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The Early Detection of Breast Cancer Treatment-Related Lymphedema of the Arm

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Abstract

Background: It is recognized that the early detection of breast cancer treatment related lymphedema (BCRL) leading to earlier intervention may improve long-term outcomes. This study aimed to determine whether limb volume measurement or bioimpedance spectroscopy (BIS) was the better tool for the early detection of BCRL. It also aimed to identify factors, which may be used to assess the risk of development of BCRL for individual patients.
Methods and Results: This was a large prospective multicenter study of 1100 patients, who had had axillary node clearance for breast cancer, carried out in the United Kingdom. Limb volumes (by Perometer) and BIS (L-Dex by Impedimed U400) measurements were taken preoperatively and postsurgery with a follow-up period of 5 years. Details of the cancer, its treatment, body mass index (BMI), and age were recorded. BCRL was defined by relative arm volume increase (RAVI) ≥10%. At 24 months, the incidence of BCRL defined by RAVI was 22.8% and that defined by L-Dex >10 was 45.6%. Independent risk factors for the development of BCRL at 36 months were RAVI ≥5%–<10%, at 1 month, 10 or more positive nodes, BMI >30 and taxane chemotherapy. A risk assessment tool based on these was developed.
Conclusions: Limb volume measurements performed better than BIS in the early detection of BCRL. Pre- and postoperative monitoring of limb volume measurements is useful in the early detection of, and prediction of those likely to develop, BCRL and allow early intervention.

Keywords: breast cancer, lymphedema, detection, risk assessment

Introduction

Breast cancer treatment-related lymphedema (BCRL) of the upper limb is well recognized to be a common problem with significant morbidity. In the United Kingdom, one in eight women will develop breast cancer during their lifetime and there were 55,000 new cases diagnosed in 2015. Approximately 80% of these women will have sentinel node biopsy alone and their risk of developing lymphedema is ~6%.[1] For the 20%, who have axillary node clearance (ANC), ~20% will develop lymphedema.

In recent years, there has been considerable interest in the early detection of BCRL, in the hope that early intervention will reduce the morbidity associated with this condition and possibly prevent its development.[2]

This is based on the premise that when lymphedema develops, there is an initial subclinical phase where there may be a buildup of fluid in the interstitial space, which is insufficient to cause clinical symptoms but is the precursor to established lymphedema. Established lymphedema is itself initially fluid in nature but as time passes, the chronic inflammatory process, which is part of the condition, leads to the deposition of adipose tissue and fibrosis.[3]

It has long been recognized clinically that lymphedema, which is fluid predominant, is easier to treat with conventional physical treatments such as compression garments. Once adipose tissue and fibrosis has developed, the swelling does not respond as well to these treatments.

Therefore, if lymphedema is recognized early then it should respond better to current treatments. It has been known for some time that these treatments reduce the incidence of cellulitis, which is a common complication of lymphedema, which can in the acute stage require hospital admission for intravenous antibiotics and in the longer term can make the lymphedema worse.[4]

Furthermore, it has been argued that the identification of subclinical lymphedema and intervention with conventional compression treatment for a limited period for example, 4 weeks, at that stage may prevent the development of established lymphedema.[2]

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There has been debate in the literature about the best method of detecting both subclinical lymphedema and early established lymphedema.[5] The two most commonly considered methods are the use of bioimpedance spectroscopy (BIS) and limb volume measurement. BIS has the potential advantage of being able to detect an early increase in extracellular fluid, which may precede the establishment of clinical lymphedema.[6] Limb volume measurements may also change in this early stage but may be affected by changing muscle bulk and fat deposition, for example, which associated with weight gain so interpretation is more difficult. In both BIS and limb volume measurements, comparison with the untreated side can help to allow for general changes such as weight gain.

To achieve early detection, it is recognized that whichever of these methods is used, screening of women undergoing treatment for breast cancer should begin preoperatively, giving a baseline measurement against which subsequent changes can be compared. However, how frequently women should be reassessed after surgery and for how long is not established.

To carry out such a surveillance program in all women being treated for breast cancer would be very resource intensive. Therefore, it would be helpful if there was a way of identifying those who are at high risk of developing BCRL compared with those who are at no risk. This could help to prioritize those at higher risk for ongoing monitoring.

A successful screening program would also require successful interventions to make it cost-effective. Although it is established that complex decongestive therapy (CDT) is effective in improving lymphedema and reducing the risk of cellulitis, a recent systematic review concluded that compression garments alone are not effective in reducing lymphedema in the acute phase of treatment but may be helpful in early mild BCRL.[7]

We carried out a large multicenter prospective study in the United Kingdom to address a number of these and other questions, including the following:

(1) Is BIS or limb volume measurement the better tool to use?
(2) Is it possible to develop a risk assessment tool, which could distinguish those at high risk versus those at low/no risk?
(3) Does early intervention with a compression garment in subclinical lymphedema prevent BCRL from developing?
(4) In those with established BCRL, does the use of a compression garment prevent progression of the condition?

This article will focus on the first two of these and make some comments on the fourth question. These results have been published.[8] The results of the study to address the third question are still being processed and have not been published. Other results from the study are included in the published article.[8]

Materials and Methods

In total, 1100 women whose planned treatment for breast cancer included ANC were recruited from nine centers across the United Kingdom. Arm volumes were measured by Perometer (an optoelectronic device) and multifrequency BIS by L-Dex® U400 preoperatively and at 1, 3, 6, 9, and 12 months, then 6-monthly up to 5 years postoperatively.

Other data collected relevant to this article included cancer details and treatment, quality of life (by FACT $B+4$), age, and body mass index (BMI).

Lymphedema was defined as a relative arm volume increase (RAVI) of >10% from baseline. At the time of commencing this study, lymphedema was defined by BIS, as a change of 10 or more L-dex units from baseline.

A compression sleeve (20–25 mmHg, circular knit) was given to those who developed a RAVI >10% and to those who were found to have lymphedema clinically but with RAVI <10%, for example, in those with localized swelling such as in the hand. Follow-up assessments continued to be made in these patients.

Predictors of lymphedema development were determined using logistic regression. Risk factor scoring models were produced based on the regression coefficients of the multivariable logistic regression. Their accuracy was assessed using the area under the receiver operating characteristic curve (AUROC) method. A final scoring tool was developed based on these.

Ethics approval and consent to participate

The study was approved by the South Birmingham Research Ethics Committee, UK. The participants all consented to take part in the study.

Results

Is BIS or limb volume measurement the more accurate tool?

The mean age was 56 (standard deviation ±12; range 22–90) years.

The main finding was that lymphedema was diagnosed in $22 \cdot 8\%$ of women by RAVI >10%, but detected in $45 \cdot 6\%$ by L-Dex (>10 U change) by 24 months. This suggests that the use of L-Dex >10 alone would give an incidence of lymphedema double that defined by RAVI >10%.

A total of $24 \cdot 5\%$ received a compression sleeve by 24 months. This included those with RAVI <10% who were felt to have lymphedema clinically. Even allowing for this slightly higher incidence defined by sleeve application, this number is still much less than that defined by the BIS.

There was moderate correlation between RAVI and L-Dex at 6 months ($r=0.62$).

Risk factors for developing BCRL and risk assessment tool

The eight factors, which were predictors of the development of BCRL at 36 months as defined by univariate analysis, are shown in Table 1. These reduced to four independent predictors by multivariable analysis (Table 2).

A change in RAVI of between ≥5% and <10% at 1 month postoperatively gave the highest odds ratio of 5.27. This suggests that an early change in limb volume strongly predicts the later development of clinical lymphedema by 36 months. Having 10 or more positive lymph nodes at ANC was also a significant predictor with an odds ratio of 3.05.

Changes in L-Dex were not found to be significant predictors by univariate or multivariable analysis.

Table 1. Predictors of BCRL (RAVI >10%) at 36 Months by Univariate Analysis (Derived from 8)

RAVI at 1 m
Feeling of swelling
Age
BMI preoperative
No. of positive nodes
Chemotherapy
Radiotherapy
Stage

BCRL, breast cancer treatment related lymphedema; BMI, body mass index; RAVI, relative arm volume increase.

Using these data a scoring tool was developed, which could be assessed at 1 month postsurgery, to estimate the subsequent risk of developing lymphedema by 36 months. This is shown in Table 3.

The AUROC of the scoring model was 0.71 (95% confidence interval: 0.66–0.75) that is, indicating acceptable accuracy.

By categorizing the scores, those at low, moderate, and high risk can be determined as shown in Table 4. Most (66%) patients came in the low-risk group but even in this group there was a 12% risk of developing lymphedema by 36 months. Thirty percent of patients came into the moderate-risk group, which had a 32% risk of developing lymphedema at 36 months. A small percentage (4%) of patients came into the high-risk group with a 77% chance of developing lymphedema by 36 months.

Response to compression sleeve application

In the study, 187 women with RAVI <20% wore a compression sleeve for 22 (IQR 11–33) months. Although the swelling did not progress in 158 cases (84.3%), progression to RAVI >20% (which may be considered to be a progression from ''mild'' to ''moderate'' lymphedema by ISL criteria) occurred in 29 patients (15.7%).

Independent factors predicting progression were age, BMI at application especially BMI >30, and estrogen receptor (ER) negative tumors (Table 5). The predictor of progression with the highest odds ratio of 7.23 was a BMI >30 at the time of sleeve application.

Discussion

In this study, limb volume measurement by Perometer performed better than BIS in the early detection of BCRL and a subclinical change in RAVI even at 1 month postsurgery was a strong predictor for the development of BCRL by 36 months.

Table 2. Independent Predictors of BCRL (RAVI >10%) at 36 Months by Multivariable Analysis with OR and 95% CI (Derived from 8)

Risk factor	*OR*	*95% CI*
RAVI ≥5– <10% at 1 m	5.27	3.30–8.41
BMI preoperative (>30)	1.72	1.03–2.57
No. of positive nodes ≥10	3.05	1.89–4.93
Chemotherapy with taxane	1.57	1.04–2.38

CI, confidence interval.

Table 3. Risk Scoring Tool (Derived from 8)

Risk factor	*Score*
RAVI at 1 m	
<3%	0
>3 < 5%	0.5
>5 < 10%	1.5
>10	2
BMI presurgery	
≤25	0
>25 ≤ 30	0
>30	0.5
ER negative	0.5
Positive nodes	
≤3	0
4–9	0.5
≥10	1
Chemotherapy	
No chemo	0.5
Chemo – no taxane	0
Chemo + taxane	1

ER, estrogen receptor.

At the time of the design of this study a RAVI of 10% or more from preoperative measurements was considered to be a reasonable, although imperfect, definition of BCRL. From clinical practice, however, some patients were known to develop localized lymphedema, for example, presenting as pitting edema in the hand, with a RAVI for the whole arm of <10%. In this study, compression garments were given to patients with such presentations as well as those with lymphedema defined by RAVI >10%. Compression garment application was, therefore, used as a surrogate measure for clinical lymphedema to allow inclusion of those with milder segmental swelling. Interestingly, this only increased the incidence of BCRL at 24 months from 22.8% measured by RAVI >10% alone to 24.5%. This suggests that RAVI >10% is a reasonable, although imperfect, definition of BCRL, in the absence of an internationally agreed ''gold standard'' (5).

In contrast, the definition of BCRL based on BIS measurements and an L-Dex >10 gave in incidence of 45.6% at 24 months that is, approximately double that defined by RAVI >10 and compression garment application. This suggests that using BIS alone in the early detection (and intervention) of BCRL is likely to result in the overtreatment of patients.

Furthermore, it has been suggested that the L-Dex definition of BCRL of >10 should be reduced to >7.1.[9] If this were used alone to assess patients at risk of BCRL, there is a potential for even greater overtreatment.

Broadly, the risk factors for the development of BCRL found in this study are similar to those in previous study (5).

Table 4. Risk of BCRL at 36 Months by Risk Assessment Tool Score (Derived from 8)

Score at 1 m	*% patients with this score (n = 826)*	*Risk of lymphedema at 36 m*
≤1	66	12%
2–3	30	32%
3.5–4.5	4	77%

Table 5. Independent Factors Predicting Progression to RAVI ≥20% with OR and CI (Derived from 8)

Factors	*OR*	*95% CI*
Older age (per year)	1.07	1.03–1.12
BMI at application >30 vs. ≤25	7.23	1.74–29.9
ER negative	3.7	1.26–10.86

However, it should be noted that our study only included patients who had had ANC.

RAVI ≥5– <10 at 1 month and 10 or more positive nodes were strong predictors of BCRL by 36 months. BMI >30 and taxane chemotherapy were also significant predictors.

Although the data are not presented in this article, RAVI ≥5– <10 at 6 months was also a strong predictor (8). There has been debate in the past about the relevance of early swelling postoperatively and whether this tends to resolve spontaneously or may lead to persistent BCRL (5). The fact that RAVI ≥5– <10 at 1 month is a strong predictor of BCRL at 36 months suggests that early swelling postoperatively is significant and should influence the discussion about when to intervene with compression treatment.

This study supports the value of preoperative measurements and postoperative surveillance in the early detection of BCRL. Breast cancer is a common condition and BCRL may affect around 25% of women treated for it. Therefore, to be able to focus resources cost-effectively, a method of identifying those at greatest risk of developing BCRL would be helpful.

The scoring tool developed in this study is a possible way forward. It enables the stratification of patients into those at low, medium, and high risks. This could be used to determine appropriate follow-up.

However, further models are being developed with these data at present and any final model would need to be validated in a separate population.

There would also need to be further consideration about how the risk assessment tool is used. Even those who are at low risk have a 12% chance of developing lymphedema by 36 months, so cannot be ignored. For those at very high risk with a 77% chance of developing BCRL by 36 months, there is the question as to whether immediate early intervention with compression would be beneficial. There is a need for further research to answer this. The results of the PLACE study also carried out by our group, which are yet to be published, may go some way toward this.

In this study, we also looked at whether those patients who received a compression garment were helped by it or whether their BCRL progressed from ''mild'' to ''moderate'' lymphedema (as defined by a RAVI >20%). Although progression did not occur in 84.3% of patients who were given a compression garment, it did in 15.7%.

These results should be treated with some caution, however. The study was not specifically designed to answer these questions. For example, we do not have data on how often patients used the garments and whether the types of garments were changed by lymphedema therapists, for example, from circular knit to flat knit.

Nevertheless, on multivariable analysis there were some significant independent predictors of progression. These were BMI, older age, and ER-negative disease.

The most important of these with a high odds ratio of 7.23 was a BMI >30 at the time of compression garment application.

In clinical practice, it is well recognized that those with lymphedema and a high BMI do not seem to respond as well to conventional CDT as those with lower BMIs. This may relate to the physics of compression and larger limb circumferences, together with the impact of adipose tissue on the effectiveness of compression in improving lymph drainage.

It is not easy to explain why ER-negative disease is a risk factor for progression although a possible reason may relate to different chemotherapy treatment, for example, neoadjuvant chemotherapy. This was not specifically examined in this study.

These findings do raise issues about the ongoing monitoring and management of patients with BCRL, particularly those with a high BMI.

Conclusions

In this study, limb volume measurements performed better than BIS in the early detection of BCRL. Pre- and postoperative monitoring are useful in the early detection of, and prediction of those likely to develop, BCRL and allow early intervention. The proposed risk assessment tool is promising, but other versions are being developed with the data and further validation is required. How it may be used needs to be considered further. The intervention used to treat early BCRL would benefit from further investigation particularly in those with BMI >30.

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