ILR group) were included for analysis (Fig. 4). The number of anastomoses for ILR was 1.24 ± 0.48. There were no immediate postoperative complications. The average follow-up periods were 21.4 ± 8.1 months. There

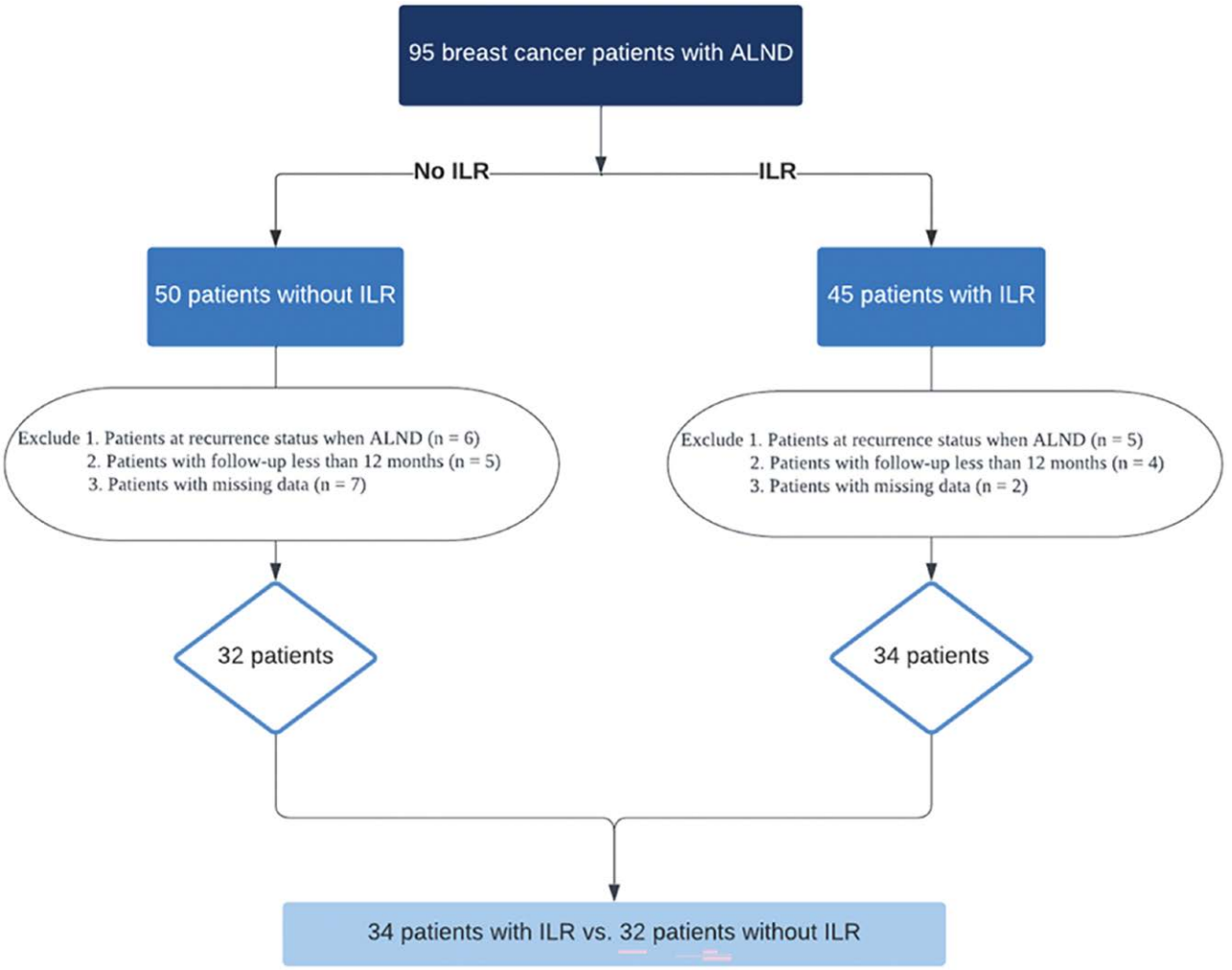

Fig. 4. Flow chart of patient selection for analysis.

was no statistically significant difference between ILR and non-ILR groups in terms of age (53.8 ± 9.2 versus 54.1 ± 12.1, P = 0.9), BMI (23.5 ± 5 versus 23.8 ± 3.8, P = 0.82), type of breast surgery (P = 0.19), pathologic cancer staging (P = 0.11), histologic type (P = 0.14) and grade of breast cancer (P = 0.72), molecular subtypes (P = 0.64), frequency of axillary lymph node metastasis (P = 0.34), or adjuvant therapy (P = 0.14; Table 1). The result of Cox regression also showed that there was no statistically significant difference in terms of distal recurrence between groups of different histologic type (unadjusted hazard ratio: 0.38, 95% CI: 0.02–6.11, P = 0.5; adjusted hazard ratio: 0.07, 95% CI: 0.000002–1927.2, P = 0.61), pathologic staging (unadjusted hazard ratio: 1.16, 95% CI: 0.62–2.19, P = 0.64; adjusted hazard ratio: 0.89, 95% CI: 0.26–3.01, P = 0.85), or ILR or not (ILR group: one distant recurrence out of 34 patients, non-ILR group: three out of 32, unadjusted hazard ratio: 0.47, 95% CI: 0.05–4.83, P = 0.52; adjusted hazard ratio: 0.88, 95% CI: 0.001–1317.7, P = 0.97) (Table 2), and the Kaplan-Meier curves were shown in Figure 5.

DISCUSSION

For locally advanced breast cancer patients with clinically positive nodes, ALND has been the treatment of choice for cancer staging and survival improvement.[23] However, approximately one-fifth of the patients are likely to experience arm lymphedema after the operation,[1] which could be explained from an anatomical point of view. Ilhan et al revealed that over a third of the patients had an overlap between arm and breast draining nodes.[24] Singhal et al also suggested that variances in the anatomy of the arm lymphatic system may be a contributing factor for BCRL.[25–27]

For any reconstructive efforts attempting to restore defects caused by surgical ablation of cancerous lesions, oncological safety remains the highest priority.[28–31] ILR, or LYMPHA, a surgical procedure combining axillary reverse mapping[32,33] and lymphovenous anastomosis,[34] is proposed to restore the disrupted lymphatic drainage during ALND.[35] Its efficacy in lowering the risk of lymphedema has been demonstrated.[5,36] However, two major concerns about ILR remain under debate, including the long-term patency of lymphovenous

Table 1. Characteristics of Patients with Breast Cancer Receiving ALND (n = 66)

Characteristic	ILR (n = 34)	Non-ILR (n = 32)	*P*
Age (y)	53.8 ± 9.2	54.1 ± 12.1	0.9
BMI (kg/m^2)	23.5 ± 5	23.8 ± 3.8	0.82
Ethnicity			
Asian	34 (100%)	32 (100%)	1
No. lymphovenous anastomoses	1.24 ± 0.4	0	<0.0001
Type of breast surgery			
ALND only	11 (32.4%)	5 (15.6%)	
MRM	17 (50%)	23 (71.9%)	0.19
Partial mastectomy and ALND	6 (17.6%)	4 (12.5%)	
Pathologic cancer staging			
IA	1 (2.9%)	1 (3.1%)	0.11
IB	7 (20.6%)	0 (0%)	
IIA	3 (8.8%)	6 (18.8%)	
IIB	8 (23.5%)	8 (25%)	
IIIA	9 (26.5%)	9 (28.1%)	
IIIB	0	1 (3.1%)	
IIIC	6 (17.7%)	7 (21.9%)	
Histologic type			
Invasive carcinoma of no specific type	31 (91.2%)	24 (75%)	0.14
Invasive lobular carcinoma	1 (2.9%)	3 (9.4%)	
Invasive carcinoma with focal micropapillary	2 (5.9%)	0	
Feature			
Encapsulated papillary carcinoma	0	1 (3.1%)	
Invasive micropapillary carcinoma	0	1 (3.1%)	
Invasive carcinoma, with extracellular mucin	0	1 (3.1%)	
Production			
Invasive carcinoma with focal squamous	0	1 (3.1%)	
Invasive ductal carcinoma	0	1 (3.1%)	
Histologic grade			
I	2 (5.9%)	4 (12.5%)	0.72
II	17 (50%)	15 (46.9%)	
III	15 (44.1%)	13 (40.6%)	
Molecular subtypes			
Luminal A	1 (2.9%)	1 (3.1%)	0.64
Luminal B	2 (5.9%)	0 (0%)	
Luminal B-like	28 (82.4%)	25 (78.1%)	
HER2-enriched	2 (5.9%)	4 (12.5%)	
Triple negative	1 (2.9%)	2 (6.3%)	
Frequency of axillary lymph node metastasis (%)	19.5 ± 23.6	25.6 ± 28.1	0.34
Adjuvant therapy			
C/T	1 (2.9%)	1 (3.1%)	0.14
C/T + H/T	13 (38.2%)	6 (18.8%)	
C/T + R/T	3 (8.8%)	5 (15.6%)	
C/T + R/T + H/T	16 (47.1%)	13 (40.6%)	
H/T	1 (2.9%)	5 (15.6%)	
R/T + H/T	0	2 (6.3%)	
Distal recurrence	1 (2.9%)	3 (9.4%)	0.35

C/T, chemotherapy; H/T, hormone therapy; MRM, modified radical mastectomy; R/T, radiotherapy.

anastomosis in the axilla after adjuvant radiation therapy, and the oncological safety of the ILR procedure. Buchan et al used ICG lymphography to demonstrate sustained patency of lymphovenous anastomosis despite adjuvant axillary radiation therapy.[37] Guzzo et al showed that ILR was not associated with axillary recurrence and seemed to be oncologically safe.[38] Our study used a retrospective comparative method to demonstrate the oncologic safety in terms of distant recurrence rates.

There could be a variety of explanations for why ILR is oncologically safe. First, the common metastasis sites of breast cancer are bone, liver, lung, brain, or ovaries.[39] ILR is a procedure about diverting arm-draining lymphatic ducts directly into nearby venules in a node-positive axillary wound. There is a concern about this procedure inadvertently inducing remaining breast cancer cells into the venous system. However, breast cancer cell metastasizing to the arm through arm-draining lymphatic ducts in a retrograde fashion is theoretically less likely and seldomly

Table 2. Cox Regression Showed No Statistically Significant Difference between ILR and Non-ILR Groups in Terms of Distant Recurrence

Variable	Univariable		Multivariable	
	Hazard Ratio	*P*	Hazard Ratio	*P*
Age	0.99 (0.91–1.09)	0.87	1.02 (0.91–1.13)	0.76
BMI	1.09 (0.91–1.31)	0.32	1.17 (0.91–1.52)	0.22
ILR	0.47 (0.05–4.83)	0.52	0.88 (0.001–1317.7)	0.97
No. lymphovenous anastomoses	0.51 (0.06–4.43)	0.54	0.43 (0.0005–369.4)	0.81
Type of breast surgery	2.22 (0.46–10.87)	0.32	4.96 (0.2–133.6)	0.34
Pathologic stage	1.16 (0.62–2.19)	0.64	0.89 (0.26–3.01)	0.85
Histologic type	0.38 (0.02–6.11)	0.5	0.07(.000002,1927.2)	0.61
Histologic grade	1.72 (0.32–9.2)	0.5	2.85 (0.39–20.8)	0.3
Molecular subtype	0.82 (0.34–1.98)	0.66	0.76 (0.27–2.12)	0.6
Frequency of axillary lymph node metastasis	5.14 (0.2–135.4)	0.33	71 (0.007–746121.3)	0.37
Adjuvant therapy	1.06 (0.47–2.37)	0.89	0.4 (0.03–5.8)	0.5

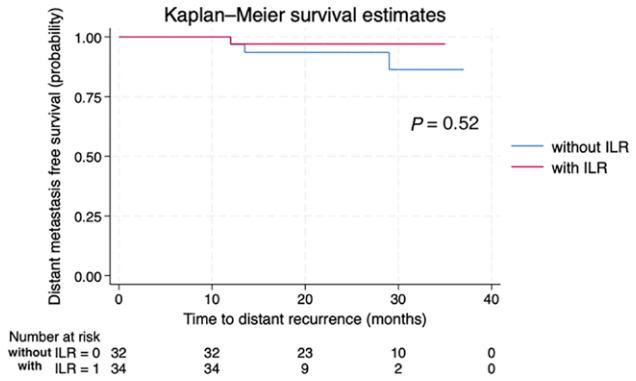

Fig. 5. Kaplan-Meier curves showed no statistical difference in terms of the distant recurrence rates between ILR and non-ILR groups.

reported. Only in 1979, a case report by Schafler et al mentioned that a patient's neoplastic arm lesions appearing 27 years after mastectomy were likely due to metastases from a newly-diagnosed lung cancer.[40] Otherwise, the neoplasms occurred in the chronic lymphedematous arms were likely the syndrome of postmastectomy lymphangiosarcoma (Stewart-Treves syndrome), which were not metastatic lesions from the initial breast cancers.[41] Second, postoperative adjuvant therapies (including either chemotherapy, radiation therapy, or hormone therapy) in node-positive patients help eradicate remaining cancerous cells and improve survival.[42–46] Third, disseminated cancer cells are biologically different from the primary tumor.[47,48] Even if a primary cancer cell spreading to the axillary node is inadvertently surgically diverted into the venous system, the chance of inducing distant metastasis is still slim, given that metastasis is a highly inefficient process involving various cell-extrinsic and cell-intrinsic factors.[49–51]

This study has a number of limitations. Firstly, breast cancer is characterized by its broad timeframe of recurrence, ranging from months to decades after definitive treatment.[52] Although we have excluded patients with follow-up intervals of less than 1 year, undetectable minimal residual disease could stay hidden and remain clinically asymptomatic for years.[53] The lengthy period between a curative treatment and tumor recurrence has been linked to the phenomenon of tumor dormancy.[54] More compelling data with a longer follow-up are needed to clarify the long-term oncological safety of ILR. Secondly, despite that we have tried to include all the likely factors influencing the risk and timing of recurrence, some modifiable risk factors for breast cancer recurrence, such as lifestyle change or smoking cessation,[22,55,56] are difficult to quantify. A patient's mental health, such as depression and anxiety, can also adversely affect the likelihood of recurrence.[57] Those aspects were not taken into consideration in our analysis. Thirdly, the Asian-only cohort in our study could limit the applicability to other ethnicities. Telli et al showed that Asian women had a significantly increased risk of being diagnosed with HER2-positive breast cancer, compared with non-Hispanic White women.[58] Weiss et al showed that there was no significant difference among White, African American, and Hispanic patients in terms of the molecular makers related to breast cancer prognosis.[59] Further studies including more diverse ethnic groups might help elucidate this issue. In addition, most of the patients in our study group have relatively advanced breast cancer, which could potentially limit the generalizability of our study. Lastly, lack of information on postoperative long-term anastomotic patency was also a drawback in this study. However, both the commonly used imaging modalities for detecting lymphatic ducts, ICG lymphography, and high-frequency ultrasound[60] could have difficulties identifying the lymphovenous anastomosis deep in the axillary wound due to the their limitations on penetration depth and postoperative fibrosis. This preliminary study sought to investigate the oncologic safety of ILR with an average follow-up of 21.4 ± 8.1 months. Currently, several randomized controlled trials are in progress worldwide (NCT03428581, NCT03941756, NCT04241341, NCT04328610, NCT05366699, and NCT05136079),[61] including one from our group (NCT05742945). The oncologic safety of ILR could be further affirmed by the outcomes of those studies.

Assuming the oncologic safety of ILR, another ongoing debate would be the indications of this procedure, given the

20% incidence rate of BCRL in patients receiving ALND. At first, Bocarrdo et al mentioned using BMI and a transport index of lymphoscintigraphy to select high-risk patients of BCRL.[3] Granoff et al mentioned using ICG lymphography to identify patients with a potential anatomic risk of developing BCRL.[25] Visser et al also summarized the genetic predisposition of BCRL.[62] In the future, ILR should be performed based on the patient's individual risk of BCRL, instead of universal implementation of the procedure.

CONCLUSIONS

In this preliminary study with a follow-up period of 21.4 ± 8.1 months, ILR with lymphovenous anastomosis in a node-positive axillary wound seemed to be oncologically safe for breast cancer patients receiving ALND. Further studies with longer follow-ups are needed to confirm the definitive oncologic safety.

Hao-Chih Tai, MD, PhD
Division of Plastic Surgery, Department of Surgery
National Taiwan University Hospital and College of Medicine
7, Zhong-Shan S. Rd
Taipei 10002, Taiwan
E-mail: taihc@ntu.edu.tw

Chiun-Sheng Huang, MD, PhD, MPH
Department of Surgery
National Taiwan University Hospital and College of Medicine
7, Zhong-Shan S. Rd
Taipei 10002, Taiwan
E-mail: huangcs@ntu.edu.tw

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

REFERENCES

1. 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.
2. 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.
3. 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.
4. Johnson AR, Singhal D. Immediate lymphatic reconstruction. *J Surg Oncol.* 2018;118:750–757.
5. Hill WF, Deban M, Platt A, et al. Immediate lymphatic reconstruction during axillary node dissection for breast cancer: a systematic review and meta-analysis. *Plast Reconstr Surg Global Open.* 2022;10:e4291.
6. Coriddi M, Dayan J, Bloomfield E, et al. Efficacy of immediate lymphatic reconstruction to decrease incidence of breast cancer-related lymphedema: preliminary results of randomized controlled trial. *Ann Surg.* 2023;278:630–637.
7. Kaplan HG, Malmgren JA, Atwood MK. Breast cancer distant recurrence lead time interval by detection method in an institutional cohort. *BMC Cancer.* 2020;20:1–11.
8. Coriddi M, Mehrara B, Skoracki R, et al. Immediate lymphatic reconstruction: technical points and literature review. *Plast Reconstr Surg Global Open.* 2021;9:e3431.
9. Adami HO, Malker B, Meirik O, et al. Age as a prognostic factor in breast cancer. *Cancer.* 1985;56:898–902.
10. Arce-Salinas C, Aguilar-Ponce J, Villarreal-Garza C, et al. Overweight and obesity as poor prognostic factors in locally advanced breast cancer patients. *Breast Cancer Res Treat.* 2014;146:183–188.
11. Neff PT, Bear HD, Pierce CV, et al. Long-term results of breast conservation therapy for breast cancer. *Ann Surg.* 1996;223:709–716; discussion 716–717.
12. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233–1241.
13. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347:1227–1232.
14. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer.* 1989;63:181–187.
15. Du Toit R, Locker A, Ellis I, et al. An evaluation of differences in prognosis, recurrence patterns and receptor status between invasive lobular and other invasive carcinomas of the breast. *Eur J Surg Oncol.* 1991;17:251–257.
16. Wasif N, Maggard MA, Ko CY, et al. Invasive lobular vs. ductal breast cancer: a stage-matched comparison of outcomes. *Ann Surg Oncol.* 2010;17:1862–1869.
17. Schwartz AM, Henson DE, Chen D, et al. Histologic grade remains a prognostic factor for breast cancer regardless of the number of positive lymph nodes and tumor size: a study of 161708 cases of breast cancer from the SEER Program. *Arch Pathol Lab Med.* 2014;138:1048–1052.
18. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature.* 2000;406:747–752.
19. Sørlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci USA.* 2003;100:8418–8423.
20. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the carolina breast cancer study. *JAMA.* 2006;295:2492–2502.
21. Voduc KD, Cheang MC, Tyldesley S, et al. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol.* 2010;28:1684–1691.
22. Lafourcade A, His M, Baglietto L, et al. Factors associated with breast cancer recurrences or mortality and dynamic prediction of death using history of cancer recurrences: the French E3N cohort. *BMC Cancer.* 2018;18:1–9.
23. Silberman AW, McVay C, Cohen JS, et al. Comparative morbidity of axillary lymph node dissection and the sentinel lymph node technique: implications for patients with breast cancer. *Ann Surg.* 2004;240:1–6.
24. Tasdoven I, Balbaloglu H, Erdemir RU, et al. Triple mapping for axillary staging after neoadjuvant therapy: axillary reverse mapping with indocyanine green and dual agent sentinel lymph node biopsy. *Medicine (Baltimore).* 2022;101:e32545.
25. Granoff MD, Pardo J, Shillue K, et al. Variable anatomy of the lateral upper arm lymphatic channel: a potential anatomic risk factor for the development of breast cancer related lymphedema. *Plast Reconstr Surg.* 2023;152:422–429.
26. Granoff MD, Pardo JA, Johnson AR, et al. Superficial and functional lymphatic anatomy of the upper extremity. *Plast Reconstr Surg.* 2022;150:900–907.
27. Friedman R, Bustos VP, Pardo J, et al. Superficial and functional imaging of the tricipital lymphatic pathway: a modern reintroduction. *Breast Cancer Res Treat.* 2023;197:235–242.

28. Mustonen P, Lepistö J, Papp A, et al. The surgical and oncological safety of immediate breast reconstruction. *Eur J Surg Oncol.* 2004;30:817–823.
29. Snoj M, Arnež Z, Sadikov A, et al. Breast reconstruction following mastectomy for invasive breast cancer by free flaps from the abdomen is oncologically safe. *Eur J Surg Oncol (EJSO).* 2007;33:541–545.
30. Tukiama R, Vieira RA, Moura EC, et al. Oncologic safety of breast reconstruction with autologous fat grafting: a systematic review and meta-analysis. *Eur J Surg Oncol.* 2022;48:727–735.
31. Thomas S, Varghese BT, Ganesh SA, et al. Oncological safety of submental artery island flap in oral reconstruction-analysis of 229 cases. *Indian J Surg Oncol.* 2016;7:420–424.
32. Thompson M, Korourian S, Henry-Tillman R, et al. Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. *Ann Surg Oncol.* 2007;14:1890–1895.
33. Ahmed M, Rubio I, Kovacs T, et al. Systematic review of axillary reverse mapping in breast cancer. *J Br Surg.* 2016;103:170–178.
34. Scaglioni MF, Fontein DB, Arvanitakis M, et al. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery.* 2017;37:947–953.
35. Weinstein B, Le NK, Robertson E, et al. Reverse lymphatic mapping and immediate microsurgical lymphatic reconstruction reduces early risk of breast cancer-related lymphedema. *Plast Reconstr Surg.* 2022;149:1061–1069.
36. Cook JA, Sinha M, Lester M, et al. Immediate lymphatic reconstruction to prevent breast cancer-related lymphedema: a systematic review. *Adv Wound Care.* 2022;11:382–391.
37. Buchan G, Cakmakoglu C, Schwarz G. ICG lymphographic findings following immediate lymphatic reconstruction in breast cancer patients. *J Plast Reconstr Aesthet Surg.* 2022;75:2164–2171.
38. Guzzo HM, Valente SA, Schwarz GS, et al. Oncologic safety of axillary lymph node dissection with immediate lymphatic reconstruction. *Breast Cancer Res Treat.* 2022;196:657–664.
39. Solomayer E-F, Diel I, Meyberg G, et al. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat.* 2000;59:271–278.
40. Schafler K, Mckenzie C, Salm R. Postmastectomy lymphangiosarcoma: a reappraisal of the concept—a critical review and report of an illustrative case. *Histopathology.* 1979;3:131–152.
41. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema. A report of six cases in elephantiasis chirurgica. *Cancer.* 1948;1:64–81.
42. Martin M, Pienkowski T, Mackey J, et al; Breast Cancer International Research Group 001 Investigators. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352:2302–2313.
43. Trudeau M, Charbonneau F, Gelmon K, et al. Selection of adjuvant chemotherapy for treatment of node-positive breast cancer. *Lancet Oncol.* 2005;6:886–898.
44. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA.* 2006;295:1658–1667.
45. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node–positive, steroid hormone receptor–positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol.* 2005;23:5973–5982.
46. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med.* 1997;337:956–962.
47. Bertucci F, Ng CK, Patsouris A, et al. Genomic characterization of metastatic breast cancers. *Nature.* 2019;569:560–564.
48. Yates LR, Knappskog S, Wedge D, et al. Genomic evolution of breast cancer metastasis and relapse. *Cancer cell.* 2017;32:169–184.e7.
49. Langley, RR, Fidler, IJ. The seed and soil hypothesis revisited—the role of tumor-stroma interactions in metastasis to different organs. *Int J Cancer.* 2011;128:2527–2535.
50. Ghajar, CM, Bissell, MJ. Pathways of parallel progression. *Nature.* 2016;540:528–529.
51. Riggio AI, Varley KE, Welm AL. The lingering mysteries of metastatic recurrence in breast cancer. *Br J Cancer.* 2021;124:13–26.
52. Karrison TG, Ferguson DJ, Meier P. Dormancy of mammary carcinoma after mastectomy. *J Natl Cancer Inst.* 1999;91:80–85.
53. Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease—latest advances and implications for cure. *Nat Rev Clin Oncol.* 2019;16:409–424.
54. Uhr JW, Pantel K. Controversies in clinical cancer dormancy. *Proc Natl Acad Sci USA.* 2011;108:12396–12400.
55. Norman SA, Potashnik SL, Galantino ML, et al. Modifiable risk factors for breast cancer recurrence: what can we tell survivors? *J womens health.* 2007;16:177–190.
56. Bishop JD, Killelea BK, Chagpar AB, et al. Smoking and breast cancer recurrence after breast conservation therapy. *Int j Breast Cancer* 2014;2014:327081.
57. Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry.* 2020;25:3186–3197.
58. Telli ML, Chang ET, Kurian AW, et al. Asian ethnicity and breast cancer subtypes: a study from the California Cancer Registry. *Breast Cancer Res Treat.* 2011;127:471–478.
59. Weiss SE, Tartter PI, Ahmed S, et al. Ethnic differences in risk and prognostic factors for breast cancer. *Cancer.* 1995;76:268–274.
60. Hayashi A, Visconti G, Giacalone G, et al. Recent advances in ultrasound technology: ultra-high frequency ultrasound for reconstructive supermicrosurgery. *J Reconstr Microsurg.* 2021;38:193–199.
61. Deban M, McKinnon JG, Temple-Oberle C. Mitigating breast-cancer-related lymphedema—A Calgary program for immediate lymphatic reconstruction (ILR). *Current oncology (Toronto, Ont).* 2023;30:1546–1559.
62. Kapellas N, Demiri E, Lampropoulos A, et al. Genetic predisposition in cancer-related lymphedema: a systematic review. *Lymphat Res Biol.* 2022;20:478–487.