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A NOVEL, VALIDATED METHOD TO QUANTIFY BREAST CANCER-RELATED LYMPHEDEMA (BCRL) FOLLOWING BILATERAL BREAST SURGERY

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ABSTRACT

*We sought to develop a formula to quantify breast cancer-related lymphedema (BCRL) after bilateral breast surgery, which functions independently of the contralateral arm and accounts for fluctuations in patient weight. Perometer arm measurements from 265 unilateral breast surgery patients were analyzed. We assessed the relationship between change in patient weight and contralateral arm volume and developed a weight-adjusted volume change formula (WAC). The WAC formula and previously-established RVC formula were compared for classification of BCRL (≥ 10% volume increase) in unilateral breast surgery patients. We then evaluated BCRL incidence using the WAC formula in 225 bilateral mastectomy patients. Change in patient weight and contralateral arm volume demonstrated an approximately linear relationship. Weight-adjusted arm volume change (WAC) was therefore calculated as WAC = (A2*W1) / (W2*A1) - 1 where A1 is pre-operative and A2 is post-operative arm volume, and W1, W2 are the patient's corresponding weights. In the unilateral analysis, there was no significant difference in number of patients classified as having BCRL using the RVC and WAC formulas (p = 0.65). In bilateral mastectomy patients 11.1% (25/225) developed BCRL, defined as ≥10% WAC. Independent risk factors for lymphedema included axillary lymph node dissection (ALND) and higher pre-operative BMI (p<0.05). Use of this weight-adjusted arm volume change formula should be of value for quantification of BCRL after bilateral breast surgery.*

Keywords: lymphedema assessment, volume formula, quality of life, bilateral surgery, breast cancer, prophylactic mastectomy

Breast cancer-related lymphedema (BCRL) is a chronic condition characterized by swelling of the upper extremity due to an abnormal collection of protein-rich fluid in the interstitial tissues. The condition occurs in approximately 5-50% of all breast cancer patients, with a risk of approximately 15-20% after axillary lymph node dissection (ALND) and 3.5-11% after sentinel lymph node biopsy (SLNB) (1-7). Established risk factors for BCRL include ALND, higher Body Mass Index (BMI), and nodal radiation (1,5,8-13). BCRL is considered one of the most-feared side effects of breast cancer treatment and is known to cause physical and psychosocial detriments including body image changes, alterations in arm function, and complications such as cellulitis (14-17).

Despite increasing research on long-term sequalae of breast cancer treatment, a standardized method for quantification of BCRL has yet to be established (18-20). This lack of standardization has made interpretation and comparison of data across studies challenging, and has hindered progress in accurate diagnosis and treatment of the condition (21). Criteria for BCRL are primarily based on comparison between the at-risk and contralateral arm, including differences between arms of >2 cm by tape circumference, >200 ml or >10% by volumetry, or an impedance ratio between arms of >3 standard deviations from the normal range by bioimpedance spectroscopy (BIS) (22-25). The importance of obtaining pre-operative measurements to account for natural asymmetry between arms when assessing arm size changes has been previously suggested, and the above criteria comparing change in arm size relative to a pre-operative baseline are increasingly used (3,19,26-29).

In a prior report, we described a protocol for BCRL screening which utilizes the perometer to obtain pre-operative and longitudinal arm volume measurements and a relative volume change (RVC) equation to quantify BCRL (28). The RVC equation calculates arm volume change in the at-risk arm compared to a pre-operative measurement, and incorporates contralateral arm volume to control for changes in arm size unrelated to BCRL. Recent reports have utilized similar formulas to quantify BCRL (19,26,27,30,31). Inclusion of the contralateral arm to calculate BCRL is important since patients may gain weight or retain body fluid, which can result in increases in size of the at-risk arm unrelated to BCRL.

We have also demonstrated that use of relative changes in arm size rather than absolute changes is a more accurate method of assessment for BCRL. In a previous analysis, we found that the magnitude of absolute changes in arm size such as 200 ml or 2 cm correlates with body size, such that larger patients are more likely to receive a false positive diagnosis for BCRL. In contrast, when relative change (i.e., the RVC equation) is utilized, the magnitude of random variation is not dependent on patient body size (32). Therefore, accurate assessment for BCRL must consist of relative change in arm size compared to a pre-operative measurement, and also take into account factors unrelated to BCRL which would cause changes in arm size such as fluctuations in patient weight.

Quantification of BCRL in patients who undergo bilateral breast surgery is particularly challenging, since these patients lack a contralateral control arm for comparative purposes. For this reason, the RVC equation cannot be utilized in patients after bilateral breast surgery who may be bilaterally at-risk for BCRL including those with bilateral breast cancer or those who develop subsequent contralateral breast cancer. In addition, women increasingly choose contralateral prophylactic mastectomy (33), and assessment for BCRL on the at-risk side must therefore occur independently of the contralateral arm. This is due to the possibility of post-surgical changes in the contralateral arm, rendering it unsuitable for use as a control. As emerging evidence suggests the importance of early detection for optimal management of BCRL, it is critical that there exists a method to quantify arm size changes for early and accurate detection of BCRL in all breast cancer patients (26,29,34-37).

In this study, we sought to develop a formula for use in the setting of bilateral breast surgery which quantifies volume change in each arm individually and accounts for fluctuations in patient weight without use of contralateral arm volume. We then applied this formula in unilateral breast surgery patients and compared the incidence of BCRL using the WAC formula with the incidence using the previously-established RVC formula. Finally, the WAC formula was utilized in patients who underwent bilateral mastectomy to assess the incidence and risk factors for BCRL in this patient population.

METHODS

Patient Population/ Study Design

Perometer arm volume measurements were prospectively obtained in 265 unilateral breast surgery patients and 225 bilateral mastectomy patients who underwent surgery at our institution between 9/2005-8/2012; the study was approved by the Institutional Review Board. The protocol for lymphedema screening at our institution has been previously published (28). Patient demographics, surgical, radiation, medical oncology treatments, and pathology were collected by medical record review.

To derive the WAC formula, the relationship between change in contralateral arm volume and change in corresponding patient weight was determined using measurements from 265 unilateral breast surgery patients. All patients included in this analysis had a pre-operative perometer measurement, a minimum of three post-operative measurements, and a weight recorded within 10 days of each measurement. The relationship between change in contralateral arm volume and patient weight was evaluated using mixed linear repeated measures models, which account for the correlation among multiple arm volume and weight measurements made on the same patient. A quadratic term for weight was included to determine whether the relationship was non-linear.

We then applied the WAC formula and the established RVC formula to measurements from the 265 unilateral breast surgery patients to calculate volume change in the at-risk arm for each post-operative measurement. A McNemar's test was used to compare the incidence of BCRL according to the RVC and WAC formulas, which we defined as an arm volume increase of ≥10% compared to pre-operative baseline. In addition, the highest at-risk arm volume change for each patient was categorized into a three-level classification (<5%, ≥5-<10% and ≥10%) for RVC and WAC. A weighted Kappa statistic was calculated to determine agreement among the RVC and WAC formulas.

Finally, the WAC formula was utilized to quantify volume change in 225 patients who underwent bilateral mastectomy. We determined the incidence and risk factors for BCRL, which we defined as an arm volume increase of ≥10% according to the WAC formula. Measurements recorded within the first 3 months after surgery were not utilized for BCRL assessment, as patients may experience transient increases in measured arm volume during this period related to post-surgical changes (18). Cox proportional hazard models were used to identify risk factors for lymphedema.

RESULTS

Relationship between Arm Volume and Patient Weight

For the 265 patients who underwent unilateral breast surgery, median post-operative follow-up was 39.2 months (range 12.6 - 68.6) and time between measurements was 6.05 months (range 0.46 - 50.2). Median pre-operative contralateral arm volume was 2085 ml (range 1247 - 4796), and pre-operative difference between arms was 6 ml (range 0 - 351). The median within-patient change in contralateral arm volume between measurements was 57.5 ml (range 0 - 1068), and within-patient change in weight was 1.4 kg (range 0 - 31.3). The relationship between mean change in contralateral arm volume and corresponding patient weight between measurements was linear, slope = 0.988, intercept = 0.003 (*Fig. 1*).

Weight Adjusted Change Formula, and Comparison with RVC

The slope of the regression line is approximately one, and therefore weight-adjusted arm volume change (WAC) can be calculated according to the formula,

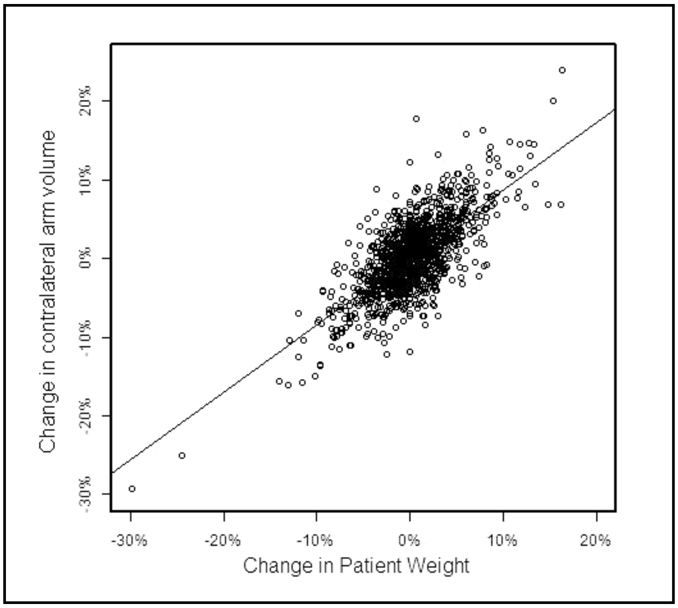

Fig. 1. Relationship between change in contralateral arm volume and corresponding change in patient weight between measurements.

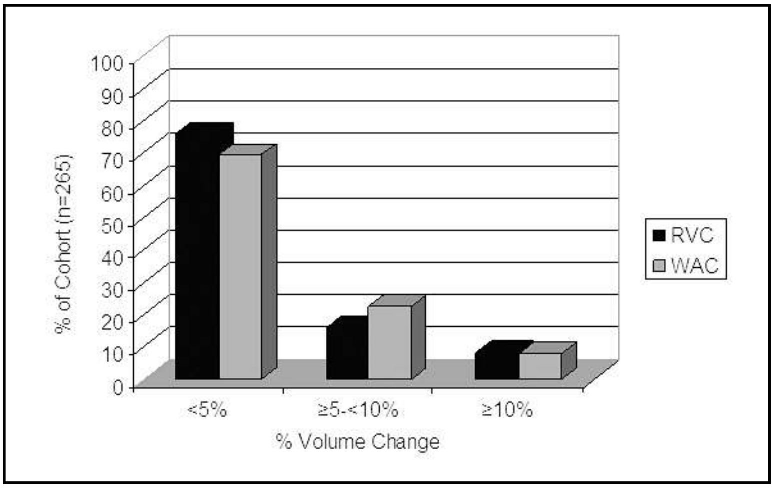

Fig. 2. Percent of unilateral breast surgery cohort classified as having arm volume increases of <5%, ≥ 5-<10% and ≥ 10% using the relative volume change (RVC) and weight-adjusted volume change (WAC) formulas.

WAC = (A2*W1) / (W2*A1) - 1 where A1 is pre-operative and A2 is post-operative at-risk arm volume, and W1, W2 are the patient's weight corresponding to these time points.

For the 265 unilateral breast surgery patients, there was no significant difference in number of patients classified as having BCRL (defined as ≥ 10%) using the RVC and WAC formulas, 8.3% (22/265) and 7.9% (21/265), respectively (p = 0.65). The RVC and WAC formulas classified patients as <5%, ≥ 5%-<10%, and ≥ 10% similarly, with a weighted Kappa statistic of 0.60 (95% CI: 0.50-0.70) (*Fig. 2*).

TABLE 1
Clinical and Pathologic Characteristics of Bilateral Mastectomy Patients

	Median (Range)	n=225 (100.0%)
Patient Characteristics		
Age at surgery, years	48 (23-72)	-
BMI at diagnosis, kg/m^2	24.5 (17.0-59.0)	-
Axillary Surgery		
Bilateral ALND	-	5 (2%)
ALND, contralateral SLNB	-	58 (26%)
ALND, no contralateral axillary surgery	-	26 (12%)
Bilateral SLNB	-	82 (36%)
SLNB, no contralateral surgery	-	54 (24%)
#LN's removed, SLNB	1 (1-10)	-
#LN's removed, ALND	14 (7-35)	-
# Positive LN's, ALND	2 (0-39)	-
Radiation Therapy†		
Chest wall only	-	15 (7%)
Chest wall with nodal††	-	63 (29%)
Chemotherapy		
Neoadjuvant	-	33 (15%)
Adjuvant	-	118 (52%)

BMI = Body Mass Index, ALND = Axillary lymph node dissection, SLNB = Sentinel lymph node biopsy, LN = lymph node; †data missing for 5 patients; ††2 patients had bilateral chest wall with nodal radiation

Weight Adjusted Change in Bilateral Mastectomy Patients

225 patients underwent bilateral mastectomy, 37 for bilateral breast cancer and 188 for unilateral breast cancer with contralateral prophylactic mastectomy. Median pre-operative BMI was 24.5 kg/m^2 and median age at surgery was 48. Of the 225 patients, 5 had bilateral ALND (2%), 58 had ALND with contralateral SLNB (26%), 26 had ALND with no contralateral axillary surgery (12%), 82 had bilateral SLNB (36%), and 54 had SLNB with no contralateral axillary surgery (24%). 63 (29%) patients underwent chest wall with nodal radiation, including 2 patients who received bilateral nodal radiation. Radiation fields were unknown for 5 patients. 145 patients (64%) received neoadjuvant and/or adjuvant chemotherapy (*Table 1*).

At a median post-operative follow-up of 21.6 months (range 3.1 - 75.0), 25 of 225 bilateral mastectomy patients (11.1%) developed BCRL ($\geq$10% WAC), which first occurred at a median of 14.6 months post-operative (range 4.9 - 63.6). One of these 25 patients developed bilateral lymphedema following bilateral ALND for a diagnosis of bilateral breast cancer. The remaining 24 patients all developed lymphedema on the side affected with cancer; there were no cases of lymphedema occurring on the side of prophylactic mastectomy with or without prophylactic SLNB.

By univariate analysis, higher pre-operative BMI, ALND, greater number of lymph nodes removed and number of positive lymph nodes, nodal radiation, and neoadjuvant chemotherapy were significantly associated with BCRL (*Table 2*). By multivariate analysis, only ALND ($p<0.0001$)

TABLE 2
Univariate Analysis of Risk Factors for BCRL (Defined as ≥10% WAC) after Bilateral Mastectomy

Variable	Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-value
Age at surgery	1.03	0.99	1.08	0.11
BMI	1.10	1.06	1.14	<0.0001
ALND	29.1	8.74	97.0	<0.0001
# LN's removed	1.14	1.10	1.18	<0.0001
# Positive LN's	1.25	1.17	1.35	<0.0001
Adjuvant chemotherapy	1.52	0.65	3.54	0.33
Neoadjuvant chemotherapy	2.47	1.04	5.92	0.04
Chest wall radiation only	14.7	5.90	36.6	<0.0001
Chest wall with nodal radiation	12.4	5.33	28.6	<0.0001

BMI = Body Mass Index; ALND = Axillary lymph node dissection; LN = Lymph Node

TABLE 3
Multivariate Analysis of Risk Factors for BCRL (Defined as ≥10% WAC) after Bilateral Mastectomy

Variable	Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-value
ALND	25.3	7.35	87.2	<0.0001
BMI	1.07	1.02	1.13	0.007

ALND = Axillary lymph node dissection; BMI = Body Mass Index

and higher pre-operative BMI (p=0.007) remained significantly associated with BCRL (*Table 3*).

DISCUSSION

In this series, we demonstrated a 1:1 linear relationship between change in patient weight and contralateral arm volume in unilateral breast surgery patients and also proposed a weight-adjusted volume change (WAC) formula to quantify BCRL after bilateral breast surgery. We found that the established RVC formula and proposed WAC formula classified unilateral breast surgery patients similarly for BCRL (≥10%). Therefore, patient weight may be substituted for contralateral arm volume when quantifying volume change in assessment for BCRL. Utilization of the WAC formula for patients who underwent bilateral mastectomy resulted in an 11.1% incidence of BCRL, with independent risk factors including ALND and higher pre-operative BMI. We propose use of the WAC formula for quantification of BCRL in patients after bilateral breast surgery.

Despite increasing research on lymphedema following treatment for breast cancer, methods to accurately quantify BCRL in patients who undergo bilateral breast surgery remain limited. Since these women may experience post-operative changes or be at-risk for BCRL in both arms, assessment is challenging due to lack of a control arm for comparison. Evaluation of change in size of the at-risk arm without consideration of factors unrelated to lymphedema such as weight gain may result in false positives for BCRL and unnecessary treatment. Given the known physical and psychosocial impacts of BCRL diagnosis and the burden of lymphedema treatment, it is important to avoid over-diagnosis of the condition (15,17,38). However, it is equally important that BCRL not be under-diagnosed, as increasing evidence suggests that early detection and intervention may lead to optimal management (26,29,34-37).

Numerous prior studies reporting on BCRL incidence and risk factors are restricted to patients with unilateral breast cancer and/or surgery (13,14,31,39,40). As a result, clinicians are limited in their ability to accurately predict the risk of BCRL for patients considering bilateral breast surgery, and post-operative screening for BCRL is limited for this growing population of breast cancer patients and survivors. Furthermore, many clinical trials investigating interventions for BCRL exclude patients with bilateral breast cancer or bilateral lymphedema (26,41-53). Exclusion of these patients from future clinical trials may significantly impact progress in research on BCRL in this patient population.

Definitions for BCRL utilized in previous studies cannot be applied for patients after bilateral breast surgery because many formulas utilize contralateral arm volume to control for arm size changes unrelated to BCRL. In a previous report, we demonstrated the accuracy of the RVC equation for quantification of unilateral arm volume change but this equation cannot be used in bilateral surgery patients due to reliance on contralateral arm volume (28,32). The importance of controlling for changes in patient weight – or change in contralateral arm volume as a reflection of change in weight – has been suggested by other authors. Mclaughlin et al state that "measurements of the ipsilateral and contralateral arm were obtained at baseline and follow-up to control for baseline asymmetry and weight change" (31). Similarly, Stout et al defined subclinical BCRL as an arm volume increase of >3% compared to a preoperative measurement "with consideration of contralateral limb volume changes" (26).

In 2008, Mahamaneerat et al proposed a BCRL criterion based on 5% BMI-adjusted limb volume change (LVC) compared to pre-operative baseline (30). The authors concluded that adjusting for BMI fluctuations when assessing change in arm size more accurately estimates BCRL occurrence. However, the equation was not applied in patients who had undergone bilateral breast surgery, and as a result, this equation has not yet been proposed for use in these patients.

Although arm volume increases of ≥ 10% are commonly considered indicative of BCRL (25), others have suggested that volume changes in the range of 5-10% may be representative of subclinical or low-level edema (19,26). In our series, almost half (49%) of unilateral breast surgery patients had a change in contralateral arm volume from pre-operative baseline exceeding 5% (data not shown). If calculation of BCRL does not account for changes in patient weight, it is possible that these patients would otherwise be considered to have subclinical BCRL in the arm on the side contralateral to their breast surgery. The unilateral breast surgery patients in our cohort also experienced weight fluctuations between measurements of up to 31 kg, and 36% had an increase in weight of over 5% between consecutive measurements (data not shown). It is therefore likely that these fluctuations in patient weight corresponded to the observed volume changes in the contralateral arm.

Comparison of the RVC and WAC formulas in patients who underwent unilateral breast surgery demonstrated that, overall, the formulas similarly classify patients for categories of arm volume increases (<5%, ≥ 5-<10%, and ≥ 10%). Importantly, the incidence of patients classified as having a ≥10% arm volume increase – often considered indicative of lymphedema – did not significantly differ between the two formulas. Given these findings as well as the 1:1 linear relationship between change in contralateral arm volume and patient weight, we propose that contralateral arm volume in the RVC formula can be replaced by patient weight to account for changes unrelated to BCRL.

Application of the WAC formula in patients who underwent bilateral mastectomy resulted in an 11.1% incidence of BCRL at a median of 21.6 months post-operative. One of the 25 patients in this cohort with BCRL developed bilateral lymphedema, demonstrating the need to assess each arm individually for BCRL. Consistent with the literature, in our series ALND and higher pre-operative BMI were independent risk factors for BCRL according to the WAC formula. Nodal radiation was significant for BCRL by univariate but not by multivariate regression in our study, likely due to the high correlation of having undergone ALND and nodal radiation. Further prospective studies involving patients who undergo bilateral breast surgery should utilize the WAC formula for arm volume quantification to confirm the risk factors associated with BCRL in this patient population. Greater length of follow-up in cohorts including patients who have undergone bilateral breast surgery should provide more useful information regarding the long-term risk of this condition in breast cancer survivors. Finally, application of this formula to bilateral lower extremities may be of interest if a 1:1 linear relationship can be established between change in patient weight and change in lower extremity limb volume. Future studies examining this relationship and confirmation utilizing patients with lower limb lymphedema is needed.

Our study is limited by the inclusion of only bilateral mastectomy patients and not those with bilateral breast conserving therapy for application of the WAC formula. Despite this, we hypothesize that the WAC formula should be equally applicable for patients who undergo bilateral lumpectomy or unilateral mastectomy with contralateral lumpectomy. Another limitation of this study is our definition of BCRL based on objective arm measurements without clinical examination or confirmation by patient report. Of note, we defined BCRL as an increase of ≥10% in arm volume compared to a pre-operative baseline, whereas others have proposed that volume changes in the range of 3-5% may be indicative of early or subclinical lymphedema (19,26). Further research is necessary to establish whether these low-level volume increases represent subclinical edema or normal fluctuations in arm size. Despite the limitations of this study, we feel that the proposed equation is a valid method for quantifying BCRL in patients after bilateral breast surgery and for those who may be bilaterally at-risk for the condition.

Lymphedema remains one of the most feared side effects of breast cancer treatment, with increasing evidence supporting the importance of screening for early detection and optimal management. It is therefore imperative that a method be established which can accurately quantify BCRL in patients after bilateral breast surgery. In this paper, we have proposed a weight-adjusted volume change formula which functions independently of the contralateral arm and accounts for changes in arm size related to patient weight, which can be used to quantify BCRL in patients after bilateral breast surgery.

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REFERENCES

1. Ashikaga, T, DN Krag, SR Land, et al: Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J. Surg. Oncol. 102 (2010), 111-118.
2. Hayes, S, TD Sipio, S Rye, et al: Prevalence and prognostic significance of secondary lymphedema following breast cancer. Lymphat. Res. Biol. 9 (2011), 135-141.
3. Armer, JM, BR Stewart: Post-breast cancer lymphedema: Incidence increases from 12 to 30 to 60 months. Lymphology 43 (2010), 118-127.
4. Gerber, L, M Lampert, C Wood, et al: Comparison of pain, motion, and edema after modified radical mastectomy vs. local excision with axillary dissection and radiation. Breast Cancer Res. Treat. 21 (1992), 139-145.
5. McLaughlin, SA, MJ Wright, KT Morris, et al: Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J. Clin. Oncol. 26 (2008), 5213-5219.
6. Wernicke, AG, M Shamis, KK Sidhu, et al: Complication rates in patients with negative axillary nodes 10 years after local breast radiotherapy after either sentinel lymph node dissection or axillary clearance. Am. J. Clin. Oncol. 36 (2013), 12-19.
7. Lucci, A, LM McCall, PD Beitsch, et al: Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J. Clin. Oncol. 25 (2007), 3657-3663.
8. Petrek, JA, RT Senie, M Peters, et al: Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 92 (2001), 1368-1377.
9. Tsai, RJ, LK Dennis, CF Lynch, et al: The risk of developing arm lymphedema among breast cancer survivors: A meta-analysis of treatment factors. Ann. Surg. Oncol. 16 (2009), 1959-1972.
10. Hayes, SB, GM Freedman, T Li, et al: Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? Int. J. Radiat. Oncol. Biol. Phys. 72 (2008), 1449-1455.
11. Coen, JJ, AG Taghian, LA Kachnic, et al: Risk of lymphedema after regional nodal irradiation with breast conservation therapy. Int. J. Radiat. Oncol. Biol. Phys. 55 (2003), 1209-1215.
12. Sener, SF, DJ Winchester, CH Martz, et al: Lymphedema after sentinel lymphadenectomy for breast carcinoma. Cancer 92 (2001), 748-752.
13. Ahmed, RL, KH Schmitz, AE Prizment, et al: Risk factors for lymphedema in breast cancer survivors, the Iowa Women's Health Study. Breast Cancer Res. Treat. 130 (2011), 981-991.
14. Hayes, SC, M Janda, B Cornish, et al: Lymphedema after breast cancer: Incidence, risk factors, and effect on upper body function. J. Clin. Oncol. 26 (2008), 3536-3542.
15. Ahmed, RL, A Prizment, D Lazovich, et al: Lymphedema and quality of life in breast cancer survivors: The Iowa Women's Health Study. J. Clin. Oncol. 26 (2008), 5689-5696.
16. Sakorafas, GH, G Peros, L Cataliotti, et al: Lymphedema following axillary lymph node dissection for breast cancer. Surg. Oncol. 15 (2006). 153-165.
17. Jager, G, W Doller, R Roth: Quality-of-life and body image impairments in patients with lymphedema. Lymphology 39 (2006), 193-200.
18. Armer, JM, BR Stewart, RP Shook: 30-Month post-breast cancer treatment lymphoedema. J. Lymphoedema 4 (2009), 14-18.
19. Cormier, JN, Y Xing, I Zaniletti, et al: Minimal limb volume change has a significant impact on breast cancer survivors. Lymphology 42 (2009), 161-175.
20. Bernas, MJ, JM Armer, JN Cormier: Lymphedema: How do we diagnose and reduce the risk of this dreaded complication of breast cancer treatment? Curr. Breast Cancer Rep. 2 (2010), 53-58.
21. Deltombe, T, J Jamart, S Recloux, et al: Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology 40 (2007), 26-34.
22. Cornish, BH, M Chapman, C Hirst, et al: Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology 34 (2001), 2-11.
23. Tsai, RJ, LK Dennis, CF Lynch, et al: The risk of developing arm lymphedema among breast cancer survivors: A meta-analysis of treatment factors. Ann. Surg. Oncol. 16 (2009), 1959-1972.
24. Cheville, AL, CL McGarvey, JA Petrek, et al: The grading of lymphedema in oncology

clinical trials. Semin. Radiat. Oncol. 13 (2003), 214-225.
25. Armer, JM, BR Stewart: A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat. Res. Biol. 3 (2005), 208-217.
26. Stout Gergich, NL, LA Pfalzer, C McGarvey, et al: Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer 112 (2008), 2809-2819.
27. McLaughlin, SA, S Bagaria, T Gibson, et al: Trends in risk reduction practices for the prevention of lymphedema in the first 12 months after breast cancer surgery. J. Am. Coll. Surg. 216 (2013), 380-389.
28. Ancukiewicz, M, TA Russell, J O'Toole, et al: Standardized method for quantification of developing lymphedema in patients treated for breast cancer. Int. J. Radiat. Oncol. Biol. Phys. 79 (2011), 1436-1443.
29. Boccardo, FM, F Ansaldi, C Bellini, et al: Prospective evaluation of a prevention protocol for lymphedema following surgery for breast cancer. Lymphology 42 (2009), 1-9.
30. Mahamaneerat, WK, CR Shyu, BR Stewart, et al: Breast cancer treatment, BMI, post-op swelling/lymphoedema. J. Lymphoedema 3 (2008), 38-44.
31. McLaughlin, SA, MJ Wright, KT Morris, et al: Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: Objective measurements. J. Clin. Oncol. 26 (2008), 5213-5219.
32. Ancukiewicz, M, CL Miller, MN Skolny, et al: Comparison of relative versus absolute arm size change as criteria for quantifying breast cancer-related lymphedema: The flaws in current studies and need for universal methodology. Breast Cancer Res. Treat. 135 (2012), 145-152.
33. Yao, K, AK Stewart, DJ Winchester, et al: Trends in contralateral prophylactic mastectomy for unilateral cancer: A report from the National Cancer Data Base, 1998-2007. Ann. Surg. Oncol. 17 (2010), 2554-2562.
34. National Lymphedema Network. Position Statement of National Lymphedema Network: Screening and Measurement for Early Detection of Breast Cancer Related Lymphedema. Available at: http://wwwlymphnetorg/pdfDocs/nlnBCLEpdf.
35. Torres Lacomba, M, MJ Yuste Sanchez, A Zapico Goni, et al: Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: Randomised, single blinded, clinical trial. BMJ 340 (2010), b5396.
36. Petrek, JA, PI Pressman, RA Smith: Lymphedema: Current issues in research and management. CA Cancer J. Clin. 50 (2000), 292-307.
37. Rockson, SG: Precipitating factors in lymphedema: Myths and realities. Cancer 83(12 Suppl American) (1998), 2814-2816.
38. Stout, NL, LA Pfalzer, B Springer, et al: Breast cancer-related lymphedema: Comparing direct costs of a prospective surveillance model and a traditional model of care. Phys. Ther. 92 (2011), 152-163.
39. Bevilacqua, JL, MW Kattan, Y Changhong, et al: Nomograms for predicting the risk of arm lymphedema after axillary dissection in breast cancer. Ann. Surg. Oncol. 19 (2012), 2580-2589.
40. Norman, SA, AR Localio, SL Potashnik, et al: Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. J. Clin. Oncol. 27 (2009), 390-397.
41. Devoogdt, N, MR Christiaens, I Geraerts, et al: Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial. BMJ 343 (2011), d5326.
42. Fife, CE, S Davey, EA Maus, et al: A randomized controlled trial comparing two types of pneumatic compression for breast cancer-related lymphedema treatment in the home. Support Care Cancer 20 (2012), 3279-3286.
43. Martin, ML, MA Hernandez, C Avendano, et al: Manual lymphatic drainage therapy in patients with breast cancer related lymphoedema. BMC Cancer 11 (2011), 94.
44. Kim do, S, YJ Sim, HJ Jeong, et al: Effect of active resistive exercise on breast cancer-related lymphedema: A randomized controlled trial. Arch. Phys. Med. Rehabil. 91 (2010), 1844-1848.
45. Ahmed Omar, MT, A Abd-El-Gayed Ebid, AM El Morsy: Treatment of post-mastectomy lymphedema with laser therapy: double blind placebo control randomized study. J. Surg. Res. 165 (2011), 82-90.
46. Schmitz, KH, RL Ahmed, AB Troxel, et al: Weight lifting for women at risk for breast cancer-related lymphedema: A randomized trial. JAMA 304 (2010), 2699-2705.
47. Damstra, RJ, H Partsch: Compression therapy in breast cancer-related lymphedema: A randomized, controlled comparative study of relation between volume and interface pressure changes. J. Vasc. Surg. 49 (2009), 1256-1263.
48. King, M, A Deveaux, H White, et al: Compression garments versus compression

bandaging in decongestive lymphatic therapy for breast cancer-related lymphedema: A randomized controlled trial. Support Care Cancer 20 (2012), 1031-1036.
49. Hamner, JB, MD Fleming: Lymphedema therapy reduces the volume of edema and pain in patients with breast cancer. Ann. Surg. Oncol. 14 (2007), 1904-1908.
50. Szuba, A, R Achalu, SG Rockson: Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomized, prospective study of a role for adjunctive intermittent pneumatic compression. Cancer 95 (2002), 2260-2267.
51. Didem, K, YS Ufuk, S Serdar, et al: The comparison of two different physiotherapy methods in treatment of lymphedema after breast surgery. Breast Cancer Res. Treat. 93 (2005), 49-54.
52. McNeely, ML, DJ Magee, AW Lees, et al: The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: A randomized controlled trial. Breast Cancer Res. Treat. 86 (2004), 95-106.
53. Forner-Cordero, I, J Munoz-Langa, A Forner-Cordero, et al: Predictive factors of response to decongestive therapy in patients with breast-cancer-related lymphedema. Ann. Surg. Oncol. 17 (2009), 744-751.

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