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Lymphedema After Axillary Lymph Node Dissection in Breast Cancer: Prevalence and Risk Factors—A Single-Center Retrospective Study

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Abstract

Background: Lymphedema may develop when axillary lymph node dissection (ALND) injures and obstructs the lymph ducts in the upper limb. In patients with breast cancer, lymphedema is difficult to treat and can cause arm swelling, heaviness, and restricted movement. We aimed to identify the prevalence and risk factors for lymphedema after ALND in patients with breast cancer.
Methods and Results: This retrospective study included 175 patients with breast cancer who underwent ALND in the Nagasaki University Hospital, Japan, between 2005 and 2018. Lymphedema was defined as symptomatic arm swelling with a >2-cm difference in the arm circumference between the affected and contralateral arms. Patients were divided into two groups according to the presence or absence of lymphedema. Surgical and pathological findings were compared between the two groups. Univariate and multivariate analyses were performed, including the chi-square test, Student's *t*-test, and logistic regression analysis. Lymphedema was prevalent in 20% of the study participants, and the mean time interval from surgery to development of lymphedema was 479 days. In the univariate analysis, a body mass index of >26 kg/m^2, smoking, radiotherapy (RT), and dissection of >18 axillary lymph nodes (ALNs) significantly increased the risk of lymphedema. In the multivariate analysis, smoking, RT, and dissection of >18 ALNs significantly increased the risk of lymphedema.
Conclusions: The prevalence of lymphedema in our study was 20%. Our findings suggest that smoking, RT, and dissection of >18 ALNs are risk factors for lymphedema. Aggressive and empiric ALND might be associated with axillary lymph duct damage.

Keywords: axillary lymph node dissection, axillary reverse mapping, breast cancer, lymphedema

Introduction

Breast cancer is the most common malignancy in women, with approximately 2.1 million new cases reported worldwide in 2018. Moreover, it is the fifth leading cause of cancer-related mortality, with approximately 620,000 deaths in both men and women in 2018.[1] The interval from diagnosis to death in patients with breast cancer is generally long, and the age-standardized 5-year net survival rate is approximately 90% worldwide.[2,3]

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Surgery, endocrine therapy, anti-human epidermal growth factor receptor 2 (HER2) therapy, chemotherapy, and radiotherapy (RT) are all effective treatment options to improve the survival of patients with breast cancer.[4–8] However, they are associated with frequent adverse events and complications.[9] Therefore, in addition to effective treatment, the prevention of adverse events and complications in patients with breast cancer has become increasingly important.

Lymphedema is one of the major complications of breast cancer; it causes arm swelling and heaviness, impaired limb mobility, and decreased quality of life. It is difficult to treat lymphedema once it occurs. Axillary lymph node dissection (ALND), RT to the regional lymph nodes (LNs), chemotherapy, obesity, and infection have been reported as risk factors for lymphedema in patients with breast cancer.[10] The extent of axillary surgery and the number of dissected LNs also appear to have a direct correlation with the risk of lymphedema.[11,12] In previous studies, the estimated incidences of lymphedema were 19.3%–24.6% in patients who underwent ALND and 2.2%–8.3% in patients who underwent sentinel lymph node biopsy (SLNB).[13–15]

Considering the findings of the ACOSOG Z0011,[16] AMAROS,[17] and IBCSG 23-01[18] trials, the use of ALND as a treatment option in patients with breast cancer has been decreasing. However, all patients with clinical axillary LN (ALN) metastasis and some patients with sentinel LN metastasis require ALND. Although ALND increases the risk of lymphedema and decreases the quality of life,[19] the surgical procedure for ALND has not changed in several decades.

In our institute, the empiric upper border for ALND is the lower edge of the axillary vein. This surgical procedure may cause injury and lymph duct obstruction in the upper limb, leading to lymphedema. Therefore, it is necessary to improve this surgical technique to prevent lymphedema. Lymphedema in patients with breast cancer has not been studied in our institute. Therefore, this study aimed to identify the prevalence and risk factors for lymphedema after ALND in patients with breast cancer.

Materials and Methods

Patients

This retrospective study was approved by the institutional review board of our hospital (approved number 20101911), and the requirement for informed consent was waived. We retrospectively reviewed the charts and collected the data of 1182 patients with breast cancer who underwent surgery at the Nagasaki University Hospital, Japan, between January 2005 and December 2018. The exclusion criteria were as follows: patients who underwent mastectomy alone or with SLNB ($n=967$) and patients who were lost to follow-up, including those who were followed up in other hospitals ($n=37$). After exclusion, the study comprised 178 ALNDs in 175 patients with breast cancer (Fig. 1). Patients were divided into two groups: patients with and without lymphedema.

Clinicopathological assessments and molecular subtypes

Patient-related variables in this study included age, body mass index (BMI), and smoking. Breast cancer related variables included estrogen receptor (ER), progesterone receptor (PgR), HER2 expression, pathological tumor-node-metastasis (TNM) staging, and lymphovascular invasion. Pathological staging was reclassified and graded according to the TNM classification system (8th edition).[20]

Breast cancer treatment

Treatment-related variables included the type of breast and axillary surgery, timing of chemotherapy and RT, number of dissected ALNs, number of metastatic LNs, and local recurrence of ALNs. For breast surgery, either partial mastectomy (Bp) or total mastectomy (Bt) was performed based on the tumor extension and surgeon's recommendations. For axillary surgery, patients clinically diagnosed with LN metastasis, and sentinel LN metastasis on SLNB, underwent ALND. In this study, SLNB was performed using the combined method (dye with a radioisotope) or indocyanine green (ICG) dye method. For ALND, level I (lateral to the pectoralis minor) and level II (under the pectoralis minor) LNs were dissected; for the dissection, the axillary vein was considered the upper border, whereas branches of the thoracodorsal vessels were considered the lower border.

In patients with HER2-positive or triple-negative breast cancer, neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC) was administered. In patients with ER-positive breast cancer, AC was administered in those at high risk of recurrence secondary to LN metastasis and with pathological T3 or T4 stage and/or lymphovascular invasion. In addition, patients with locally advanced breast cancer, who preferred to undergo Bp, despite a large tumor size, received NAC. In general, NAC and AC regimens were a combination of an anthracycline-containing regimen and taxane (such as four cycles of doxorubicin and cyclophosphamide, fluorouracil, epirubicin, and cyclophosphamide or epirubicin and cyclophosphamide, followed by four cycles of docetaxel).

The NAC regimen plus trastuzumab was administered in patients with HER2-positive breast cancer. Chemotherapy was not administered to patients with an advanced age, a low-performance status, and who refused to undergo chemotherapy.

In almost all patients who underwent Bp, the residual breast was irradiated, which included a certain amount of irradiation to the axillary region. Moreover, in patients with four or more LN metastases, the regional LNs (axillary, supraclavicular, and internal mammary nodes, if necessary) were irradiated; the chest wall and regional LNs were irradiated in patients who underwent Bt. Furthermore, irradiation was delivered to patients with three or fewer LN metastases, provided they did not receive chemotherapy and/or had a high risk of recurrence. RT was performed at a dose of 2 Gy per fraction (50 Gy/25Fr). If the surgical margins were positive, the patients received boosted irradiation (10 Gy/5Fr) to the tumor bed or underwent an additional excision to prevent local recurrence.

Evaluation of lymphedema

The diagnostic criteria for lymphedema included symptomatic arm swelling and a >2-cm difference in the arm circumference compared with that of the contralateral arm at a 5-cm distal or 10-cm proximal distance from the elbow fossa line. Patients who met both criteria were considered as

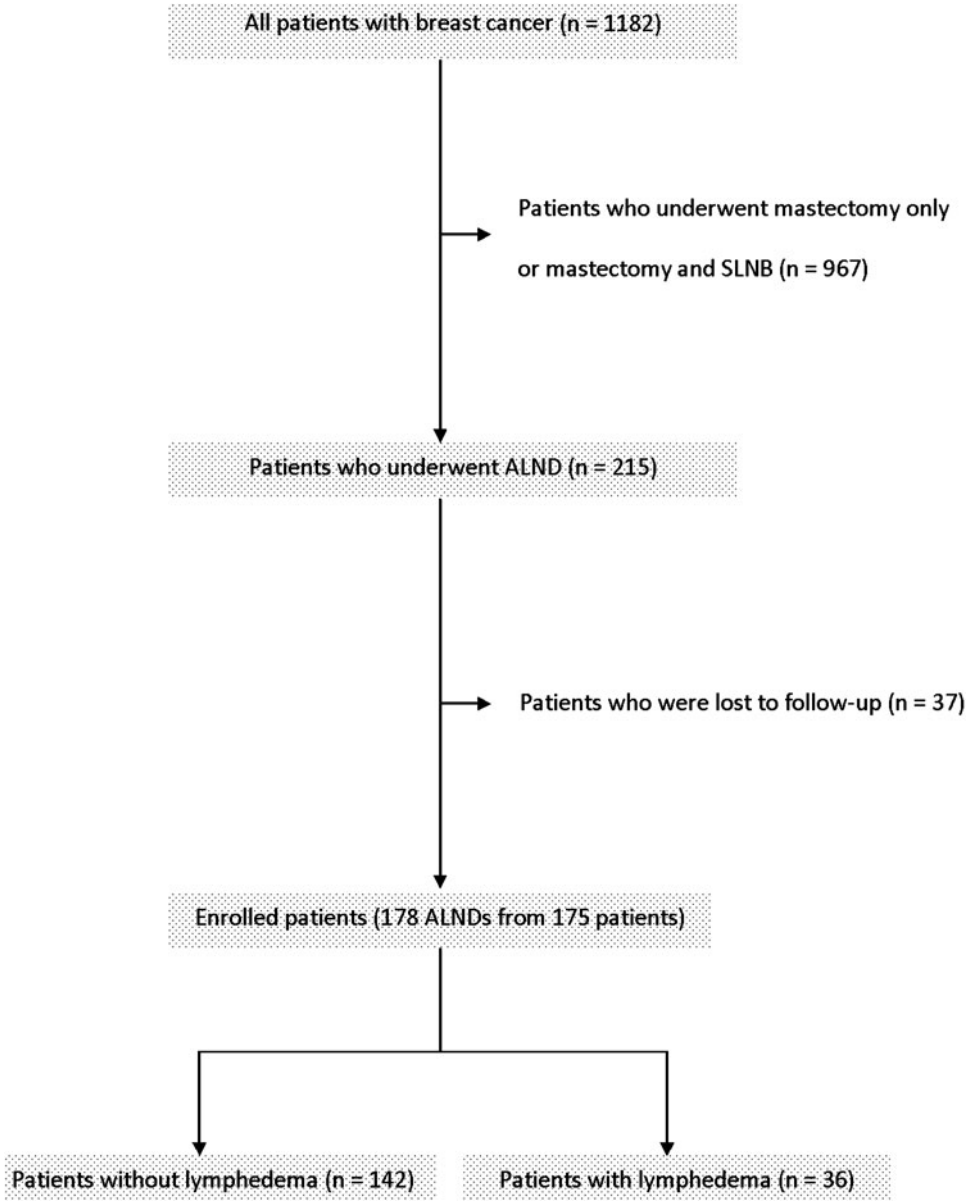

FIG. 1. Flowchart of the selection process of the study participants. ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

having lymphedema. The time interval from surgery to the development of lymphedema was calculated from the date of surgery to the date of diagnosis of lymphedema.

Statistical analyses

Univariate and multivariate analyses were performed to evaluate the risk factors for lymphedema using the chi-square test, Student's *t*-test, and logistic regression analysis. Continuous data were expressed as mean (standard deviation [SD]) [median]. The level of significance was set at $p \leq 0.1$ for the univariate analysis; all significant variables from the univariate analysis were assessed in a multivariate analysis. Risk factors with $p < 0.05$ in the multivariate analysis were considered statistically significant. In addition, we calculated the odds ratios (ORs) and 95% confidence intervals (CIs) in the multivariate analysis. All statistical analyses were performed using JMP Pro software version 15 (Statistical Analysis System Institute, Inc., Cary, NC, USA).

Results

The characteristics of the patients with and without lymphedema are shown in Table 1. The results of the assessed variables expressed as mean (SD) [median] were as follows: the observation period in all patients was 2052 (959) [2080] days, the age was 56 (13.2) [55] years, the BMI was 23.3 (4.07) [22.5] kg/m^2, the number of ALNs was 18.0 (7.29) [16], and the number of metastatic LNs was 3.75 (5.83) [2]. Eleven patients (6.2%) had a history of smoking. One hundred two patients (57%) received RT to the regional LNs. One hundred fifty-seven patients (88%) received

Table 1. Characteristics of Patients with Breast Cancer (N= 178) With and Without Lymphedema

Characteristic	*Without lymphedema* (n = *142*)	*With lymphedema* (n = *36*)	*Univariate,* p-*value*
Observation period (days)	2008 (960) [2077]	2225 (948) [2151]	0.23
Age (years)	57 (13.3) [55]	55 (12.7) [52.5]	0.41
BMI (kg/m^2)	23.2 (4.13) [22.4]	23.8 (3.84) [22.8]	0.43
≤26	114 (80)	24 (67)	0.08
>26	28 (20)	12 (33)	
Smoking	6 (4.2)	5 (14)	0.04
Expression status			
ER+	111 (78)	28 (78)	0.96
PgR+	100 (70)	23 (64)	0.45
HER2+	23 (16)	9 (25)	0.22
Lymphovascular invasion			
ly (+)	96 (68)	20 (56)	0.37
v (+)	82 (58)	23 (64)	0.22
Stage			0.44
I	8 (5.6)	3 (8.3)	
IIA	34 (24)	12 (33)	
IIB	25 (18)	8 (22)	
IIIA	37 (26)	9 (25)	
IIIB	13 (9.2)	2 (5.6)	
IIIC	10 (7.0)	1 (2.8)	
IV	3 (2.1)	1 (2.8)	
RT to the regional LNs	77 (54)	25 (69)	0.09
Chemotherapy			
None	15 (11)	1 (2.8)	0.14
NAC	43 (30)	14 (39)	0.50
AC	80 (56)	20 (56)	
Surgery			
Bp	36 (25)	8 (22)28 (78)	0.70
Bt	106 (75)	28 (78)	
SLNB → ALND	57 (40)	18 (50)	
ALND	85 (60)	18 (50)	0.28
No. of ALNs	17 (7.28) [16]	19 (7.27) [18]	0.18
≤18	96 (68)	18 (50)	0.05
>18	46 (32)	18 (50)	
No. of metastatic LNs	3.6 (5.58) [2]	3.9 (6.82) [2]	0.86

Continuous data are expressed as mean (SD) [median]. Categorical data are expressed as *n* (%).

AC, adjuvant chemotherapy; ALN, axillary lymph node; ALND, axillary lymph node dissection; BMI, body mass index; Bp, partial mastectomy; Bt, total mastectomy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node; ly, lymphatic invasion; NAC, neoadjuvant chemotherapy; PgR, progesterone receptor; RT, radiotherapy; SD, standard deviation; SLNB, sentinel lymph node biopsy; v, vascular invasion.

chemotherapy, of whom 57 (32%) received NAC and 100 (56%) received AC. Forty-four patients (25%) underwent Bp, and 134 patients (75%) underwent Bt.

One hundred thirty-nine patients (78%) had ER-positive tumors, 123 (69%) had PgR-positive tumors, and 32 (18%) had HER2-positive tumors. Eleven (6.2%), 46 (26%), 33 (19%), 46 (26%), 15 (8.4%), 11 (6.2%), and 4 (2.2%) patients had stage I, IIA, IIB, IIIA, IIIB, IIIC, and IV tumors, respectively. Lymphedema occurred in 36 patients (20%), and 142 patients did not develop lymphedema. The mean (SD) [median] time interval from surgery to the development of lymphedema was 479 (502) [330] days. Two patients (1.1%) had local ALN recurrence. A BMI >26 kg/m^2 and >18 ALNs were set as the cutoff values because these represented the maximum area under the curve in the receiver operating characteristic curve analysis.

In the univariate analysis, the significant variables were smoking (p = 0.04), RT to the regional LNs (p = 0.095), BMI >26 kg/m^2 (p = 0.08), and dissection of >18 ALNs (p = 0.05). Of these, smoking (p = 0.025; OR, 4.79; 95% CI: 1.23–18.47), RT (p = 0.032; OR, 2.42, 95% CI: 1.07–5.88), and dissection of >18 ALNs (p = 0.047, OR: 2.20, 95% CI: 1.01–4.84) remained significant in the multivariate analysis, whereas BMI >26 kg/m^2 (p = 0.160, OR: 1.85, 95% CI:

Table 2. Multivariate Analysis of Variables Significant in the Univariate Analysis

	Multivariate analysis	
Variable	*OR (95% CI)*	p
BMI (kg/m^2) (≤26/>26)	1.85 (0.78–4.26)	0.160
Smoking	4.79 (1.23–18.47)	0.025
RT	2.42 (1.07–5.88)	0.032
No. of ALNs (≤18/>18)	2.20 (1.01–4.84)	0.047

CI, confidence interval; OR, odds ratio.

0.78–4.26) was no longer significant (Table 2). The prevalence of lymphedema in patients with ≤18 dissected ALNs was 15.8%. In patients with >18 dissected ALNs, the prevalence of lymphedema was 28.1%.

Discussion

In this study, we showed that smoking, RT to the regional LNs, and dissection of >18 ALNs were associated with an increased risk of lymphedema. These results are consistent with those of previous studies that have shown that axillary surgery and RT increase the risk of lymphedema.[10,13,19,21] The prevalence of lymphedema in our study was within the estimated range of 19.3%–24.6% that has been previously reported in patients who underwent ALND.[13–15]

One study reported that the risk of lymphedema was highest during the first 6–12 months postoperatively in patients who underwent ALND and the first 18–24 months postoperatively in patients who underwent ALND, followed by post-mastectomy RT within 12–30 months.[13] These findings were similar to the findings of this study, in which the mean time intervals from surgery to the development of lymphedema were 351 days in patients who underwent ALND and 526 days in patients who underwent ALND and RT.

Previous studies suggest that the prevalence of lymphedema is associated with the number of dissected ALNs. Kilbreath et al.[11] reported that the prevalence of lymphedema was 3.3% in patients with ≤5 dissected ALNs; however, it was 18.2% in patients with >5 dissected ALNs. Similarly, Kim et al.[12] reported that the prevalence of lymphedema was 6.0% in patients with ≤10 dissected ALNs but 27% in patients with >10 dissected ALNs. In our study, dissection of >18 ALNs was a significant risk factor for lymphedema.

An accurate diagnosis of the ALN status requires the resection of ≥10 ALNs. However, the definition of an adequate ALND is controversial. The age of the patient and surgeon-related factors are associated with the number of dissected ALNs. In particular, younger patients and academic-affiliated surgeons were more likely to be associated with a higher number of dissected ALNs.[22,23] In addition, several studies have shown that a high BMI is a risk factor for lymphedema in patients with breast cancer.[24–26] However, in this study, a high BMI did not significantly increase the risk of lymphedema, although the patients with a BMI >26 kg/m^2 tended to develop lymphedema.

Whether NAC and AC are risk factors for lymphedema remain unclear. Some studies have shown that chemotherapy, especially taxane-based chemotherapy, significantly increases the risk of lymphedema,[14,27] whereas other studies have revealed that chemotherapy is not a risk factor for the development of lymphedema.[28,29] In our study, NAC and AC did not increase the risk of lymphedema.

Our findings suggest that extensive ALND might increase the risk of lymphedema. Axillary surgery, especially ALND, may damage the lymphatic system of the upper limb. Recently, new surgical techniques have been developed to prevent lymphedema. The Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) technique is a prophylactic surgical procedure that creates lymphatic venous anastomoses between the lymphatics of the arm and the branch of the axillary vein.[30,31] Boccardo et al.[31] reported that the LYMPHA technique reduced the incidence of lymphedema and that lymphedema developed in only 4.05% of patients who underwent ALND using the LYMPHA technique. However, it is difficult for breast surgeons to perform ALND with LYMPHA alone as it requires the involvement of plastic surgeons with microsurgical techniques.

Axillary reverse mapping (ARM) has also been developed to preserve axillary lymphatic drainage.[32,33] ARM is based on the theory that the upper limb and breasts have separate lymphatic drainage pathways. The resection of visualized LNs and lymph ducts can be avoided by injecting a dye (blue dye or ICG) into the upper limb while performing ALND.[21,34,35] We have started clinical trials on ARM using ICG, to reduce the risk of lymphedema in patients with breast cancer undergoing ALND.

Although smoking was a risk factor for lymphedema in this study, similar results have not been reported previously. The mechanism by which smoking causes lymphedema is unknown, and data on ex-smokers were not available for this study. Further studies are required to determine whether smoking cessation reduces lymphedema and whether smoking definitely increases the risk of lymphedema.

This study had several limitations. First, this study was limited by its retrospective design. We were unable to remove the selection bias and collect data for all objectives because of inadequate medical records or untraceable patients. For example, we may not have picked up asymptomatic patients who had a >2-cm difference in arm circumference. Second, we did not analyze the range of ALND, the number of ALNs present, specimen handling, and pathologist- and surgeon-related factors affecting the range of ALND. However, the number of dissected ALNs has previously been used as a surrogate measurement owing to its association with the range of ALND.[22]

Conclusions

In conclusion, in our study, the prevalence of lymphedema among patients who underwent ALND was 20%. Our findings suggest that smoking, RT to the regional LNs, and dissection of >18 ALNs are risk factors for lymphedema. Aggressive and empiric ALND might be associated with axillary lymph duct damage. Therefore, we have started clinical trials on ARM using ICG to reduce the risk of lymphedema in patients with breast cancer undergoing ALND.

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Authors' Contributions

Y.H. and R.O. contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Y.H., R.O., and S.S. The first draft of the article was prepared by Y.H. and R.O. All authors commented on the previous versions of the article. All authors read and approved the final article.

Statement of Ethics

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki

and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Nagasaki University Hospital, Nagasaki, Japan (No. 20101911). The need for informed consent was waived due to the retrospective nature of the study.

Author Disclosure Statement

No competing financial interests exist.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394–424.
2. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995–2009: Analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015; 385:977–1010.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68:7–30.
4. 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.
5. Reinbolt RE, Mangini N, Hill JL, et al. Endocrine therapy in breast cancer: The neoadjuvant, adjuvant, and metastatic approach. Semin Oncol Nurs 2015; 31:146–155.
6. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011; 365:1273–1283.
7. Early Breast Cancer Trialists' Collaborative Group, Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet 2012; 379:432–444.
8. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011; 378:1707–1716.
9. Waks AG, Winer EP. Breast cancer treatment: A review. JAMA 2019; 321:288–300.
10. Rockson SG. Lymphedema after breast cancer treatment. N Engl J Med 2018; 379:1937–1944.
11. Kilbreath SL, Refshauge KM, Beith JM, et al. Risk factors for lymphoedema in women with breast cancer: A large prospective cohort. Breast 2016; 28:29–36.
12. Kim M, Kim SW, Lee SU, et al. A model to estimate the risk of breast cancer-related lymphedema: Combinations of treatment-related factors of the number of dissected axillary nodes, adjuvant chemotherapy, and radiation therapy. Int J Radiat Oncol Biol Phys 2013; 86:498–503.
13. McDuff SGR, Mina AI, Brunelle CL, et al. Timing of lymphedema after treatment for breast cancer: When are patients most at risk? Int J Radiat Oncol Biol Phys 2019; 103:62–70.
14. 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.
15. Miller CL, Specht MC, Skolny MN, et al. Risk of lymphedema after mastectomy: Potential benefit of applying ACOSOG Z0011 protocol to mastectomy patients. Breast Cancer Res Treat 2014; 144:71–77.
16. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (alliance) randomized clinical trial. JAMA 2017; 318:918–926.
17. 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.
18. Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol 2018; 19:1385–1393.
19. Penn IW, Chang YC, Chuang E, et al. Risk factors and prediction model for persistent breast-cancer-related lymphedema: A 5-year cohort study. Support Care Cancer 2019; 27:991–1000.
20. Sobin LH, ed. *TNM Classification of Malignant Tumours* (8th edn). West Sussex: John Wiley & Sons; 2017.
21. Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG. Breast cancer-related lymphedema: Risk factors, precautionary measures, and treatments. Gland Surg 2018; 7:379–403.
22. Petrik DW, McCready DR, Sawka CA, Goel V. Association between extent of axillary lymph node dissection and patient, tumor, surgeon, and hospital factors in patients with early breast cancer. J Surg Oncol 2003; 82:84–90.
23. Chagpar AB, Scoggins CR, Martin II RC, et al. Factors determining adequacy of axillary node dissection in breast cancer patients. Breast J 2017; 13:233–237.
24. Bevilacqua JL, Kattan MW, Changhong Y, et al. Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. Ann Surg Oncol 2012; 19:2580–2589.
25. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 2001; 92:1368–1377.
26. Ahmed RL, Schmitz KH, Prizment AE, Folsom AR. Risk factors for lymphedema in breast cancer survivors, the Iowa women's health study. Breast Cancer Res Treat 2011; 130: 981–991.
27. Zhu W, Li D, Li X, et al. Association between adjuvant docetaxel-based chemotherapy and breast cancer-related lymphedema. Anticancer Drugs 2017; 28:350–355.
28. Gärtner R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment: A nationwide study of prevalence and associated factors. Breast 2010; 19: 506–515.
29. Swaroop MN, Ferguson CM, Horick NK, et al. Impact of adjuvant taxane-based chemotherapy on development of breast cancer-related lymphedema: Results from a large prospective cohort. Breast Cancer Res Treat 2015; 151: 393–403.

30. 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.
31. Boccardo F, Casabona F, De Cian 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.
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. Nos C, Lesieur B, Clough KB, Lecuru F. Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection. Ann Surg Oncol 2007; 14:2490–2496.
34. Han C, Yang B, Zuo WS, Zheng G, Yang L, Zheng MZ. The feasibility and oncological safety of axillary reverse mapping in patients with breast cancer: A systematic review and meta-analysis of prospective studies. PLoS ONE 2016; 11:e0150285.
35. Nos C, Kaufmann G, Clough KB, et al. Combined axillary reverse mapping (ARM) technique for breast cancer patients requiring axillary dissection. Ann Surg Oncol 2008; 15:2550–2555.

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