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ORIGINAL ARTICLE – BREAST ONCOLOGY

Timing of Breast Cancer Related Lymphedema Development Over 3 Years: Observations from a Large, Prospective Randomized Screening Trial Comparing Bioimpedance Spectroscopy (BIS) Versus Tape Measure

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ABSTRACT

Background. The PREVENT randomized control trial monitored progression to chronic breast cancer-related lymphedema (cBCRL) following intervention for subclinical breast cancer-related lymphedema (sBCRL) assessed by bioimpedance spectroscopy (BIS) versus tape-measure (TM). This multi-institutional trial demonstrated a 92% risk reduction of developing cBCRL. This secondary analysis reviews the timing of sBCRL and cBCRL following breast cancer (BC) treatment.

Patients and Methods. Women at risk of cBCRL ($n = 919$) were screened regularly up to 36 months after BC treatment using either BIS or TM. Following diagnosis of sBCRL, patients underwent a 4-week compression sleeve intervention. The time in months from BC treatment to detection was reviewed at 3-month intervals.

Results. In total 209 patients developed sBCRL (BIS: $n = 89$, TM: $n = 120$) and were eligible for intervention. 30 progressed to cBCRL postintervention (BIS: 7, TM: 23). More than half of patients had measurements consistent with sBCRL within 9 months of BC treatment. Patients continued to have initial detections of sBCRL, regardless of screening method, with rates remaining consistent in years two and three ($p > 0.242$) post surgery. Additionally, 39 patients progressed to cBCRL without developing sBCRL or receiving intervention across the 3-year period.

Conclusions. The timing of sBCRL detection demonstrates that patients continue to be at risk years after treatment and may continue to progress to cBCRL years after surgery. Early detection of sBCRL allows for early intervention decreasing the likelihood of progression to cBCRL. Patients should continue to be monitored for a minimum of 3 years following completion of cancer treatment. Specifically, careful targeted monitoring over the initial 9-month period is important.

Keywords Breast cancer · Lymphedema · Bioimpedance spectroscopy (BIS) · Tape measure · Prevent

Chronic breast cancer related lymphedema (cBCRL) continues to be a feared side effect that is understudied.[1] While much progress has been made in reducing the treatment to the axilla including the advent of sentinel node mapping and biopsy, the reduced use of axillary dissection, the omission of surgical axillary staging in selected lower risk patients, and the reduction in the use of axillary radiation, lymphedema continues to occur. While some physicians may not routinely prospectively monitor their patients for arm lymphedema following treatment, research has demonstrated that early detection of presymptomatic lymphedema can be performed reliably and can result in significant reductions in the progression to chronic lymphedema when treated early.[2–4]

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The PREVENT trial was a randomized controlled trial comparing the use of tape measurements (TM) with bioimpedance spectroscopy (BIS) for detecting early breast cancer-related lymphedema (BCRL). The study demonstrated a 21.9% likelihood of identifying a measurement consistent with subclinical breast cancer-related lymphedema (sBCRL), followed by a 4-week treatment with a compression garment when such a trigger was detected, regardless of the method that found the trigger (TM or BIS). This protocol resulted in 92% of patients in the BIS group not progressing to cBCRL, a significant reduction compared with surveillance with TM.

The present study forms part of a supplementary analysis performed on data collected as part of the PREVENT randomized controlled trial. This study specifically examines the time to trigger sBCRL and the time to progression to cBCRL in an effort to provide guidance on the frequency and duration of screening for BCRL.

PATIENTS AND METHODS

PREVENT Study

The PREVENT trial was an international multicenter trial designed to determine if detection of subclinical increases in extracellular fluid of the arm monitored using bioimpedance spectroscopy (BIS) with subsequent early treatment improved rates of cBCRL [using complex decongestive physiotherapy (CDP) as a surrogate] compared with the same treatment triggered from monitoring using volume measurements derived from circumferential tape measures. The trial was registered at clinicaltrials.gov with identifier NCT02167659 and study protocols were approved by all relevant institutional review boards (IRB). The primary outcomes of the PREVENT study previously demonstrated the benefits of prospective surveillance using BIS screening with early intervention treatment for the prevention of progression to clinical lymphedema. Further details and associated consort diagram along with primary and secondary outcome analyses have been published elsewhere,[2,5,6] while a brief summary of the methodology is summarized here.

Newly diagnosed breast cancer patients attending 13 breast clinics across both the US (nine sites) and Australia (four sites) who were at risk of developing cBCRL were recruited to be monitored for subclinical breast cancer related lymphedema (sBCRL) of the arms following informed consent. Inclusion criteria included: females aged 18 years or older with histologically confirmed invasive breast cancer or ductal carcinoma in situ (DCIS) and a planned surgical procedure. Exclusion criteria included: previous history of breast cancer and/or treatment to breast, chest wall or axilla, active implanted medical device, conditions that could cause swelling, pregnancy, previous treatment for lymphedema of the arm, uncontrolled intercurrent illness, psychiatric illness that would limit compliance, known allergy to adhesives or compression garments, bilateral breast cancer, or planned bilateral mastectomy.

Screening was performed by trained research staff at each facility. BIS monitoring was performed using the L-Dex U400 (ImpediMed Limited, Australia) which measures the impedance of both arms and reports an L-Dex score for the assessment of lymphedema, reflective of the difference in extracellular fluid between the arms. Monitoring using volume measurements was performed using a nonflexible Gulick II tape measure and a marked board to measure the circumference of both arms twice at 10 cm intervals from the wrist up to 50 cm along the arm. The average of the two volumes calculated using the truncated cone formula was used to monitor relative volume changes.

Initial baseline measures were recorded for each participant using both screening methods prior to breast cancer treatment, after which the participant was randomized to be monitored by either BIS or volumetric tape measurement screening and followed at regular intervals for up to 3 years. Scheduled visits were required at 3, 6, 12, 18, 24, 30, and 36 months post surgery with optional visits at 15 and 18 months post surgery.

If participants were identified as having sBCRL at any visit, early intervention treatment was initiated. sBCRL was defined in the study as an increase in L-Dex score ≥ 6.5 units from baseline for the participants monitored by BIS or a relative increase in volume difference from baseline $\geq 5\%$ and $< 10\%$ for the tape measure group. Participants undergoing early intervention treatment wore a 22–32 mmHg compression sleeve and gauntlet for 12 h per day for 4 weeks. At the end of the intervention period, participants were measured again using both screening tools to determine outcome of treatment. In addition, when a participant triggered subclinical lymphedema in either group, the other screening tool was also used to assess lymphedema. A relative volume change $\geq 10\%$ from baseline at any visit during the study, or post intervention, was considered progression to cBCRL regardless of monitoring group and the participant was referred directly to therapy. In some cases, participants were referred without undergoing any preventative intervention treatment.

In this secondary analysis, all participants who had follow up measurements after baseline were included. Each participant was categorized into one of three outcome groups on the basis of their BCRL status at the end of the study. The first group triggered for sBCRL and did not progress to cBCRL after intervention. The second group triggered for sBCRL and progressed to cBCRL after intervention. The third group progressed straight to cBCRL without triggering for sBCRL or receiving intervention treatment. The time in months from breast cancer treatment to subclinical lymphedema detection and/or progression to clinical

lymphedema was calculated and reviewed at 3-month intervals to examine the timing of lymphedema over 3 years. The time in months between the trigger visit and the previously attended visit was also calculated. The timing was compared across monitoring group and outcome group. The L-Dex score, relative volume change, and change from baseline were determined and compared across monitoring and outcome groups. Comparisons were performed using Mann–Whitney, Independent *t*-tests, Chi-squared, and analysis of variance (ANVOA) tests.

RESULTS

Over the duration of the study, 918 participants were randomized into the two groups (BIS, $n = 461$ and TM, $n = 457$) and had follow up measurements after the baseline visit. The median follow-up time was 35.6 months for all participants (IQR: 27.2–36.9). A summary of patient demographics and treatment characteristics for the outcome groups is shown in Table 1. As previously reported, risk factors for BCRL include BMI, stage of cancer, axillary surgery, and radiation therapy.[5–7,8] In particular, Pearson's chi-squared tests show significant differences between patients who triggered for sBCRL and did or did not progress to cBCRL for stage of cancer ($p < 0.001$), axillary surgery ($p = 0.003$), and chemotherapy treatment ($p = 0.015$).

In total, 209 (22.8%) patients developed sBCRL and were eligible for the 4-week compression sleeve intervention. Monitoring with BIS detected 89 patients (19.3%), and 120 patients were detected by TM monitoring (26.3%). Of those triggered for sBCRL, 30 patients progressed to cBCRL postintervention. Of these, 7 patients (7.9%) were in the BIS cohort and 23 patients were in the TM cohort (19.2%). In addition, 39 patients progressed to cBCRL without previously being identified with sBCRL between visits or prior to receiving intervention and were subsequently referred directly to CDP. Of these, 19 patients (4.1% of 461) were in the BIS cohort and 20 patients (4.4% of 457) were in the TM cohort ($p = 0.848$).

The number of sBCRL triggers in each 3-month interval over the 3-year monitoring period is shown in Fig. 1a for the 209 patients who triggered across the two monitoring cohorts. While patients continued to trigger across the entire 3-year follow-up period, there is a higher proportion that triggered earlier in the monitoring period. More than half of patients triggered (110 of 209; 52.6%) within 9 months of completing breast cancer treatment. Patients also continued to have sBCRL triggers regardless of screening method used for detection out to 3 years post-surgery. The rate of triggers remains consistent in year two and three ($p > 0.242$) and did not decrease over time. Figure 1b demonstrates the distribution of sBCRL triggers over the 3-year period stratified by screening method. In the first 9 months following BC treatment, the TM group has a higher trigger rate than the BIS group (TM: 16.7% vs. BIS: 7.2%, $p < 0.0001$), while during the remaining monitoring period, the trigger rate remains similar for both groups (TM: 9.3% vs. BIS:12.3%, $p = 0.1744$).

The timing of triggers for sBCRL for only those patients who progressed to cBCRL despite receiving interventional treatment is summarized in Fig. 2 for both screening methods ($n = 30$). The number of patients who progressed in each 3-month interval is shown. As with all sBCRL triggers, the number of patients who triggered and progress to cBCRL is higher in the first 9 months after BC treatment. For the TM cohort, the rate of progression after intervention in the first 9 months is higher than that for the BIS group in the same time period (TM: 19/77 triggers, 24.7% vs. BIS: 2/33 triggers, 6.1%; $p = 0.0446$).

Figure 3a shows the distribution of the timing of progression to cBCRL for patients who received 4 weeks of compression garment treatment but continued to progress. Despite the early intervention, these patients progressed over the entire duration of the study, with a median time to progression of 18.8 months (IQR 10.9–26.5 months). Patients who progressed to cBCRL between visits and prior to receiving intervention also did so across the entire 3-year monitoring period as shown in Fig. 3b, with a median time to progression of 10.2 months (IQR 3.9–28.3 months).

The median time to trigger, median time to progression and the median time between the trigger visit and the previous screening visit are shown in Table 2 for each outcome group. Patients who triggered and progressed after intervention had a lower median time to trigger than those who triggered and did not progress after intervention for the entire duration of the study (trigger, progression: 5.8 months, IQR 3.2–10.8 months vs. trigger, no progression: 8.9 months, IQR 4.5–19.2 months, $p = 0.007$). There was no significant difference between the triggered outcome groups for the time between the previous visit and the trigger visit (trigger, progression: 4.2 months, IQR 3.0–5.6 months vs. trigger, no progression: 3.8 months, IQR 3.0–5.7 months, $p = 0.4599$), suggesting that monitoring more frequently than every 3–4 months, may not improve outcomes.

When comparing time to progression in all patients who progressed to cBCRL, those who triggered for sBCRL and received early intervention have been shown to have a delayed time to progression than those who did not receive early intervention in the first 2 years of monitoring (year 1: trigger, progression, 8.0 ± 2.5 months vs. progress, no intervention, 4.9 ± 2.4 months, $p = 0.0039$, year 2: trigger, progression, 18.9 ± 3.1 months vs. progress, no intervention, 15.9 ± 2.9 months $p = 0.0428$).

For patients who did not receive any early intervention prior to progressing to cBCRL, the median time between the progression visit and the previous screening visit was

TABLE 1 Patient demographics and treatment characteristics

	No sBCRL triggers	sBCRL trigger, no progression	sBCRL trigger, progression	Progression, no intervention	*p* value
No of participants	670	179	30	39	
Age at baseline (years)	58 (50–66)	59 (51–66)	60.5 (50–69.5)	56 (47–67)	0.715
BMI at baseline	27.7 (24.6–31.9)	28.2 (25.0–34.3)	29.6 (26.0–34.5)	30.4 (26.8–39.7)	**< 0.001**
Race					0.605
Asian	61 (9.1%)	15 (8.5%)	0	2 (5.1%)	
Black or African American	51 (7.6%)	11 (6.2%)	5 (16.7%)	4 (10.3%)	
White	515 (77.0%)	139 (78.5%)	25 (83.3%)	31 (79.5%)	
Multiracial or other	34 (5.1%)	12 (6.7%)	0	2 (5.1%)	
Ethnicity					0.552
Non-hispanic or latina	613 (91.6%)	165 (92.2%)	27 (90.0%)	36 (92.3%)	
Hispanic or latina	26 (3.9%)	4 (2.2%)	0	2 (5.1%)	
Missing	31 (4.6%)	10 (5.6%)	3 (10.0%)	1 (2.6%)	
Stage of cancer					**< 0 .001**
0 (DCIS)	50 (7.5%)	5 (2.8%)	1 (3.3%)	0	
I	380 (57.0%)	98 (54.7%)	10 (33.3%)	13 (33.3%)	
II	208 (31.2%)	58 (32.4%)	7 (23.3%)	18 (45.2%)	
III	28 (4.2%)	18 (10.1%)	12 (40.0%)	8 (20.5%)	
IV	1 (0.1%)	0	0	0	
Type of breast surgery					0.051
Conservative surgery only	534 (79.7%)	130 (72.6%)	19 (63.3%)	30 (76.9%)	
Mastectomy and conservative surgery	136 (20.3%)	49 (27.4%)	11 (36.7%)	9 (23.1%)	
Axillary surgery					**< 0.001**
ALND	89 (13.3%)	43 (24.0%)	17 (56.7%)	23 (59.0%)	
SNB only	552 (82.4%)	128 (71.5%)	13 (43.3%)	16 (41.0%)	
Other	8 (1.2%)	5 (2.8%)	0	0	
No node surgery	21 (3.1%)	3 (1.7%)	0	0	
Chemotherapy					**< 0.001**
No chemo	408 (61.0%)	98 (54.7%)	8 (26.7%)	14 (35.9%)	
Chemo, no taxane	36 (5.4%)	6 (3.4%)	1 (3.3%)	2 (5.1%)	
Taxane	225 (33.6%)	75 (41.9%)	21 (70.0%)	23 (59.0%)	
Radiation therapy					
None	110 (16.4%)	27 (15.1%)	7 (23.2%)	13 (33.3%)	
Breast/chest wall	553 (82.5%)	150 (83.3%)	22 (73.3%)	25 (64.1%)	
Supraclavicular fossa	69 (10.3%)	35 (19.6%)	11 (36.7%)	9 (23.1%)	
Infraclavicular fossa	6 (0.9%)	4 (2.2%)	3 (10.0%)	0	
Internal mammary chain	43 (6.4%)	22 (12.3%)	4 (13.3%)	4 (10.3%)	
Axilla level 1	36 (5.4%)	17 (9.5%)	3 (10.0%)	2 (5.1%)	
Axilla level 2	21 (3.1%)	7 (3.9%)	1 (3.3%)	2 (5.1%)	
Axilla level 3	12 (1.8%)	8 (4.5%)	2 (6.7%)	2 (5.1%)	
Endocrine therapy					0.174
Some	513 (77.0%)	135 (75.4%)	19 (63.3%)	26 (66.7%)	

Bold indicates a significance level of $p < 0.05$

determined and is consistent with the measurement frequency of 6 monthly visits as defined in the protocol of the study during year 2 and year 3 (year 2: 6.3 months, IQR 5.0–8.0 months, $p = 0.5420$; year 3: 6.2 months, IQR 5.8–6.9 months, $p = 0.4962$). Further review shows 94.9% of these patients complied with protocol, suggesting 6 that monthly screening may not be adequate in the later years post surgery for high-risk patients.

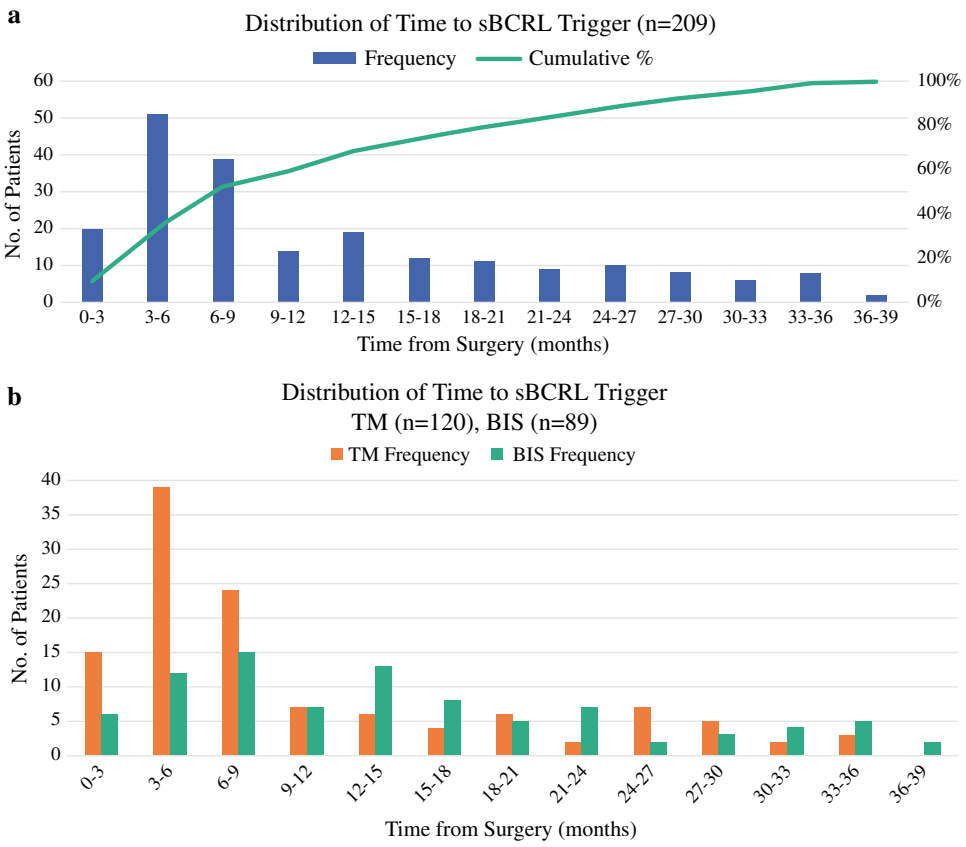

FIG. 1 Distribution of sBCRL timing for subjects **a** who triggered in both monitoring cohorts and **b** for subjects stratified by screening method over 3 years post BC treatment

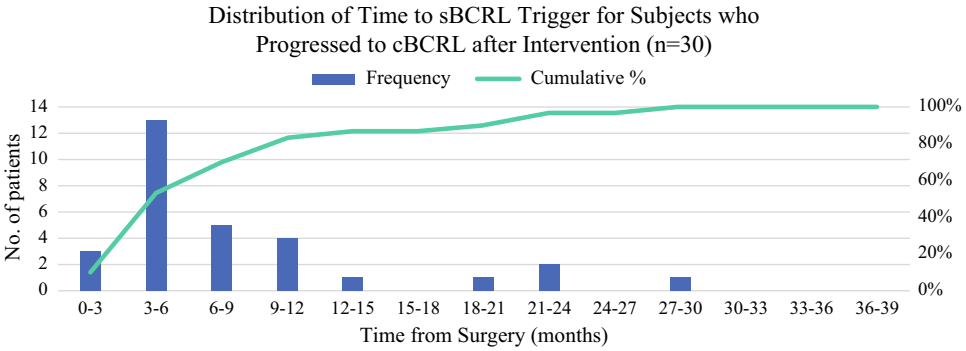

FIG. 2 Distribution of sBCRL timing for subjects who progressed to cBCRL after intervention over 3 years post BC treatment

Figure 4 shows the distribution of the timing of triggers for sBCRL stratified by outcome group for those who did and did not progress to cBCRL after identification of sBCRL. Patients in both outcome groups continued to trigger across the follow-up period. The cumulative rate of trigger increases earlier for patients who progressed to cBCRL, suggesting that detection in the early months of monitoring may be indicative of progression to cBCRL. However, no statistically significant difference was found, except for those who triggered between 3 and 6 months (no progression: 21.2%, progression: 43.3%, $p = 0.0173$).

Table 3 shows the L-Dex and relative volume differences as well as changes from baseline stratified by outcome group. For patients who triggered on the third visit or later, the L-Dex and relative volume differences as well as changes from baseline at the previous visit are also shown across the outcome groups. No significant differences are found between the outcome groups for the relative volume measurements. Significant difference was shown for the absolute L-Dex score at the time of trigger between those who did not progress and those who did progress after intervention (no progression: L-Dex = 7.4 ± 5.6 vs. progression: L-Dex = 13.3 ± 14.7, $p = 0.0283$). The odds ratio for patients with an L-Dex score greater than 10 at the time of sBCRL trigger was calculated to be 2.27 [95% confidence interval (CI) 0.94–5.5, $p = 0.0683$], which nearly reached statistical significance.

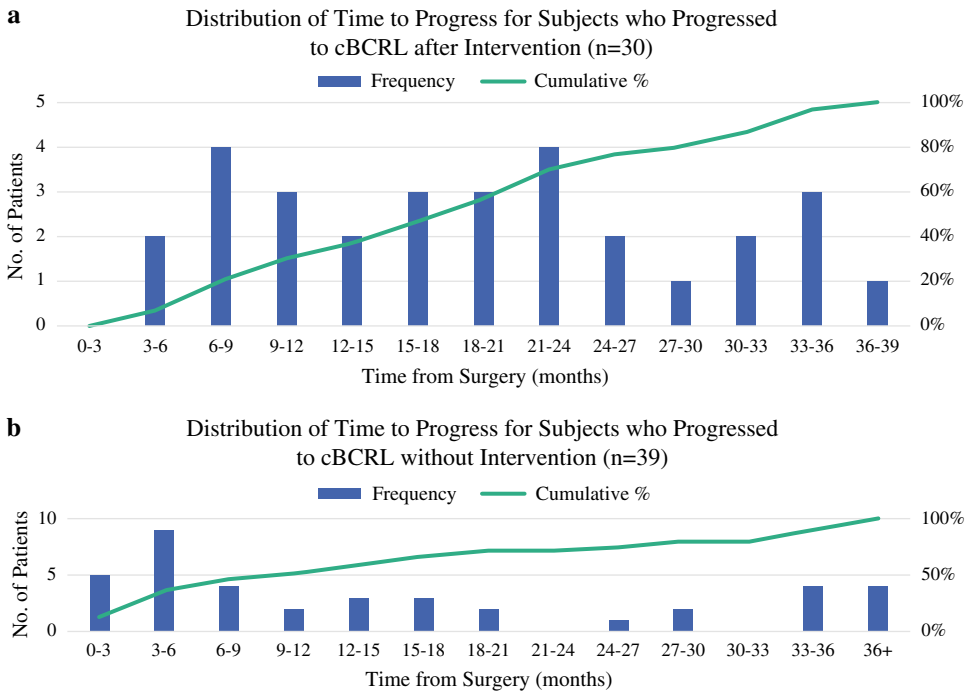

FIG. 3 Distribution of time to progression for subjects who progressed to cBCRL **a** after and **b** without intervention over three 3 post BC treatment

TABLE 2 Stratification of time to events by outcome group

	sBCRL trigger, no progression	sBCRL trigger, progression	Progression, no intervention	*p* value
sBCRL triggers				
Study duration	179	30	–	
Year 1	100	25	–	
Year 2	47	4	–	
Year 3	32	1	–	
Median time to trigger, months (IQR), study duration (months)	8.9 (4.5–19.2)	5.8 (3.2–10.8)	–	**0.0070**
Year 1	5.3 (3.3–6.8)	4.6 (3.1–6.5)	–	0.6412
Year 2	16.4 (13.2–19.3)	20.4 (15.7–22.3)	–	0.3013
Year 3	30.2 (25.8–34.3)	29.6	–	–
Median time between previous visit and trigger visit, months (IQR), study duration (months)	3.8 (3.0–5.7)	4.2 (3.0–.6)	–	0.4599
Year 1	3.6 (3.0–4.4)	4.2 (3.0–5.0)	–	0.1442
Year 2	4.1 (2.6–5.8)	4.7 (3.5–5.8)	–	0.5751
Year 3	6.1 (5.0–6.7)	6.3	–	–
cBCRL progressions				
Study duration	–	30	39	
Year 1	–	9	20	
Year 2	–	12	8	
Year 3	–	9	11	
Median time to progression, months (IQR) (months)	–	18.8 (10.9–26.5)	10.2 (3.9–28.3)	0.1521
Year 1	–	7.3 (6.7–10.4)	3.9 (2.9–6.5)	**0.0039**
Year 2	–	18.8 (16.7–21.8)	16.1 (13.0–18.5)	**0.0428**
Year 3	–	31.6 (27.6–35.1)	35.0 (30.9–36.4)	0.2348

Bold indicates a significance level of $p < 0.05$

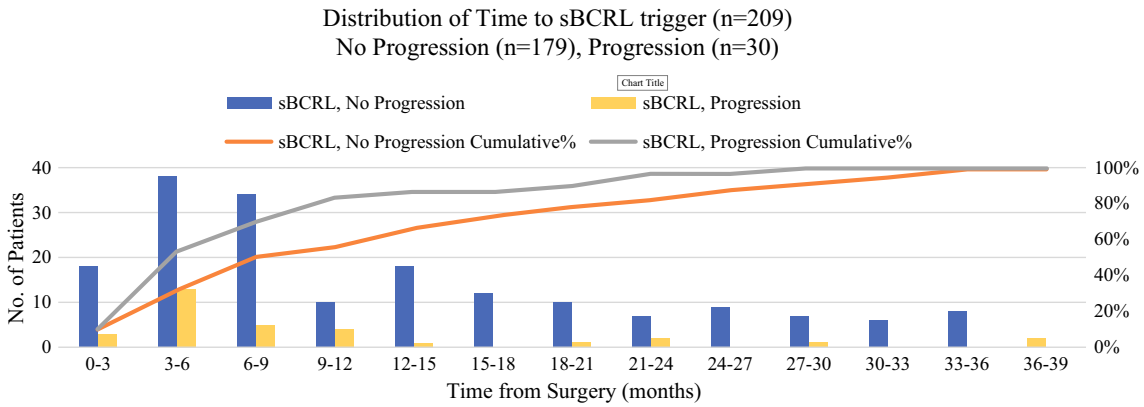

FIG. 4 Distribution of sBCRL timing for subjects stratified by outcome group over 3 years post BC treatment

TABLE 3 Stratification of L-Dex and relative volumes at trigger times by outcome group

	All sBCRL triggers	sBCRL trigger, no progression	sBCRL trigger, progression	*p* value
BIS monitoring				
N	89	82	7	
Mean L-Dex @ trigger visit	7.9 ± 6.8	7.4 ± 5.6	13.3 ± 14.7	**0.0283**
Mean ΔL-Dex @ trigger visit	10.3 ± 5.0	10 ± 3.7	13.7 ± 12.9	0.8370
Mean L-Dex @ previous visit	− 0.2 ± 4.7	− 0.2 ± 4.6	2.4 ± 4.4	0.1222
Mean ΔL-Dex @ previous visit (excluding baselines)	(*n* = 69) 0.2 ± 4.5	(*n* = 63) 2.7 ± 3.5	(*n* = 6) 3.3 ± 3.5	0.6985
TM monitoring				
N	120	97	23	
Mean rel vol @ *Trigger Visit*	5 ± 4.2	4.8 ± 4.1	5.7 ± 4.5	0.2301
Mean Δrel vol @ trigger visit	6.8 ± 1.4	6.8 ± 1.3	6.9 ± 1.4	0.923
Mean rel vol @ previous visit	− 1.1 ± 4.8	− 1.3 ± 4.9	− 0.2 ± 4.6	0.2076
Mean Δrel vol @ previous visit (excluding baselines)	− 0.3 ± 4.9	− 0.7 ± 5.0	2.2 ± 3.9	0.5540

Bold indicates a significance level of $p < 0.05$

Analysis was performed to compare the lymphedema timing profiles for type of axillary surgery, as this was identified as a risk factor for progression. The distribution of the timing of triggers for sBCRL and cBCRL was grouped by ALND vs SNB patients, but no statistically significant difference was found between the rates of triggers for the two groups (all p values > 0.08).

DISCUSSION

This study demonstrates that, while the first year following completion of treatment is the highest risk period for detecting sBCRL, sBCRL continues to occur for at least the study period of 3 years. Those subclinical triggers, when undetected can progress to chronic, potentially irreversible BCRL. Thus, long-term survivorship plans for patients at risk for BCRL should include routine screening for lymphedema utilizing measurements and symptomatology. When detected, even years out, early intervention can still be beneficial. More frequent monitoring during years 2 and 3 may provide the opportunity for these patients to undergo early intervention and delay or prevent progression.

Monitoring for BCRL

The most recent NCCN Clinical Practice Guidelines in Oncology (NCCN® Guidelines) for Breast Cancer Management (Version 2.2024, March 22, 2024)[9] continue to recommend clinicians "educate, monitor, and refer for lymphedema management" as part of the comprehensive care of breast cancer patients. The NCCN Clinical Guidelines (for Survivorship, Version 1.2024, 29 March 2024),[10] recommend "survivors at risk of lymphedema should be regularly screened for lymphedema by symptom assessment,

clinical exam, and, if available, bioimpedance spectroscopy." To that end, there are currently two common methodologies for clinicians to provide this standard of care recommendation: volume-based techniques and BIS. TM is the most common form of volume measurement. The use of TM can detect lymphedema but can be subject to significant variability based on the person doing the measurement. Additional volume-based methods that provide more reproducibility include perometry and volume displacement tanks. Additionally, there are emerging digital volumetric measuring tools that may prove valuable. The use of BIS may detect small changes in fluid not easily found by TM and thus may allow for earlier detection and treatment.[11,12]

Notably, TM is a technique focused on total volume and is less specific for identifying extracellular fluid changes in subclinical lymphedema. These findings highlight not only the sensitivity of BIS but also its specificity, as the increased triggers with TM are likely false positive owing to intra- or interobserver variability with the technique, as summarized in a recent systematic review.[2,7,13] This likely explains the higher initial trigger rate which may be related to postoperative volume changes, which can confound the diagnosis of lymphedema. This likely also explains the finding that TM volume differences were less predictive of outcomes than the absolute L-Dex score at the time of the trigger. Notably those that did not progress had a demonstrably lower absolute L-Dex score at the time of sBCRL trigger.

Alternatively, TM may have lower sensitivity to true subclinical LY as the patients in the TM group are triggering early, but still have a higher progression rate to cBCRL than those in the BIS group. Given the published evidence suggesting sBCRL can be reversed with early intervention,[3,4] this suggests that if patients monitored in the TM group continue to progress to cBCRL despite early intervention, while those monitored with BIS do not, then perhaps TM has a lower sensitivity to detection of sBCRL, and the TM triggers are occurring too late to stop the progression to cBCRL.

An alternate explanation may be that the trigger point utilized for sBCRL by BIS may trigger in some people who do not have sBCRL, but instead owing to some other physiologic process. This is the equivalent of a false positive test. In that scenario, it would not be surprising that those in the BIS group did not progress frequently and variable performance of sBCRL detected by BIS as a predictor of progression to cBCRL has previously been reported when compared with volume displacement and tape measure.[14,15] This possibility is mitigated as the PREVENT trial was a randomized study such that one would expect more closely matched cBCRL lymphedema rates if BIS was not triggering in time to prevent progression. This is particularly true given the lower trigger rate compared with TM. Likewise, even if this was true, the consequences of a false positive is the use of compression for 4 weeks. Given the low likelihood of adverse events of unnecessarily wearing a compression garment for that time, it would be rational to accept a reasonable number of false positives even if they were occurring.

Patients who did not trigger for sBCRL but progressed directly to cBCRL prior to early intervention had a median time between visits close to 6 months as per trial protocol. These high-risk patients may benefit from more frequent monitoring in later years post surgery, allowing the opportunity to intervene earlier and stop progression to cBCRL. For patients who triggered for sBCRL, there was no significant difference between the timing of visits for those that did and did not progress to cBCRL throughout the entire duration of the study. This median interval of screening approximately every 3–4 months, especially in the first 3 years post-surgery, may be the ideal frequency of screening to ensure the best outcomes for women at risk of cBCRL.

Study Limitations

This analysis reviews the timing of sBCRL triggers and cBCRL progression by retrospectively categorizing event timing into 3-month intervals despite trial protocol timing requiring 3–6 monthly screening in the first year and 6 monthly screening in year 2 and 3. This was done to understand the timing of triggers at a more granular level but does not take into consideration high- versus low-risk patients, nor practical implications, such as compliance and/or burden to patients, that every 3 monthly screening may introduce.

CONCLUSIONS

This study provides additional evidence supporting the need for continued lymphedema follow-up and the use of BIS as the preferred method, when available, in the NCCN survivorship guidelines.[10] The length and frequency of follow-up should be at least 3 years, and patients may benefit from longer follow-up beyond that with the intensity of follow-up likely taking into account patient risk factors, treatment risk factors, and overall health.

The timing of sBCRL detection demonstrates that patients continue to be at risk for developing sBCRL years after treatment and thus may continue to progress to cBCRL even years after surgery. Early detection of sBCRL allows for early intervention for lymphedema that decreases the likelihood of progression to cBCRL. As such, patients should continue to be monitored for 3 years minimum following the completion of BC treatment, ideally with BIS technology where available owing to the demonstrated reduction in risk of developing cBCRL. Over 50% of sBCRL detection occurred in the first 9 months after treatment, suggesting the importance of careful targeted monitoring over this initial period.

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