Review Article | Symptom Management in Palliative Medicine and Palliative Care

Prospective surveillance and early intervention to prevent chronic breast cancer-related arm lymphedema—what are the barriers?

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Abstract: Up to one in five early breast cancer patients develop chronic upper limb lymphedema after breast cancer treatments. This treatment complication is irreversible and can significantly impact the quality of life of breast cancer survivors. The model of prospective surveillance and early intervention has emerged as a potential strategy to prevent the development of this debilitating treatment-related complication. However, the widespread implementation of such programs worldwide is challenging. The aim of this review is to identify barriers of implementation, including selecting suitable patients to be enrolled, determining the optimal method for lymphedema screening, and choosing the most effective treatment to prevent progression when early or subclinical breast cancer-related arm lymphedema (BCRAL) is detected. Future research should develop accurate predictive models for the development of upper limb lymphedema using population based datasets with artificial intelligence and investigate the comparative efficacy of different screening methods and treatment options for early intervention for BCRAL. The medical community should also regularly review whether new treatments such as immunotherapy, targeted therapies and new surgical or radiation techniques could contribute to the development of arm lymphedema. By overcoming these barriers, we can improve the feasibility of implementing early prospective surveillance programs in clinical practice, ultimately improving the care and outcomes for breast cancer survivors at risk of treatment-related upper limb lymphedema.

Keywords: Breast cancer; arm lymphedema; prospective surveillance program

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Introduction

Lymphedema is characterised by progressive edema of a body site due to lymphatic fluid retention and the persistent deposition of fibroadipose tissue (1). In the context of breast cancer, upper limb lymphedema occurs as a consequence of damage to the lymphatic system following axillary interventions such as axillary lymph node dissection (ALND), sentinel lymph node (SLN) biopsy, postoperative axillary radiation therapy and chemotherapy (2-4). Chronic breast cancer-related arm lymphedema (BCRAL) is characterised by persistent symptoms despite initial treatments and can significantly impact the quality of life of breast cancer survivors (5-8). The incidence of lymphedema in breast cancer patients after anticancer treatments is estimated to be as high as one in five individuals (9). The prevalence of BCRAL could vary significantly across different countries. In a systematic review by Torgbenu *et al.*, the prevalence of BCRAL was reported to be 5.9% in Romania versus 56.7% in India (10). While the onset of lymphedema peaks at 12 to 30 months after surgery, it can also manifest up to 20 years after surgery (11). The traditional model of BCRAL care focuses on referring patients to lymphedema therapists only after they become symptomatic, often missing the opportunity for early intervention that could potentially reverse the disease trajectory.

Emerging high-level evidence highlights the potential benefits of prospective surveillance and early intervention in preventing chronic BCRAL (12,13). While effective, such programs could be labour- and resource-intensive. The aim of this review is to discuss the barriers to implementing prospective surveillance programs in survivorship clinics, recognizing the importance of addressing these challenges to enhance the care and outcomes for breast cancer survivors.

Selecting the right patient

The reported incidence of BCRAL in the literature exhibits significant variation depending on patients' individual risk of BCRAL (2,14). Implementing surveillance programs for all patients is not feasible due to the potential physical, psychological, financial and time burden it would impose, particularly in individuals with a low risk of developing BCRAL. Therefore, it is crucial to correctly recruit patients with a high risk of developing BCRAL into early surveillance programs.

The development of BCRAL is influenced by multiple factors, as reported in numerous systematic reviews and meta-analyses (15,16). These risk factors could be broadly classified into patient, tumour and treatment related factors. Important patient related factors are body mass index (BMI) and ethnicity (17-21). Treatment related risk factors, such as taxane-based chemotherapy regimens (22) and extent of axillary surgery (17,19-21) can also predispose patients to BCRAL. Tumour related factors, including tumour size and number of involved axillary lymph nodes (23,24), further contribute to the complex risk profile.

Although we understand which factors can increase the risk of BCRAL, we are uncertain about the precise contribution of each risk factor in the development of BCRAL. This poses challenges when determining which patients are most suitable to be recruited in prospective surveillance programs. There are ongoing efforts for the development of risk stratification scores to predict the risk of BCRAL in individual patients. In a study led by Kwan *et al.*, different patient, disease and treatment factors were identified as independent prognostic variables affecting the development of BCRAL, namely age, BMI, mammographic breast density, number of pathologically involved lymph nodes, and whether there was ALND (25). Based on the risk factors identified, the authors developed an equation that predicted the lymphedema volume in breast cancer patients after surgery. When the predicted volumes were compared with the measured volumes, a statistically significant moderate correlation was demonstrated. A higher predicted volume translates to a greater risk of severe BCRAL, whereas a negative value means that the patient has a low likelihood of developing any BCRAL. Recently, a group from Korea also developed a BCRAL risk prediction nomogram based on more than 8,000 breast cancer patients treated from 2007 to 2017 (26). While these tools are easy to use, these studies may require updates as more advanced treatments for breast cancer are introduced. Systemic therapies like immunotherapy, antibody drug conjugates and targeted therapies, as well as advances in radiation therapy and surgical techniques are increasingly incorporated in the treatment algorithm of early breast cancer. It is crucial to continually evaluate their impact on the development of BCRAL.

Artificial intelligence and machine learning are increasingly implemented in the field of oncology. It has the power to analyse large datasets to generate a prediction model for treatment outcomes (27,28). The PRE-ACT study successfully used data from three prospective clinical trials of more than 6,000 breast cancer patients to generate

a model for the prediction of BCRAL up to three years after the start of radiation therapy (29). In the next phase, the study team will be adding genomic and radiomic factors on top of the 32 treatment and disease related factors to enhance the accuracy of the model and test it in prospective clinical trials. The results of these follow-up studies of the PRE-ACT project are eagerly awaited. This robust model will enhance risk stratification and provide valuable guidance for the implementation of prospective surveillance programs (30).

While the complex interplay of different risk factors remains to be resolved, there is a growing body of evidence that ALND is the main risk driver of BCRAL development (16,31,32). In a systematic review and network meta-analysis by Shaitelman *et al.*, the increased risk of BCRAL after adjuvant radiation therapy is mainly observed in patients who underwent ALND, while not significant for those who underwent SLN biopsy or axillary lymph node sampling (31). Similarly, in a prospective screening trial of more than 1,800 patients by Naoum *et al.*, patients with ALND, in comparison to SLN biopsy had a higher chance of BCRAL regardless of adjuvant radiation therapy (32). Before more robust prediction models are available, patients with ALND should be prioritised to be recruited in prospective surveillance programs.

Selecting the appropriate method of measurement

Clinical BCRAL is conventionally defined as a 2-cm or greater difference in arm circumference at a specific anatomical point, or a discrepancy of 200 mL in limb volume between the affected and unaffected limbs (33-35). The main objective of early detection is to identify patients with subclinical BCRAL so early interventions can follow to prevent progression into irreversible BCRAL. However, the definition of subclinical BCRAL to trigger treatment is defined differently in the literature (12). Apart from inter-arm difference, intra-arm difference based on changes from pre-surgery is of paramount importance when defining BCRAL (36,37). Conventionally, all randomised controlled trials (RCTs) used inter-arm difference to define BCRAL (36). However, there are concerns for misclassification due to arm asymmetry (37). Using intra-arm differences compared with presurgical values is the most ideal and can empower patients to measure themselves at home, but pre-surgical values are not always available (36). There are also various techniques available for measuring early BCRAL in surveillance programs, such as bioimpedance spectroscopy (BIS), tape measurement (TM) of arm circumference, perometry, lymphangiography and lymphoscintigraphy (38). Choosing the right measurement method poses a challenge when it comes to establishing prospective surveillance programs for preventing BCRAL.

TM involves using a tape to assess the arm circumference, specifically 10 cm below and 10 cm above either the olecranon or the lateral epicondyle (39). This method is convenient to implement and widely available. While TM may seem straightforward, maintaining inter-rater and intra-rater consistency poses a challenge (40). BIS emerged as a promising new tool for early detection of subclinical BCRAL. BIS objectively assesses the difference in extracellular fluid levels between a limb at risk and a healthy limb using a weak electrical current (41).

The PREVENT trial is a multi-institutional RCT that evaluated the role of BIS in a prospective surveillance program (42). More than 800 patients were actively screened with BIS or TM for 3 years. Compression sleeves were used when there was an L-Dex increase of 6.5 by BIS or an increase in volume of 5% to 10% by TM from pre-surgery. Fewer participants in the BIS group received compression intervention compared to the TM group (20.1% versus 27.5%, P=0.001) after a median follow up of 2.7 years. Patients in the TM group had a higher rate of chronic BCRAL (10% arm volume change from baseline after intervention for subclinical lymphedema) compared to the BIS group overall. Hence, the authors concluded that BIS is superior to TM in identifying patients who benefit from early intervention. However, the compliance of compression intervention in each group is not mentioned, which might be a confounding factor for development of chronic BCRAL.

There are also concerns from researchers regarding whether BIS can be recommended as a gold standard for early detection in surveillance programs. Several studies have identified that BIS tends to overestimate the incidence of subclinical BCRAL (43,44). For example, in a study by Barrio *et al.*, only 4 out of 25 patients with BIS abnormalities developed clinical BCRAL (44). Similarly, in a study by Bundred *et al.* involving over 600 patients, the sensitivity of BIS was only 73% (43). There are also some methodological flaws in trials favouring BIS. For instance, in the PREVENT trial, there was no random assignment without any intervention to a control group despite being a RCT (45). Future randomised studies should screen patients with both methods with proper risk factor stratification

and randomization. Early interventions should be triggered according to different assessment methods in each arm. This approach will reflect which assessment modality can better identify patients to receive early intervention to prevent progression into chronic BCRAL.

BIS is also relatively more costly and requires training of personnel to perform the test and interpret the results as compared to TM (46,47). Formal cost-effectiveness analyses are needed to compare different measurement methods in order to identify alternatives for underserved populations and low and middle income countries. Furthermore, since the majority of these studies have been carried out in North America, it is crucial to validate their findings in patients of more diverse racial backgrounds.

Real world studies should be performed to validate and evaluate the outcomes of various measurement techniques to enable early identification of BCRAL, ideally aligning with routine breast cancer follow-up schedules. These efforts would enhance the practicality and accessibility of prospective surveillance programs for breast cancer survivors.

Selecting the appropriate treatment

The selection of a suitable treatment after early BCRAL detection poses another obstacle in the establishment of prospective surveillance programs. A majority of clinical trials have used compression sleeves as the treatment option of choice after early BCRAL is detected (12). However, no systematic review or meta-analysis has been published to date that confirms its superiority to other interventions (36). Compression sleeves vary in type, coverage and pressure, and the duration in which the sleeves are applied after early BCRAL detection is heterogeneous in the literature (12). In the PREVENT trial, more than one fourth of patients who received ALND still developed chronic BCRAL despite early intervention with compression sleeves (42). Further research is required to understand whether prophylactic compression sleeves or prospective surveillance with early intervention after detection of subclinical BCRAL is better, how to enhance the long term effectiveness of compression sleeves, such as incorporation of weight reduction programs, massage therapy and exercise interventions.

Furthermore, treatment of early BCRAL may have significant implications on patients' quality of life. Patients have reported their treatment for BCRAL could disrupt their social, emotional, and occupational aspects, even more than the disease itself sometimes (48). When early BCRAL is detected through prospective surveillance programs, it is paramount to select an intervention that is not only effective but at the same time has minimal impact on patients' quality of life.

Apart from prospective surveillance programs, there are also other emerging interventions that have been shown to be effective in preventing BCRAL. The comparative efficacy and the impact on patients' quality of life of these approaches remain to be further understood. In the study conducted by Paramanandam *et al.*, over 300 women with ALND were randomised to prophylactic compression sleeves from operation until three months after completion of adjuvant treatment or usual care (49). The incidence of BCRAL was lower in the prophylactic compression group compared to the control group (49). However, the study only had a follow up of around one year, there have been concerns regarding the long term efficacy of the prophylactic sleeves. There are currently two ongoing RCTs, one in China (NCT06095323) and one in Korea (NCT04787029), which further investigate the role of prophylactic compression sleeves. The Chinese study led by Liu *et al.* tests a compression sleeve that has a lower pressure of 15 to 20 mmHg (50). With the primary endpoint of incidence of BCRAL at 2 years, the study can test whether sleeves are efficacious in BCRAL risk reduction in the long run.

In addition, there is another ongoing prospective trial (NCT06144164) led by the Memorial Sloan Kettering Cancer Center that evaluates the efficacy of a comprehensive prevention program, which involves immediate lymphatic reconstruction, post-operative lymphatic massage, motion exercises, and compression garments. The results of this study may shed light on whether combination treatments can enhance the efficacy of compression garments alone in preventing progression of early BCRAL.

Apart from prospective surveillance programs, there are also other emerging interventions that have been shown to be effective in preventing BCRAL. The comparative efficacy and the impact on patients' quality of life of these approaches remain to be further understood.

Advanced surgical techniques such as prophylactic lymphatic reconstruction and axillary reverse mapping have shown promise in reducing the incidence of BCRAL. Cook *et al.* analysed five related studies and showed that immediate lymphatic reconstruction reduced risk of BCRAL from 30% to 6% (51). Co *et al.* reviewed five RCTs involving over 1,600 patients and found that axillary reverse mapping reduced the incidence of BCRL from 18% to 4% without increasing the axillary recurrence rate (52).

Table 1 Summary of measures to prevent BCRAL

	Prospective surveillance programs	Prophylactic compression sleeves	Prophylactic lymphatic reconstruction	Axillary reverse mapping
Pros	Early detection and intervention of BCRAL	Cheap Readily available	To restore regional lymphatics after ALND	Preserve regional lymph nodes without need for reconstruction
Cons	Regarding use of BIS Costly Trained personnel to document and interpret results according to L-Dex score Overestimation of BCRAL	High degree of compliance required with daily use of at least 8 hours	Requires expertise and resources	Requires expertise and resources Might missed involved lymph nodes during preservation of draining lymph nodes
Questions remained	What is the best method to detect subclinical BCRAL? How often should we monitor for BCRAL?	Which type of compression garment is the best in prevention of BCRAL? What pressure should be used for compression sleeves? How long should compression sleeves be used? Whether prospective surveillance programs with early intervention by compression sleeves are better than prophylactic compression sleeves to all patients?	How many axillary lymph nodes removed are required to trigger prophylactic lymphatic reconstruction?	How to balance the risk of missed involved lymph nodes versus preservation of draining lymph nodes?

BCRAL, breast cancer related arm lymphedema; BIS, bioimpedance spectroscopy; ALND, axillary lymph node dissection.

Summary of pros and cons of measures to prevent BCRAL is listed in *Table 1*. Future research should prioritise the comparison of prospective surveillance programs with different prophylactic treatment approaches as well as their impact on quality of life. When these interventions are employed, the additional benefit of recruiting these patients into prospective surveillance programs needs to be evaluated. Furthermore, investigating the effectiveness of subsequent interventions for patients who have progression of BCRAL after initial treatments is crucial. By addressing these research areas, we can gain valuable insights into effective treatment strategies and enhance patient outcomes in the prevention of BCRAL.

Conclusions

The model of prospective surveillance combined with early intervention holds great promise in reducing the risk of chronic BCRAL among breast cancer survivors. However, further research is necessary to develop programs that ensure only patients at sufficient risk of BCRAL are enrolled, identify assessment methods that are accurate in detecting subclinical disease and effective interventions to prevent progression while having minimal impact on patients' quality of life. By addressing these challenges, we can develop programs that are effective, while low risk patients do not have to suffer from unnecessary physical, psychological and financial burden. In the meanwhile before these studies are available, prospective surveillance programs should be designed taking into account the expertise and resources of the healthcare team. Interventions for early BCRAL should be tailor-made to patients' preferences and continuously evaluated in local audits to improve treatment outcomes.

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