Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpedance spectroscopy

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Abstract
This single-institution experience evaluated the use of bioimpedance spectroscopy to facilitate early detection and treatment of breast cancer-related lymphedema (BCRL) in a cohort of 596 patients (79.6% high risk). Seventy-three patients (12%) developed an elevated L-Dex score with axillary lymph node dissection (P < .001), taxane chemotherapy (P = .008), and regional nodal irradiation (P < .001) associated. At last follow-up, only 18 patients (3%) had unresolved clinically significant BCRL requiring complete decongestive physiotherapy. This rate of BCRL is lower than reported in contemporary studies, supporting recent NCCN guidelines promoting prospective screening, education and intervention for BCRL.

KEYWORDS
bioimpedance, breast cancer, early detection, lymphedema, surveillance

1 | INTRODUCTION

Breast cancer-related lymphedema (BCRL) represents a sequelae of treatment that can lead to a significant detriment in quality of life. Rates of BCRL following treatment vary widely based on local and systemic therapies utilized with rates as high as 50% noted with more aggressive locoregional therapy, radiation therapy, and taxane-based chemotherapy. Therefore, it is imperative to identify patients at high risk for developing symptomatic BCRL so that they can be monitored and receive simple, preemptive intervention, thereby reducing the development of irreversible, chronic BCRL.

Multiple published studies and current guidelines have shown early detection and treatment of subclinical BCRL (using newer techniques and technologies) can prevent progression to its chronic stage, eliminating morbidity and the need for more intensive, costly treatments. New techniques, including bioimpedance spectroscopy (BIS) and perometry have been developed to allow for the diagnosis of subclinical BCRL. While a randomized trial evaluating BIS is underway, until the results are published, it is useful to review outcomes in large, single-institution experiences where a structured and consistently applied program of BCRL surveillance using BIS is being employed. Therefore, the purpose of the present analysis was to evaluate outcomes with prospective surveillance in a large number of patients (79.6% high risk) monitored and treated consistently using BIS at a single institution.

Between April 2010 and November 2016, a single institution (Nashville Breast Center, Nashville, TN) enrolled patients in a prospective BCRL surveillance program using the L-Dex U400 Device (ImpediMed, Brisbane, Australia). Patients were followed prospectively using a standard protocol, including upfront BCRL education and a preoperative baseline L-Dex measurement, then postop follow-up measurements. Patients were considered to have an elevated reading if their L-Dex score increased >10 points from baseline (defined as ‘subclinical BCRL’). Intervention was then triggered and consisted of applying an over-the-counter (OTC) compression sleeve for 4 weeks followed by a recheck of their L-Dex score. The need for complete decongestive physiotherapy (CDP) was defined as "chronic BCRL" for this analysis (surrogate for chronic BCRL).
Patients were considered high risk (n = 475) if they had an elevated body mass index (BMI, >25) (n = 379), axillary lymph node dissection (ALND) (n = 93), received regional nodal irradiation (RNI) (n = 17), or received taxane chemotherapy (n = 163).

Patient characteristics (n = 596) are presented in Table 1. Of those with elevated BMI, 61 underwent ALND, 311 SLNB, and 9 had an unknown axillary procedure, one-third of patients had more than one risk factor. Median follow-up for all patients was 17 months (range 0.2-80.4) and the median number of follow-up visits was 4 (range: 2-19). Overall, 73 patients (12% of all patients) had an abnormal L-Dex score at some point during surveillance. Of these 73 patients, the L-Dex score returned back to baseline in 55 patients (75%). In the remaining 18 patients (3% of total), the L-Dex score did not return to baseline and/or they had clinically apparent/significant BCRL requiring CDP. All patients that went on to CDP were initially identified with elevated L-Dex readings (no false negatives). Patients undergoing ALND were more likely to develop an abnormal L-Dex score (31% vs 8%, P < .001) and to have unresolved BCRL (11% vs 1%, P < .001). Median time to first elevated L-Dex score was 4.5 months (range: 0-193) with median time to resolution of 3.8 months from diagnosis (range: 0.1-51.7). Table 2 presents a comparison of patient and treatment characteristics for those patients who developed subclinical BCRL as compared to those that did not.

Those developing subclinical BCRL were less likely to undergo SLNB and more likely to have received adjuvant systemic therapy, taxane-based therapy, and/or RNI. Those developing irreversible, chronic BCRL were less likely to undergo SLNB and more likely to have undergone mastectomy, received adjuvant systemic therapy, taxane-based therapy, high tangents, or RNI.

The results of the current analysis support the concept that prospective surveillance using BIS can detect subclinical BCRL in patients (79.6% of whom were considered high risk), facilitating simple preemptive intervention and resulting in very low rates of chronic BCRL. These results compare favorably to rates of BCRL ranging from 10-50% in multiple large series using conventional surveillance and treatment paradigms.1,9-12 Additionally, the overall lymphedema rate of 3% (persistent L-Dex elevation or clinical BCRL following an OTC sleeve) is lower than reported in modern studies of low-risk patients; the lymphedema rate in over 5000 patients in the ACOSOG Z0010 trial (sentinel node biopsy in T1-2N0 breast cancers) was 7% at only 6 months.13 Based on these comparisons, the current analysis supports prospective BCRL surveillance in at-risk patients starting with a presurgical L-Dex measurement (with subsequent follow-up measurements and conservative intervention as needed), to help reduce the morbidity associated with BCRL.1,5

### TABLE 1 Characteristics of patients by axillary surgery

|                        | ALND | SLNB | Total | P-value |
|------------------------|------|------|-------|---------|
| **Number**             | 93   | 484  | 596   |         |
| **Age**                | 53 (32-87) | 56 (28-90) | 55 (28-90) | .10 |
| **Mastectomy**         | 79 (85) | 260 (54) | 343 (59) | <.001 |
| **BMI**                |      |      |       |         |
| Elevated               | 61 (66) | 311 (67) | 372 (67) | .50 |
| Median                 | 28    | 27   | 27    |         |
| **Systemic therapy**   |      |      |       |         |
| Adjuvant chemotherapy  | 49 (53) | 106 (22) | 155 (26) | <.001 |
| Neo-adjuvant therapy   | 20 (22) | 79 (16) | 101 (17) | .29 |
| Taxane chemotherapy    | 51 (55) | 110 (23) | 163 (27) | <.001 |
| (any time)             |      |      |       |         |
| Targeted therapy (Herceptin/TKI) | 10 (11) | 45 (9) | 55 (9) | .81 |
| **Radiation therapy**  |      |      |       |         |
| Breast/chest wall irradiation | 39 (42) | 159 (33) | 203 (34) | .12 |
| High tangents          | 14 (15) | 12 (2) | 26 (4) | <.001 |
| Regional nodal irradiation | 8 (9) | 9 (2) | 17 (3) | .001 |
| APBI                   | 0 (0) | 102 (21) | 103 (17) | <.001 |

Values in parentheses are percentages.
APBI = accelerated partial breast irradiation, TKI = tyrosine kinase inhibitor.

### TABLE 2 Characteristics of patients by presence of subclinical BCRL

|                        | No   | Yes  | Total | P-value |
|------------------------|------|------|-------|---------|
| **Number**             | 523  | 73   | 596   |         |
| **Age**                | 55 (28-90) | 55 (34-87) | 55 (28-90) | .89 |
| **Surgery**            |      |      |       |         |
| Mastectomy             | 302 (59) | 41 (59) | 343 (59) | 1.00 |
| SLNB                   | 444 (87) | 40 (58) | 484 (84) | <.001 |
| **Systemic therapy**   |      |      |       |         |
| Adjuvant chemotherapy  | 125 (24) | 30 (41) | 155 (26) | .003 |
| Neo-adjuvant therapy   | 86 (16) | 15 (21) | 101 (17) | .48 |
| Taxane chemotherapy     | 133 (25) | 30 (41) | 163 (27) | .008 |
| (any time)             |      |      |       |         |
| Targeted (Herceptin or TKI) | 45 (9) | 10 (14) | 55 (9) | .23 |
| **Radiation therapy**  |      |      |       |         |
| Breast/chest wall irradiation | 174 (33) | 29 (40) | 203 (34) | .34 |
| High tangents          | 20 (4) | 6 (8) | 26 (4) | .16 |
| Regional nodal irradiation | 9 (2) | 8 (11) | 17 (3) | <.001 |
| APBI                   | 95 (18) | 8 (11) | 103 (17) | .17 |

Values in parentheses are percentages.
APBI = accelerated partial breast irradiation, TKI = tyrosine kinase inhibitor.
While some previous studies evaluating early detection and intervention used perometry, the present study utilized BIS and had similar findings.\(^7\) Taken together (with data supporting the ease and efficiency of monitoring L-Dex scores), these results support the use of BIS prospectively as part of current NCCN recommendations for BCRL education and surveillance.\(^5\)

An essential component of any prospective surveillance program is a diagnostic technique that allows for early, subclinical detection of BCRL. Well-documented high sensitivity techniques include perometry and BIS.\(^4,15\) Perometry utilizes infrared optical-electronic scanning to evaluate limb volume while BIS uses low-level electrical currents to measure impedance, which changes in step with changes in extracellular volume. An increase in L-Dex value >10 units from a preoperative baseline is consistent with subclinical BCRL.\(^8\) Bioimpedance spectroscopy has been consistently shown to allow for the subclinical detection of BCRL and just as importantly, evidence-based guidelines are available to provide clinicians with trigger points using L-Dex scores to initiate simple preemptive management.\(^8,16\)

An additional component for designing surveillance programs is the need for efficiency with respect to cost, space, and time. Bioimpedance spectroscopy using L-Dex has a minimal space footprint and has been found to add minimal time in its application, allowing for follow-up BCRL assessments at the same time as clinical visits rather than additional follow-ups.\(^16\) As such, with data supporting its utility in prospective surveillance similar to perometry, BIS may be a more attractive option for clinicians due to its minimal space requirements and ease of use. Moving forward, additional data will help quantify the magnitude of improvements in the long-term outcomes of such approaches with respect to chronic BCRL, quality of life, toxicity, and cost.

While prospective surveillance is increasingly being recommended based on randomized and prospective studies,\(^3,4,6\) one concern is identifying patients at highest risk for BCRL in order to allocate screening resources in the most cost-efficient manner. For example, the Torres Lacomba trial demonstrated that BCRL can be prevented by treatment from day one, prior to any BCRL; however, when evaluating the outcomes, only 25% of patients not receiving preventative intervention were found to have BCRL suggesting that advanced, highly sensitive diagnostic techniques are needed to identify which patients are best served by early preventative intervention techniques.\(^6\) This is compelling, because data have demonstrated a significant cost to the management of chronic BCRL and as such, the cost associated with early detection and intervention is minimal compared to active treatment (if the appropriate patient population is screened).\(^17\) The first step toward effective allocation of resources is to incorporate factors associated with the development of BCRL including patient characteristics as well as locoregional and systemic therapy as was done in this analysis and is consistent with the literature to date.\(^1\)

It should be noted that all patients that ultimately required CDP were first identified with an elevated L-Dex measurement. In the vast majority of patients with elevated L-Dex scores, BCRL was reversible with a simple OTC compression sleeve applied for 4 weeks. In those that did not respond to this conservative management, it might be that BCRL needs to be detected even sooner in order to prevent progression to its chronic form. Recent data have demonstrated higher sensitivity and specificity of L-Dex when using a 2 standard deviation (SD) trigger, or an L-Dex increase of >6.5 from presurgical baseline rather than the current criterion of 3 SD (L-Dex increase of >10).\(^18-20\) This may lead to a higher sensitivity to mild-to-moderate volume changes, something clinicians can use consistently in evaluating their patients for BCRL treatment.

In summary, prospective surveillance of breast cancer patients (most of whom were considered high risk) for the development of BCRL using BIS permitted the detection and simple preemptive management of subclinical disease resulting in a very low rate of chronic lymphedema compared to the established, expected range. These findings (which represent the largest group of patients monitored in a structured, program for early detection of BCRL using BIS) support the cost-effective allocation of resources for prospective, BIS-assisted, BCRL surveillance within guidelines-based breast cancer survivorship programs. For women at risk for BCRL, this protocol represents a useful option to meet NCCN guidelines for the education, monitoring and treatment of BCRL.

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