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 survivability, 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 Bowl 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].
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 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

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Breast cancer related lymphedema (BCRL) is increasingly being recognized as a major, quality of life impacting sequela 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 [64]. Similarly, a prospective 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 sequela 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


