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Review Article

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Breast Cancer Related Lymphedema: A Review of Recent Developments

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Abstract

With improved methods of detection and advancing treatment paradigms, breast cancer outcomes continue to improve. Along with this improved survivorship, an increased focus on long term sequelae of treatment must occur. Breast cancer related lymphedema (BCRL) represents one of the most frequently recognized complications following breast cancer treatment and has been found to be associated with the extent of locoregional therapy. With regards to incidence rates, several randomized trials have found that with utilization of less aggressive axillary staging (i.e., sentinel lymph node biopsies), that rates of BCRL are reduced compared with axillary lymph node dissections. Quantification of the rates of BCRL by treatment technique remains difficult as significant heterogeneity exists in incidence rates based on treatment delivered and diagnostic criteria employed. Diagnosis of BCRL remains a challenge as traditional modalities are limited by low sensitivity and inconsistent definitions; new diagnostic modalities including bioimpedance spectroscopy may allow for the detection of BCRL in the sub-clinical phase of the disease process with defined, reproducible criteria. Treatment modalities for BCRL utilized include compression devices, exercise, and complex decongestive physiotherapy (CDP) with recent data supporting the utilization of CDP over standard modalities; importantly, data has emerged supporting the utilization of treatment in the sub-clinical and early phases of treatment in order to minimize long term complications associated with BCRL.

Keywords

Lymphedema; Breast cancer; Incidence; Diagnosis; Treatment

Introduction

With an annual incidence of approximately 300,000 cases and an estimated prevalence of 2.4 million women, breast cancer represents the most common non-cutaneous malignancy diagnosed for women in the United States [1]. Due to advances in imaging, surgery, systemic therapy and radiation therapy, outcomes for women diagnosed with breast cancer have continued to improve significantly over the past several decades [2]. As noted with other malignancies, when improved outcomes are achieved and the number of long term survivors expands, increased focus on long-term toxicities of treatment can and should occur. Evaluation of chronic toxicities is essential in breast cancer, as toxicities such as breast cancer related lymphedema (BCRL) can significantly impact the quality of life for long-term survivors such that while they are cured of their malignancy, the complications from treatment render them incapable of enjoying their life as they once did.

Unfortunately, there exists limited data or evidence based recommendations with regards to incidence, diagnosis, and management of BCRL and what data exists is often complicated by differences in treatment regimens and assessments. For example, the rates of BCRL in the literature can vary significantly from less than 5% with lumpectomy alone to greater than 50% when treatment includes axillary lymph node dissection and irradiation [3-5]. Currently, there are an estimated 800,000 women with some form of BCRL in the United States [4]; the significance of this number is the potential for BCRL to become a chronic process that can cause long-term swelling, numbness, skin changes, infection, pain, and functional impairment along with psychosocial effects [6-8]. Therefore, the purpose of this review is to examine the literature surrounding BCRL and in particular examine recent developments as it pertains to changes in the incidence of BCRL, diagnosis of BCRL in the sub-clinical phase of the disease, and management with a focus on early intervention.

Discussion

BCRL incidence rates; historical perspective and modern data

As previously noted, significant heterogeneity exists with regards to the incidence of BCRL. When examining rates of BCRL from older randomized trials, the rates of any BCRL were up to 60% and the rates of severe BCRL approached 20%. For example, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial randomized patients to a radical mastectomy or a total mastectomy with or without axillary radiation. Using circumference measurements, the rates of any BCRL (2 cm increase or more) were 58.1%, 38.2%, and 49.1% for the radical mastectomy, total mastectomy, and total mastectomy with axillary radiation arms respectively and the rates of severe BCRL (greater than a 4 cm increase) were 21.5%, 11.4%, and 13.1% respectively [9]. It is important to point out that while this data provides a reference point for previous rates of BCRL, these data are difficult to extrapolate to current patients due to differences in surgical technique/axillary staging, systemic therapy, and radiation therapy. A recent large series of over 3,000 patients treated with more modern techniques evaluated the incidence of BCRL via a patient survey and found the rates of BCRL to be 13% for breast conservation with sentinel lymph node biopsy (SLN), 51% for breast conservation with axillary lymph node dissection, and 53% for breast conservation with regional irradiation with higher rates noted for those receiving chemotherapy. The same patient survey study found the rates of BCRL to be 13%, 42%, and 58% respectively for patients undergoing mastectomy with SLN, mastectomy with Axillary Lymph Node Dissection ALND, and mastectomy with regional irradiation [4].

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With regards to recent developments, the two most important issues that have emerged with regards to incidence rates are the extent of axillary sampling and regional irradiation. Over the past two decades, SLN biopsy has gone from an experimental procedure to the standard of care in the management of the axilla, based on multiple randomized trials which evaluated SLN biopsy compared to the previous gold standard of ALND. One of the most important trials was NSABP B-32, which randomized patients to SLN biopsy versus SLN biopsy followed by ALND. Results from this trial demonstrated that SLN biopsy was associated with a reduction in BCRL at 36 months (8% v. 14%) [5]. These findings have been confirmed by randomized trials from Italy and the United Kingdom which demonstrated reductions in lymphedema, shoulder mobility, and numbness with SLN biopsy compared with ALND along with improved quality of life [10-13]. While sentinel lymph node biopsy alone has emerged as the standard for axillary assessment in patients with clinically node negative disease, for those patients with positive SLNs, completion ALND had remained the standard. However, recently, the American College of Surgeons Oncology Group (ACOSOG) Z0111 trial was published offering an alternative option which could further reduce rates of BCRL. In this study, 891 women with 1-2 positive SLNs were randomized to completion ALND or no further axillary treatment (ALND or regional irradiation). With over six years of follow-up, no difference was noted in the rates of regional recurrence, disease free survival, or overall survival [14]. While BCRL data has not been presented, based on the previous studies comparing ALND and SLN, the expectation is that the omission of ALND for those patients with 1-2 SLNs positive would lead to a significant reduction of BCRL in this patient population as seen in previous studies comparing SLN and ALND. However, further data is required as it remains unclear if patients randomized to the SLN only arm in this trial had a difference in the radiation fields administered compared with the completion ALND cohort. For example, although a third field was excluded (i.e. regional nodal irradiation), deep or partially deep tangents were not. These fields can cover a significant part of the axilla so it is not certain if the degree and extent of radiation coverage of the axilla was comparable between treatment arms.

Another area of increasing interest is the role of radiation therapy on the development of BCRL. While previous studies have found that radiation was associated with BCRL, over the past decade, more data has been published, confirming the impact of regional irradiation on rates of BCRL. A series of 727 patients treated with or without the inclusion of regional lymphatics in the treatment field found that the rate of BCRL was 2% with breast only treatment compared with 9% when the radiation field included regional nodes [15]. This was further confirmed by an analysis of over 2,100 patients from the Fox Chase Cancer Center. In this series, the rates of BCRL were 16%, 23%, and 31% for those patients treated to the breast, breast and supraclavicular lymph nodes, and breast with a posterior axillary boost respectively ($p<0.001$) [16]. Radiation was associated with higher rates of BCRL ($p=0.0002$) and the use of a regional field ($p<0.001$) was also significantly associated with BCRL [16]. One potential strategy to reduce the incidence of BCRL associated with radiation therapy is to limit the utilization of regional nodal irradiation and posterior axillary boosts. While recent data suggesting an improvement in disease free survival with the addition of regional irradiation warrants the use of a third field in appropriate cases, in those patients with low-risk node-negative disease, utilization of such techniques as accelerated partial breast irradiation may further reduce rates of BCRL secondary to lower doses to the axilla [17,18]. An alternative to traditional WBI that has been utilized is a high tangent technique; however, dosimetric data has demonstrated that this technique is associated with greater axillary coverage. Reznik et al. [19] found that high tangents led to 86%, 71%, and 73% of levels I, II, and III receiving the prescribed dose with high tangents compared with 66%, 44%, and 33% with standard tangents.

An important distinction to make is between BCRL which is typically associated with arm edema (related to axillary treatment) and breast edema. Breast edema can be seen following surgery alone but is typically associated with adjuvant radiation therapy [20]. The incidence rates of breast edema vary significantly due to varying diagnostic assessments utilized and range from 10% to greater than 75% [20-23]. One concern with breast edema is the difficulty of making an accurate diagnostic assessment; frequently, breast edema is a clinical diagnosis but increasing data supports the utility of MRI and/or high frequency ultrasound in diagnosing and following breast edema [23-25].

Diagnosis: limitations of traditional modalities and sub-clinical diagnosis

As previously noted, BCRL does not begin as a chronic, clinically apparent process but rather sub-clinically due to an impairment of the lymphatic system which subsequently manifests itself as clinically evident lymphedema. Traditional modalities utilized to diagnose BCRL include circumference measurements, patient surveys, and water displacement; however, these modalities are frequently based on diagnosis at the point of clinically apparent disease rather than during the sub-clinical phase. Multiple recently published studies have suggested that early intervention can reduce the frequency of chronic complications of BCRL and therefore, new modalities of diagnosis have been developed allowing for sub-clinical diagnosis and early intervention [26-28].

One of the most commonly utilized diagnostic modalities is circumference measurement; this technique appeals to clinicians due to the simplicity of implementation, low costs associated, lack of invasiveness, and potential for serial measurements with reproducible measuring points. Unfortunately, this technique is limited by its lack of sensitivity as a significant increase in volume is required to capture an increase in circumference [29-31]. Further, as noted by McLaughlin et al. [31] there exist many regimens utilized for circumference measurement without a clear standardized approach present. Another commonly utilized technique is water displacement; patient arm volume is measured placing the limb in a canister of water and subsequently the difference in water level with and without the arm in place is measured. While this technique has been validated, concerns remain including a lack of sensitivity, a lack of standardized criteria for assessment and interpretation, and the inability to utilize this technique in patients with infections [32]. Another concerns for both circumference and water displacement techniques is a lack of intra and inter-observer agreement [29,33,34]. Patient assessment has frequently been utilized to assess for BCRL and allows for the evaluation of large numbers of patients [4]; while it is limited in sensitivity, many clinicians utilize this to assess for BCRL due its simplicity and the fact that it also can assess for changes in quality of life associated with BCRL. While frequently employed a recent study found that compared with newer diagnostic techniques, that self assessment is only “moderately reliable” [33].

One of the recent developments in BCRL diagnosis is bioimpedance spectroscopy (BIS); BIS uses determinations of resistance to induced electrical currents to correlate to the volume of the extracellular space. One key study that identified BIS's ability to detect subclinical disease comes from Cornish et al; this prospective trial of 162 patients found that BIS had a 100% sensitivity to detect BCRL and was able to make a diagnosis 10 months prior to clinically apparent symptoms [35,36]. Other series have also documented that BIS has increased sensitivity compared to traditional assessment modalities with an average detection of 4 months earlier than traditional diagnostic modalities [37-39].

As with any new diagnostic tool, one key to the implementation of a new BCRL diagnostic modality is ensuring that it can be utilized in a clinic with limited space requirements and ease of implementation. A recent study from Vicini et al, highlighted the ease of implementing such a program, provided guidelines for measurement and assessment. Further, this study of 64 patients identified that BIS could accurately identify increases in lymphedema index ratios (LIRs) associated with more aggressive loco-regional treatment within 3 months of treatment [40]. These findings have been confirmed by a larger multi-institutional series of 125 patients which found that BIS was able to identify increases in extracellular volume within 6 months of treatment and stratify increases based on the extent of surgery and radiation therapy [41]. One key feature of BIS is that a standardized cutoff (increase above three standard deviations) has been identified, providing clinicians with a metric to make decisions regarding intervention [36,38,39]. Limitations of BIS include a lack of data supporting its ability to measure breast edema and a lack of data supporting its utility in advanced BCRL. Alternative new diagnostic modalities being investigated include dual energy x-ray absorptiometry (DXA) and optoelectronic perometry; however, despite the potential for sub-clinical BCRL diagnosis with these techniques, to date limited data has been published on these techniques and further study is required [42,43]. A series of 24 patients with BCRL found that DXA was significantly more consistent in volume measurements compared with traditional diagnostics such as circumference and water displacement [42]. With regards to optoelectronic perometry, a retrospective study of 46 patients suggested that segmental changes on perometry represent a harbinger of BCRL, allowing for sub-clinical diagnosis [43,44]. While these new diagnostic modalities can be incorporated into the clinic at this time, it must be noted that none of these techniques have been studied on large patient populations and all require further validation prior to being integrated into the routine standard of care for breast cancer patients following locoregional treatment.

Treatment modalities and timing of interventions

Multiple treatment options are available for the management of BCRL with treatment decisions based on the volume of disease at presentation, clinical symptoms present and patient co-morbidities. Standard treatment options include compression therapy, exercise, and multi-modality treatment or complex decongestive physiotherapy. While pharmacology has been investigated to help relieve BCRL, limited data supports its efficacy and it should not be routinely utilized off-protocol. In particular, benzopyrones have been studied at length with conflicting evidence regarding its efficacy [45,46]. Future investigations may target free radical scavengers, including selenium, with recent data suggesting a potential improvement in lymphedema volumes [47].

One of the most frequently utilized but controversial treatment options is compression therapy which includes compression garments as well as gradient and pneumatic compression devices. Based on currently available data, one area where compression devices have shown benefit is in the management of patients with low volume BCRL; data from Stout Gergich et al. [28] demonstrated that in patients diagnosed with BCRL in the early phase of the disease, excellent responses to treatment with a compression garment with minimal long term sequelae of BCRL or progression were noted. Further, while multiple randomized studies have demonstrated that using modern compression devices, arm volumes are reduced, they have failed to address which method of compression represents the current standard [48-50]. Other questions that have yet to be answered include whether compression devices change the natural history of BCRL or simply reduce arm volumes when being utilized and the optimal duration of usage. Complex decongestive physiotherapy (CDP) is currently utilized in the acute phase of BCRL and is considered the standard of care for BCRL management. CDP is multi-modality therapy and incorporates compression, exercise/manual lymphatic drainage, and skin care. The efficacy of such an approach has been documented in retrospective, prospective, and randomized studies with significant volume reductions noted. For example, a prospective series of 66 patients found that use of CDP led to a 70% volume reduction at the completion of treatment which has been confirmed by a larger series of 537 patients [51-56]. Just as importantly, recent studies have demonstrated that the use of CDP is associated with improvements in quality of life for those women with BCRL [55]. A randomized trial comparing CDP with standard techniques (bandage, elevation, skin care) found that CDP significantly reduced BCRL volumes; however, this small study needs to be validated [57]. Further, future studies will need to address the lack of long term follow-up data and the lack of a clear definition of what CDP entails in terms of interventions. Manual lymphatic drainage (MLD) is often a part of CDP but limited data is available to support its efficacy as monotherapy or in conjunction with other treatment options. To date, studies have been inconsistent in documenting a reduction in arm volumes with MLD with a study of 42 patients finding no additional benefit in arm volumes with the addition of MLD to standard compression therapy [58-60].

Finally, exercise has been studied as a modality to manage BCRL based on the premise that exercise can stimulate lymph flow via repetitive muscle stimulation. To date, limited data is available supporting the use use of exercise with a recent study of mild gentle exercise demonstrating at trend for reduced arm volumes and a feasibility study demonstrating a reduction in arm volume in a cohort of 23 women [61,62]. While the potential benefit of exercise for BCRL remains uncertain, a recently published randomized trial of 104 women did confirm that exercise was not associated with an increase in arm volume and did lead to improved quality of life [63].

The timing of treatment for BCRL represents a rapidly expanding focus in the literature with recent data suggesting benefits to early intervention; this does not represent the standard of care as the currently published series are limited by small numbers, and a lack of long term follow-up. However, the results are intriguing and warrant further study. One randomized trial evaluated 120 women following locoregional treatment for breast cancer, with patients randomized to early intervention (education, exercise/massage, manual lymphatic drainage) or education alone and found that early intervention

reduced the change of developing BCRL at one year (25% v. 7%, p=0.01) [26]. Similar findings were noted in smaller randomized trial of 65 patients that randomized patients to physiotherapy or no intervention following locoregional treatment. At two years, the rate of BCRL was reduced (30% v. 11%) with early intervention [27]. An alternative method of evaluating early intervention that avoids treating all patients requires newer diagnostic modalities to assess for early small volume changes. A non-randomized prospective trial from the National Naval Medical center enrolled 196 patients who underwent pre and post-operative volume assessments utilizing perometry with a 3% threshold; of this initial cohort, 43 patients were diagnosed with BCRL and treated with a compression garment. Results of this study confirmed that early intervention reduced arm volumes and limited the need for future more aggressive therapies [28].

The concept of early intervention and improved outcomes when patients have low volume disease is consistent with older, retrospective data from Ramos et al. which found that the mean reduction of volumes was 78% for patients with less than 250 cc of initial edema compared with only 56% for patients presenting with 250-500 cc of edema and 38% for patients with greater than 500 cc of edema [64]. Similarly, a retrospective series of 1,713 patients found improved rates of freedom from progression for those patients presenting with mild lymphedema (0.5-2.0 cm circumference increase) compared with those presenting with larger pre-treatment increases in volumes [65]. At this time, several studies are underway to further define the role of early intervention in BCRL with results to be published in the next few years [66-68].

Conclusion

Breast cancer related lymphedema (BCRL) is increasingly being recognized as a major, quality of life impacting sequelae of breast cancer treatment. Due to improvements in breast cancer outcomes, increasing numbers of long-term survivors are developing BCRL. However, the overall incidence rate appears to be decreasing due to the incorporation of sentinel lymph node biopsy as the standard axillary assessment tool. Future directions that may further reduce incidence rates include the omission of completion axillary lymph node dissection in those patients with positive sentinel lymph nodes and limiting the use of regional irradiation. Diagnosing BCRL remains a challenge as traditional modalities lack the sensitivity for sub-clinical diagnosis; however, recent publications have suggested that new diagnostic modalities offer the potential for sub-clinical diagnosis and early intervention. With regards to treatment of BCRL, complex decongestive physiotherapy remains the standard for the acute phase of BCRL. However, an important development in the treatment of BCRL is the increasing evidence that suggests that early treatment may prevent progression to chronic BCRL. Future studies are required to further elucidate the optimal diagnostic algorithm and time point for intervention that reduces BCRL without over utilizing resources; further, future studies need to move beyond just assessing arm volume and focus on quality of life outcomes using validated instruments such as the EORTC or Nottingham scales [69-71].

References

1. Jemal A, Siegel R, Ward E (2007) Cancer Statistics, 2007. CA Cancer J Clin 2007 57: 43-66.
2. Ho A, Morrow M (2011) The evolution of the locoregional therapy of breast cancer. Oncologist 16: 1367-1379.
3. Mazeron JJ, Otmezguine Y, Huart J, Pierquin B (1985) Conservative treatment of breast cancer: results of management of axillary lymph node area in 3353 patients. Lancet 1: 1387.
4. Gartner R, Jensen MB, Kronborg L, Ewertz M, Kehlet H, et al. (2010) Self-reported arm-lymphedema and functional impairment after breast cancer treatment- A nationwide study of prevalence and associated factors. The Breast 19: 506-515.
5. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, et al. (2010) Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol 102: 111-118.
6. McLaughlin SA, Cohen S, Van Zee KJ (2010) Chapter 45: Lymphedema. In: Harris JR, Lippman ME, Morrow M, Osborne CK (Eds.), Diseases of the Breast (4thedn), Lippincott Williams and Wilkins, Philadelphia, USA.
7. Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, et al. (1995) EORTC Late Effects Working Group. Late effects toxicity scoring: The SOMA scale. Radiother Oncol 31: 1043-1047.
8. National Institutes of Health (2010) Common Terminology Criteria for Adverse Events.
9. Deutsch M, Land S, Begovic M, Sharif S (2008) The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project Study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. Int J Radiat Oncol Biol Phys 79: 1020-1024.
10. Zavagno G, De Salvo GL, Scalco G, Bozza F, Barutta L, et al. (2008) A randomized clinical trial of sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. Ann Surg 247: 207-213.
11. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, et al. (2006) Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst 98: 599-609.
12. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, et al. (2006) Sentinel-lymph node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Lancet Oncol 7: 983-990.
13. Wernicke AG, Goodman RL, Turner BC, Komarnicky LT, Curran WJ, et al. (2011) A 10-year follow-up of treatment outcomes in patients with early stage breast cancer and clinically negative axillary nodes treated with tangential breast irradiation following sentinel lymph node dissection or axillary clearance. Breast Cancer Res Treat 125: 893-902.
14. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, et al. (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305: 569-575.
15. Coen JJ, Taghian AG, Kachnic LA, Assaad SI, Powell SN (2003) Risk of lymphedema after regional nodal irradiation with breast conservation therapy. Int J Radiat Oncol Biol Phys 55: 1209–1215.
16. Hayes SB, Freedman GM, Li T, Anderson PR, Ross E (2008) Does axillary boost increase lymphedema compared with supraclavicular alone after breast conservation? Int J Radiat Oncol Biol Phys 72: 1449-1455.
17. Whelan TJ, Olivotto I, Ackerman I, Chapman JW, Chua B, et al. (2011) NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol 29: LBA1003.
18. Wallace M, Martinez A, Mitchell C, Chen PY, Ghilezan M, et al. (2010) Phase I/II study evaluating early tolerance in breast cancer patients undergoing accelerated partial breast irradiation treated with the MammoSite balloon breast brachytherapy catheter using a 2-Day dose schedule. Int J Radiat Oncol Biol Phys 77: 531-536.
19. Reznik J, Cicchetti MG, Degaspe B, Fitzgerald TJ (2005) Analysis of axillary coverage during tangential radiation therapy to the breast. Int J Radiat Oncol Biol Phys 61: 163-168.
20. Adriaenssens N, Belsack D, Buyl R, Ruggiero L, Breucq C, et al. (2012) Ultrasound elastography as an objective diagnostic measurement tool for lymphedema of the treated breast in breast cancer patients following breast conserving surgery and radiotherapy. Radiol Oncol 46: 284-295.
21. Goffman TE, Laronga C, Wilson L, Elkins D (2004) Lymphoedema of the arm

and breast in irradiated breast cancer patients: risks in an era of dramatically changing axillary surgery. Breast J 10: 405–411.

22. Meek AG (1998) Breast radiotherapy and lymphoedema. Cancer 83: 2788–2797.
23. Wratten C, Kilmurray J, Wright S, O'Brien PC, Back M, et al. (2000) Pilot study of High-Frequency Ultrasound to assess cutaneous oedema in the conservatively managed breast. Int J Cancer 90: 295–301.
24. Rönkä RH, Pamilo MS, von Smitten KAJ, Leidenius MHK (2004) Breast lymphoedema after breast conserving treatment. Acta Oncol 43: 551–557.
25. Padhani AR, Yarnold J, Regan J, Husband JE (2003) Dynamic MRI of breast hardness following radiation treatment. J Magn Reson Im 17: 427–434.
26. Torres LM, Yuste Sanchez MJ, Zapico GA, Merino DP, Del Moral OM, et al. (2010) Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. BMJ 340: b5396.
27. Box RC, Reul-Hirche HM, Bullock-Saxton JE (2002) Physiotherapy after breast cancer surgery: results of a randomized controlled study to minimise lymphedema. Breast Cancer Res Treat 75: 51-64.
28. Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH, et al. (2008) Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer 112: 2809-2819.
29. Chen YW, Tsai HJ, Hung HC, Tsauo JY (2008) Reliability study of measurements for lymphedema in breast cancer patients. Am J Phys Med Rehabil 87: 33-38.
30. Hutson P (2003) Assessing changes in arm lymphedema. Bioelectrical impedance vs. standard methods: Delivering the promise. Susan G. Komen Breast Cancer Foundation Conference.
31. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, et al. (2008) Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 26: 5213-5219.
32. Sagen A, Kåresen R, Skaane P, Risberg MA (2009) Validity for the simplified water displacement instrument to measure arm lymphedema as a result of breast cancer surgery. Arch Phys Med Rehabil 90: 803-809.
33. Czerniec SA, Ward LC, Refshauge KM, Beith J, Lee MJ, et al. (2010) Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. Cancer Invest 28: 54-62.
34. Armer JM, Stewart BR (2005) A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat Res Biol 3: 208-217.
35. Cornish BH, Bunce IH, Ward LC, Jones LC, Thomas BJ (1996) Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. Breast Cancer Res Treat 38: 169-176.
36. Cornish BH, Chapman M, Hirst C, Mirolo B, Bunce IH, et al. (2001) Early diagnosis of lymphedema using multiple frequence bioimpedance. Lymphology 34: 2-11.
37. Hayes S, Cornish B, Newman B (2005) Comparison of methods to diagnose lymphedema among breast cancer survivors: 6-month follow-up. Breast Cancer Res Treat 89: 221-226.
38. Ward LC, Dylke E, Czerniec S, Isenring E, Kilbreath SL (2011) Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy. Lymphat Res Biol 9: 47-51.
39. Ward LC, Dylke E, Czerniec S, Isenring E, Kilbreath SL (2011) Reference ranges for assessment of unilateral lymphedema in legs by bioelectrical impedance spectroscopy. Lymphat Res Biol 9: 43-46.
40. Vicini F, Shah C, Lyden M, Whitworth P (2012) Bioelectrical Impedance for Detecting and Monitoring Patients for the Development of Upper Limb Lymphedema in the Clinic. Clin Breast Cancer 12: 133-137.
41. Vicini F, Arthur DW, Lyden M, Shah C. The use of bioelectrical impedance spectroscopy (BIS) to detect subclinical changes potentially associated with the development of breast cancer-related lymphedema. J Clin Oncol 30: s89.
42. Gjorup C, Zerahn B, Hendel HW (2010) Assessment of volume measurement of breast cancer-related lymphedema by three methods: circumference measurement, water displacement, and dual energy x-ray absorptiometry. Lymphat Res Biol 8: 111-119.
43. Stanton AW, Northfield JW, Holroyd B, Mortimer PS, Levick JR, et al. (1997) Validation of an optoelectronic limb volumeter (Perometer). Lymphology 30: 77-97.
44. Jain MS, Danoff JV, Paul SM (2010) Correlation between bioelectrical spectroscopy and perometry in assessment of upper extremity swelling. Lymphology 42: 85-94.
45. Casley-Smith JR, Morgan RG, Piller NB (1993) Treatment of lymphedema of the arms and legs with 5,6-Benzo-a-pyrone. New Eng J Med 329: 1158-1163.
46. Loprinzi CL, Kugler JW, Sloan JA, Rooke TW, Quella SK, et al. (1999) Lack of effect of Coumarin in women with lymphedema after treatment of breast cancer. New Eng J Med 340: 346-350.
47. Micke O, Bruns F, Mücke R, Schäfer U, Glatzel M, et al. (2003) Selenium in the treatment of radiation-associated secondary lymphedema. Int J Radiat Oncol Biol Phys 56: 40-49.
48. Franks PJ, Moffatt CJ, Murray S, Reddick M, Tilley A, et al. (2013) Evaluation of the performance of a new compression system in patients with lymphoedema. Int Wound J 10: 203-209.
49. Fife CE, Davey S, Maus EA, Guilliod R, Mayrovitz HN (2012) A randomized controlled trial comparing two types of pneumatic compression for breast cancer-related lymphedema treatment in the home. Support Care Cancer 20: 3279-3286.
50. King M, Deveaux A, White H, Rayson D (2012) Compression garments versus compression bandaging in decongestive lymphatic therapy for breast cancer related lymphedema: a randomized controlled trial. Support Care Caner 20: 1031-1036.
51. de Godoy JM, Godoy Mde F (2013) Evaluation of a new approach to the treatment of lymphedema resulting from breast cancer therapy. Eur J Intern Med 24: 59-62.
52. Vignes S, Porcher R, Arrault M, Dupuy A (2012) The effect of combined decongestive therapy and pneumatic compression pump on lymphedema indicators in patients with breast cancer related lymphedema. Iran Red Crescent Med J 14: 210-217.
53. Vignes S, Porcher R, Arrault M, Dupuy A (2007) Long-term management of breast cancer-related lymphedema after intensive decongestive physiotherapy. Breast Cancer Res Treat 101: 285-290.
54. Liao SF, Huang MS, Li SH, Chen IR, Wei TS, et al. (2004) Complex decongestive physiotherapy for patients with chronic cancer-associated lymphedema. J Formos Med Assoc 103: 344-348.
55. Kim SJ, Yi CH, Kwon OY (2007) Effect of complex decongestive therapy on edema and the quality of life in breast cancer patients with unilateral lymphedema. Lymphology 40: 143-151.
56. Karadibak D, Yavuzsen T, Saydam S (2008) Prospective trial of intensive decongestive physiotherapy for upper extremity lymphedema. J Surg Oncol 97: 572-577.
57. Didem K, Ufuk YS, Serdar S, Zümre A (2005) The comparison of two different physiotherapy methods in treatment of lymphedema after breast surgery. Breast Cancer Res Treat 93: 49-54.
58. Piller NB, Swedborg I, Wilking N, Jensen G (1994) Short-term manual lymph drainage treatment and maintenance therapy for post-mastectomy lymphoedema. Lymphology 27: 589-592.
59. Andersen L, Højris I, Erlandsen M, Andersen J (2000) Treatment of breast-cancer related lymphedema with or without manual lymphatic drainage- a randomized study. Acta Oncol 39: 399-405.
60. McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, et al. (2004) The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized control trial. Breast Cancer Res Treat 86: 95-106.
61. Moseley AL, Piller NB, Carati CJ (2005) The effect of gentle arm exercise and deep breathing on secondary arm lymphedema. Lymphology 38: 136-145.
62. Jeffs E, Wiseman T (2013) Randomised controlled trial to determine the benefit

of daily home-based exercise in addition to self-care in the management of breast cancer-related lymphedema: a feasibility study. Support Care Cancer 21: 1013-1023.

63. Anderson RT, Kimmick GG, McCoy TP, Hopkins J, Levine E, et al. (2012) A randomized trial of exercise on well-being and function following breast cancer surgery: the RESTORE trial. J Cancer Surviv 6: 172-81.

64. Ramos SM, O'Donnell LS, Knight G (1999) Edema volume, not time, is the key to success in lymphedema treatment. Am J Surg 178: 311-315.

65. Bar Ad V, Cheville A, Solin LJ, Dutta P, Both S, et al. (2010) Time course of mild arm lymphedema after breast conservation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys 76: 85-90.

66. National Institutes of Health: Clinical Trials (2009) Early detection and intervention for mild to moderate lymphedema in patients treated with breast cancer.

67. National Institutes of Health: Clinical Trials (2012) The use of bioimpedance to determine pre-clinical lymphedema in the post-operative breast cancer patient (L-Dex).

68. Kilbreath SL, Refshauge KM, Beith JM, Ward LC, Simpson JM, et al. (2006) Progressive resistance training and stretching following surgery for breast cancer: study protocol for a randomised controlled trial. BMC Cancer 6: 273.

69. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, et al. (1996) The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country study. J Clin Oncol 14: 2756-2768.

70. Sitzia J, Sobrido L (1997) Measurement of health-related quality of life of patients receiving conservative treatment for limb lymphedema using the Nottingham Health Profile. Qual Life Res 6: 373-84.

71. Keeley V, Crooks S, Locke J, Veigas D, Riches K, et al. (2010) A quality of life measure for limb lymphedema (LYMQOL). J Lymphoedema 5: 26-37.

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