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ORIGINAL ARTICLE

Prospective surveillance of breast cancer-related lymphoedema in the first-year post-surgery: feasibility and comparison of screening measures

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Abstract
Purpose To examine the feasibility of a breast cancer-related lymphoedema (BCRL) screening programme. Additionally, to investigate the efficacy of bioimpedance analysis (BIA) compared to circumferential measurements (CM) in detecting BCRL.
Methods This was a 12-month prospective feasibility study. Participants were recruited from two diagnostic breast clinics and consented to be screened for BCRL. Pre-surgical assessments were conducted, and participants were followed up at quarterly intervals. BIA and CM measurements were conducted at all time points. An L-Dex score of >10 or a 10-U increase from baseline or a ≥5 % increase in proximal, distal or total percentage volume difference (PVD) from baseline was indicative of BCRL. Information was collected on subjective symptoms, potential risk factors, demographics and medical data. Feasibility was based on uptake and retention.
Results One hundred twenty-six participants were recruited with an attrition rate of 16.2 %. Participants' mean age was 59 years with the majority having stage I (63.9 %), infiltrating ductal carcinoma (87.4 %). 31.6 % were identified as having BCRL, 90.3 % detected by CM and 35.5 % by BIA (p=≤0.0001). We found no significant correlation between BIA and CM. Participants identified as having BCRL had a higher BMI, a recent injury to their 'at-risk' arm and more lymph nodes excised (p=<0.05). These findings were not evident across all time points. A large percentage of participants had transient BCRL when assessed by a lymphoedema physiotherapist.
Conclusions BCRL screening is acceptable and valued by breast cancer survivors. Work needs to continue to establish the most effective screening tool and the natural behaviour of BCRL within the first-year post-surgery.

Keywords Breast cancer · Lymphoedema · Surveillance · Bioimpedance · Circumferential measurement

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Introduction

Breast cancer is the most common female cancer worldwide [1] with approximately 48,988 new cases diagnosed annually within the UK [2] and 1.38 million worldwide [1]. Survival rates are steadily increasing; thus, issues surrounding cancer survivorship are much the focus of current research [3] and clinical practice. Breast cancer-related lymphoedema (BCRL) is one of the most common and dreaded complications of breast cancer treatment. It is an accumulation of protein-rich fluid in the interstitial spaces of the arm, due to a reduction in lymph transport capacity, secondary to cancer and its treatment [4]. BCRL is a chronic condition which impacts negatively on quality of life [5, 6], developing any time post-surgery, although the majority (70–80 %) present within the first year [7, 8]. The true incidence of lymphoedema is notoriously difficult to quantify due to the lack of standardised diagnostic criteria, assessment methodology [9] and associated risk factors. Incidence rates of 21.4 % have been reported [10], extrapolating to 10,483 breast cancer survivors in the UK and 295,320 worldwide who will develop BCRL.

Early detection and treatment are vital in reversing or slowing the progression of BCRL [11], proving to be cost-effective by reducing complications and the need for intensive

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treatment [12]. Despite this and the promotion of surveillance programmes [11], BCRL screening is not commonplace. This notwithstanding, before BCRL screening, can be widely implemented, we need to establish its feasibility, appropriate screening tools and the cohort that should be targeted.

Upper limb circumferential measurement (CM) has commonly been used as a diagnostic tool and outcome measure [10]. CM can be used to compute relative limb volume difference, comparing the surgically ipsilateral arm with the contralateral arm. This method is ideal as it is not reliant on physique [13] and has minimal associated cost. While Taylor et al. [14] state that CM is a reliable and valid measurement of BCRL, others question its sensitivity [15]. This debate, in part, may be due to the lack of a standardised approach. Studies have measured at one fixed point on the upper arm only [16]; others have used a fixed point on both the upper and forearm [17–19]. Few have taken multiple anatomical measurements of the whole arm [20], which is likely to give a more accurate calculation of limb volume [14]. Diagnostic criteria is also inconsistent, with some studies using CM differences of >1 to ≥5 cm as an indication of BCRL, while others use volume differences ranging from >150 ml to >200 ml and percentage volume differences (PVD) between 3 and 20 % [21–23, 10].

Bioimpedance analysis (BIA) has been developed for the assessment of lymphoedema, comparing the surgically ipsilateral arm with the contralateral arm, generating an L-Dex™ score (normal range −10 to +10). It is proposed that BIA can differentiate between extracellular fluid and total limb volume [21]. BIA has been reported as a reliable measure of BCRL [22, 23] with excellent sensitivity and specificity [24]. Studies claim BIA to be four times more sensitive than CM [25]; others report no advantage [26].

Little research exists in relation to BCRL screening programmes and those that do have varied aims. Specht et al. [27] utilised a screening programme to explore interventional thresholds for patients with BCRL, while others focused on treatment outcomes/surveillance models [28]. To our knowledge, this is the first to report on the feasibility of a clinical BCRL screening programme. Additionally, the efficacy of advocating one screening tool over another has yet to be established, and the evidence-base is limited, inconclusive and perhaps marred by the issues outlined earlier. We also aim to investigate the efficacy of single frequency BIA compared to upper limb CM in identifying early BCRL and factors which may influence its development.

Methods

Design, setting and participants

This was a 12-month prospective feasibility study which was approved by the Office for Research Ethics Committee, Northern Ireland, and Research Governance within both the Belfast and South Eastern Health and Social Care Trusts. The research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Women, aged 18–99 years, newly diagnosed with stages I–III unilateral breast cancer, were eligible. Exclusions are listed in Table 1. Participants were recruited between April and December 2012 from specialist diagnostic breast clinics at the Belfast City Hospital and Ulster Hospital, Dundonald. Patients were screened for eligibility by their breast care team, and those suitable were informed of the study and given a participant information sheet. Interested individuals were followed up by the principle investigator (JB). Those agreeable to take part provided written informed consent, and participants' GPs were informed of their involvement. Figure 1 outlines participants' flow through the study.

Table 1 Summary of reasons for exclusion, declining to participate and withdrawal

Reason for exclusion	Frequency (%) *n*=46
Previous history of breast cancer	8 (17.4 %)
Prior severe trauma/surgery upper limb	8 (17.4 %)
Patients fitted with cardiac device or metal implant	6 (13.0 %)
Unable to obtain baseline assessment—referral received after/on day of surgery	6 (13.0 %)
Patients with stage IV disease/locally advanced	5 (10.9 %)
Dementia/Alzheimer's/memory/communication difficulties	4 (8.7 %)
Patients with renal failure/heart failure	3 (6.5 %)
Not appropriate for surgery	2 (4.3 %)
Bilateral breast cancer	1 (2.2 %)
Patients reporting pre-operative swelling of the upper limb	1 (2.2 %)
Previous history of lymphoedema	1 (2.2 %)
Did not attend baseline assessment	1 (2.2 %)
Reasons for declining to participate	*n*=21 (%)
No reason offered	10 (47.6 %)
Too far to travel	4 (19.0 %)
Too much going on	3 (14.3 %)
Out of country for long periods of time	2 (9.5 %)
Unable to attend additional appointments	1 (4.8 %)
Carer for husband with dementia	1 (4.8 %)
Reason for withdrawal	*n*=19 (%)
Did not attend follow-up assessment/no response from participant	8 (42.1 %)
Too much going on	5 (26.3 %)
Unable to attend additional appointments	4 (21.0 %)
No reason offered	1 (5.3 %)
Care transferred to another hospital trust—not prepared to travel	1 (5.3 %)

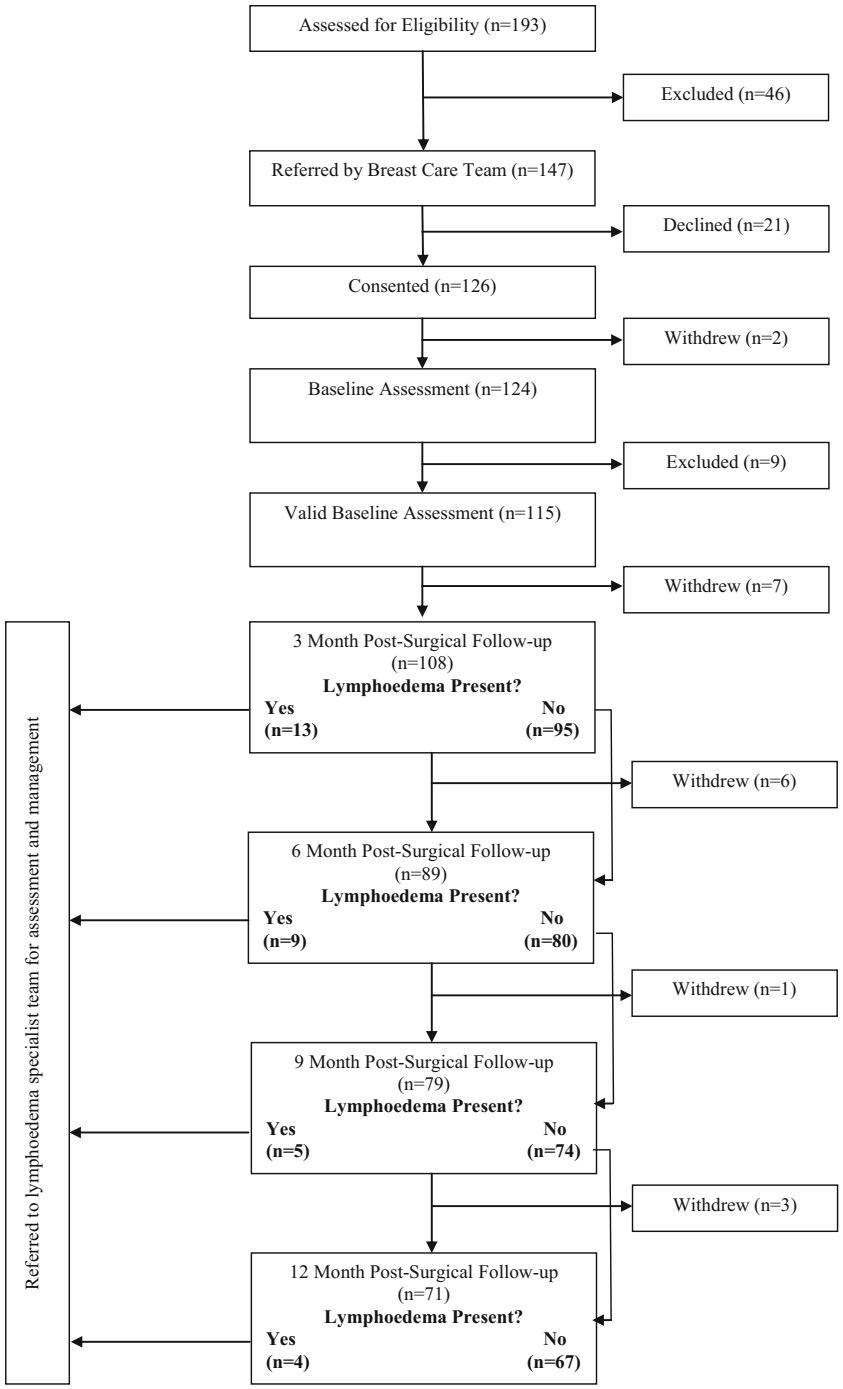

Fig. 1 Participants' flow through the study

Data collection and outcome measures

Baseline assessments were conducted prior to surgery and repeated 3, 6, 9 and 12 months later. All assessments were carried out by the same individual (JB) and included upper limb CM and BIA. BMI, subjective BCRL symptoms and risk factors were also assessed (including, BP/venipuncture taken on ipsilateral arm, cording, decreased range of movement). Demographic, medical and treatment information was collected using an investigator-developed questionnaire and participants' medical records. Assessments lasted approximately 25–30 min.

CM of the ipsilateral (surgical) and contralateral arms were measured using a retractable, flexible tape measure (cm). Distance from the nail bed of the middle finger to the midposition of the radial and ulnar bones was measured in zero

degrees flexion. This was the starting position of the first arm measurement and then sequentially every 4 cm to the approximate level of the axilla. Proximal, distal and total volume differences (ml and %) were computed (ipsilateral arm vs. contralateral) using LymCalc™ (Haddenham Healthcare Ltd, UK). A ≥5 % increase in participants' proximal, distal or total percentage volume difference (PVD) from baseline was indicative of lymphoedema [29]. This ≥5 % PVD relates to absolute volume difference as a percentage of the ipsilateral arm (at-risk arm) versus the contralateral arm (not at-risk arm).

BIA was conducted using ImpediMed XCA® (ImpediMed, Brisbane, Australia) single frequency (<30 kHz) bioimpedance analyser. An L-Dex score of >10 or a 10 U increase from baseline was indicative of lymphoedema [30]. Manufacturer guidelines were adhered to for patient preparation and positioning of single-tab electrodes. Two electrodes were placed on each arm, one on the dorsum of the wrist at the level of the radial and ulnar bones and a second 5 cm distally (midline to midline of electrode tabs). The final electrode placement was on the dorsum of the right foot, 1 cm from the base of the third metatarsal.

Any participants identified by PVD or BIA cut-offs were referred to their local physiotherapy lymphoedema service for assessment and management.

Statistical analysis

Feasibility was measured by recruitment, uptake and retention. McNemar's test examined the percentage of participants identified as having lymphoedema by CM and BIA. Partial correlation was used to explore the relationship between BIA and PVD, controlling for BMI and age. Independent samples *t* tests (or non-parametric equivalent) examined continuous data differences between participants identified as having lymphoedema and those who were not. Categorical data was analysed using chi-square. Statistical significance was set at $p=\leq 0.05$ level. Data was analysed using SPSS, version 18 (Chicago, IL, USA).

Results

Recruitment, attrition and participants

One hundred ninety-three patients were screened for eligibility (Table 1). One hundred forty-seven (76.2 %) met the criteria and 126 (85.7 %) patients consented. Nine (7.1 %) participants' data were excluded from analysis as it emerged post-baseline assessment that $n=4$ had stage IV disease, $n=2$ had ductal carcinoma in situ, $n=1$ reported pre-operative upper limb swelling and $n=2$ were identified as having lymphoedema external to the screening programme. Attrition was 16.2 % ($n=19$; Table 1): 10.5 % withdrew prior to undertaking baseline assessment, 36.8 % before 3-month follow-up (MFU), 31.6 % before 6 MFU, 5.3 % before 9 MFU and 15.8 % prior to 12 MFU. No significant differences existed between those who were retained and withdrew in relation to age, BMI, cancer stage, socioeconomic status or distance from home to hospital.

Table 2 describes participant characteristics and treatment received. Mean age at baseline was 59.2 years (±12.8, range 30–89) and 33 % were classed as overweight and 30.7 % obese (World Health Organisation Classification). 87.4 % had infiltrating ductal carcinoma, 34.8 % had a mastectomy and 58.8 % sentinel lymph node dissection (SLND). The median number of lymph nodes dissected within the total cohort was 5 (interquartile range (IQR) 13; range 1–38). 78.2 % had radiotherapy, 39.1 % had chemotherapy and 33.3 % were treated with both chemotherapy and radiotherapy.

Baseline percentage volume difference and L-Dex scores

The mean total PVD was 0.24 % (±4.3 %), distal PVD was −0.13 % (±4.7 %) and proximal PVD was 0.52 % (±5.0 %). Categorically, 11.3 % of participants had a total PVD ranging between −9.9 and −5.0 % and 40.9 % between −4.9 and 0 %; 31.3 % that fell in to the category of 0.1 to 4.9 % and 16.5 % were between 5.0 and 9.9 % at baseline. The mean baseline L-Dex score was 0.1 (±4.0). 7.8 % of participants' L-Dex scores were between −9.9 and −5.0 U, 44.3 % between −4.9 and 0 U, 34.2 % between 0.1 and 4.9 U and 13.7 % between 5.0 and 9.9 U.

Lymphoedema

During the study, 31.6 % ($n=31/98$) of participants who were screened over a 12-month period were identified as having lymphoedema based on CM or BIA (Table 3). Incidence rates based on CM were 28.6 and 11.2 % based on BIA. Median time from surgery to BCRL identification was 22 weeks (IQR 24; range 10–55 weeks), with the majority being identified at 3 MFU (41.9 %) and 6 MFU (29.0 %). 90.3 % of participants were identified by CM, 35.5 % by BIA ($p=\leq 0.0001$). There was agreement between the two measures in 25.8 % of cases.

In 50.0 %, only the proximal segment of the ipsilateral arm was affected and for 28.5 %, only the distal segment (Table 3). A ≥5 % difference in both distal and proximal segments only affected 21.4 % of participants. Table 3 also details the average L-Dex difference from baseline (DFB) score and distal, proximal and total PVDs from baseline across all time points. As before and with the exception of 9 MFU, there is a general trend towards proximal PVD being greater than distal.

Just over one third ($n=11$) of the participants identified as having lymphoedema reported subjective symptoms. There were no significant differences in distal (4.4, 4.4; $p=0.97$),

Table 2 Baseline participant characteristics and treatment received

Participant characteristics (n=115)	Statistics
Age[a]	59.2 (12.8; range 30–89)
Weight (kg)[b] (n=114)	70.4 (17.1; range 46.3–169.1)
BMI[b] (n=114)	26.7 (6.9; range 17.8–64.8)
BMI category[c] (n=114)	
Underweight	2 (1.8 %)
Normal range	39 (34.2 %)
Overweight	38 (33.3 %)
Obese class I	21 (18.4 %)
Obese class II	9 (7.9 %)
Obese class III	5 (4.4 %)
Socioeconomic status (deprivation based on postcode)[c]	
Quintile 5 (most deprived)	25 (21.7 %)
Quintile 4	23 (20.0 %)
Quintile 3	17 (14.8 %)
Quintile 2	21 (18.3 %)
Quintile 1 (least deprived)	29 (25.2 %)
Occupation status[c]	
Retired	55 (47.8 %)
Sick leave	24 (20.9 %)
Housewife/unemployed	16 (13.9 %)
Part time	10 (8.7 %)
Full time	10 (8.7 %)
Dominant limb at risk[c]	52 (45.2 %)
Tumour type[c] (n=111)	
Infiltrating ductal carcinoma	97 (87.4 %)
Infiltrating lobular carcinoma	12 (10.8 %)
Mixed ductal/lobular carcinoma	2 (1.8 %)
Tumour stage[c] (n=108)	
I	69 (63.9 %)
II	35 (32.4 %)
III	4 (3.7 %)
Tumour grade[c] (n=112)	
I	14 (12.5 %)
II	50 (44.6 %)
III	48 (42.9 %)
Baseline assessment to surgery (days)[b] (n=114)	9 (11.0)
Total number of breast surgeries[c]	
1	100 (87.0 %)
2	11 (9.6 %)
3	4 (3.5 %)
Final surgery[c]	
Mastectomy	40 (34.8 %)
Breast conserving surgery	73 (63.5 %)
Prophylactic bilateral mastectomy	2 (1.7 %)
Axillary lymph node surgery[c] (n=114)	
SLND only	67 (58.8 %)
ALND only	27 (23.7 %)
SLND and ALND	20 (17.5 %)
Average number of nodes removed[b] (n=114)	
SLND	3 (2; range 1–16)
ALND[a]	15 (7; range 3–34)
Total	5 (13; range 1–38)
Number of lymph nodes positive[b]	
SLND	0
ALND	1 (3)
Total	1 (2)
Radiotherapy[c]	90 (78.2 %)
Breast site (%)	79 (87.8 %)
Breast and supraclavicular fossa	11 (12.2 %)
Radiotherapy dose[c]	
50 Gy	20 (22.2 %)
40 Gy	69 (76.7 %)
42.57 Gy	1 (1.1 %)
Radiotherapy boost	34 (37.8 %)
Boost dose	
16 Gy	1 (2.9 %)
10 Gy	18 (53.0 %)
9 Gy	15 (44.1 %)
Chemotherapy	45 (39.1 %)
Taxane	22 (48.9 %)
Chemotherapy cycles (n=45)	
6	41 (91.1 %)
5	1 (2.2 %)
4	1 (2.2 %)
3	1 (2.2 %)
2	1 (2.2 %)
Radiotherapy and chemotherapy (n=111)	37 (33.3 %)
Hormone therapy (n=110)	95 (86.4 %)

[a] Mean (SD)

[b] Median (IQR)

[c] Frequency (%)

proximal (6.8, 5.0; p=0.31) or total (5.8, 4.8; p=0.39) PVD in those who reported subjective symptoms and those who did not. This was similar of L-Dex DFB scores (12.7, 16.1; p=0.29).

Table 4 details the partial correlation analysis between distal, proximal, total PVD and L-Dex DFB scores across time points and for the total cohort. Analysis demonstrates that there is a lack of consistency regarding the relationship between BIA and PVD, with a mixture of positive and negative r-values. These were not statistically significant.

At 3 MFU (Table 5), those identified as having lymphoedema had a significantly higher BMI (32.7, 25.9;

Table 3 Breast cancer-related lymphoedema incidence as defined by circumferential measurements (PVD) and bioimpedance analysis (L-Dex score)

Method/measurements	3 MFU (n=13)	6 MFU (n=9)	9 MFU (n=5)	12 MFU (n=4)	Total (n=31)
Identified by CM	12 (92.3 %)	8 (88.9 %)	5 (100.0 %)	3 (75.0 %)	28 (90.3 %)
Identified by BIA	7 (53.8 %)	2 (22.2 %)	1 (20.0 %)	1 (25.0 %)	11 (35.5 %)
Agreement	6 (46.2 %)	1 (11.1 %)	1 (20.0 %)	0	8 (25.8 %)
Average PVD from baseline	(n=12)	(n=8)	(n=5)	(n=3)	(n=28)
Distal PVD	4.8 (4.5)[a]	3.8 (2.1)[a]	7.5 (4.5)[a]	2.8 (3.3)[a]	4.3 (4.0)[b]
Proximal PVD	8.3 (4.1)[a]	4.8 (2.2)[a]	9.2 (7.2)[a]	7.2 (0.3)[a]	6.8 (4.9)[b]
Total PVD	6.9 (3.0)[a]	4.3 (1.2)[a]	8.3 (5.7)[a]	5.4 (1.3)[a]	5.1 (2.9)[b]
PVD category	(n=12)	(n=8)	(n=5)	(n=3)	(n=28)
≥5 % Distal PVD only	2 (16.7 %)	3 (37.5 %)	3 (60.0 %)	0	8 (28.5 %)
≥5 % Proximal PVD only	6 (50.0 %)	4 (50.0 %)	2 (40.0 %)	2 (66.7 %)	14 (50.0 %)
≥5 % Both distal and proximal PVD	4 (33.3 %)	1 (12.5 %)	0	1 (33.3 %)	6 (21.4 %)
≥5 % Total PVD	8 (66.7 %)	5 (62.5 %)	2 (40.0 %)	1 (33.3 %)	16 (57.1 %)
Average L-Dex difference from baseline					
	(n=13)	(n=9)	(n=5)	(n=4)	(n=31)
L-Dex	8.1 (8.7)[a]	4.7 (4.8)[a]	4.2 (5.2)[a]	5.1 (7.3)[a]	3.8 (11.8)[b]

PVD percentage volume difference, *MFU* month follow-up, *CM* circumferential measurements, *BIA* bioimpedance analysis

[a] Mean (SD)

[b] Median (IQR)

p=0.004), and a significantly higher proportion reported an injury to their surgical arm (15.4 %, 1.1 %; p=0.04). These findings however were not apparent across time; in fact, there were no significant differences found between groups at 6 MFU or at 9 MFU. At 12 MFU, a significantly higher percentage of participants in the BCRL group had either axillary lymph node dissection (ALND; 50.0 % vs. 22.4 %) or both SLND followed by ALND (50.0 vs. 11.9 %; p=0.02) and had significantly more lymph nodes removed (n=18 vs. n=4; p=0.02).

PICC line

Coincidentally during follow-up assessments, we noted that on average, participants who had a peripherally inserted central catheter (PICC) line in situ had significantly lower BIA DFB scores than those who did not. That is, their 'at-risk' arm had decreased in terms of extracellular fluid compared to the contralateral/PICC arm. At 3 MFU, median BIA DFB scores for those with a PICC (n=27) were −1.40 (IQR 3.6) compared

Table 4 Partial correlation of percentage volume difference and L-Dex difference from baseline

Method/measurements	3 MFU (n=13)		6 MFU (n=9)		9 MFU (n=5)		12 MFU (n=4)		Total (n=31)	
Correlation CM and L-Dex DFB	r	p	r	p	r	p	r	p	r	p
Distal PVD and L-Dex DFB										
Age	0.27	0.40	0.50	0.21	−0.44	0.56	−0.95	0.20	0.13	0.48
BMI	0.17	0.59	0.57	0.14	−0.63	0.37	−0.68	0.52	0.06	0.75
Proximal PVD and L-Dex DFB										
Age	−0.18	0.57	−0.34	0.42	0.65	0.35	−0.97	0.16	−0.01	0.97
BMI	−0.17	0.60	−0.32	0.44	0.17	0.83	−0.69	0.51	−0.08	0.69
Total PVD and L-Dex DFB										
Age	−0.1	0.97	0.09	0.84	0.46	0.54	−0.94	0.22	0.04	0.85
BMI	−0.3	0.92	0.05	0.92	−0.12	0.87	−0.85	0.36	−0.05	0.80

PVD percentage volume difference, *MFU* month follow-up, *CM* circumferential measurements, *DFB* difference from baseline

Table 5 Comparisons of participants identified as having lymphoedema versus no lymphoedema across time points

Variable	Lymphoedema at 3 MFU			Lymphoedema at 6 MFU			Lymphoedema at 9 MFU			Lymphoedema at 12 MFU		
	Yes (n=13)	No (n=95)	p	Yes (n=9)	No (n=80)	p	Yes (n=5)	No (n=74)	p	Yes (n=4)	No (n=67)	p
Age	65.2 (16.3)	58.6 (12.2)	0.08[a]	58.1 (9.3)	59.1 (13.0)	0.83[a]	59.8 (14.8)	59.5 (12.9)	0.96[a]	51.8 (21.4)	60.2 (12.4)	0.21[a]
BMI	32.7 (5.8)	25.9 (5.82)	0.004[b]	25.5 (3.2)	25.9 (7.50	0.78[b]	26.5 (12.9)	25.9 (5.9)	0.41[b]	25.1 (10.0)	25.3 (6.8)	0.73[b]
Mastectomy	38.5 %	32.6 %	0.92[c]	44.4 %	28.8 %	0.56[c]	40.0 %	28.4 %	0.97[c]	50.0 %	28.4 %	0.72[c]
LND category			0.18[c]			0.80[c]			0.61			0.02[c]
SLND	38.5 %	62.1 %		55.6 %	61.3 %		40.0 %	62.2 %		0	65.7 %	
ALND	30.8 %	24.2 %		22.2 %	25.0 %		40.0 %	24.3 %		50.0 %	22.4 %	
SLND and ALND	30.8 %	13.7 %		22.2 %	13.8 %		20.0 %	13.5 %		50.0 %	11.9 %	
Total lymph nodes dissected	7 (14)	4 (12)	0.31[b]	4 (20)	5 (12)	0.96[b]	5 (9)	5 (13)	0.71[c]	18 (11)	4 (10)	0.02[b]
Chemotherapy	38.5 %	40.0 %	1.0[c]	33.3 %	42.5 %	0.86[c]	40.0 %	41.9 %	1.0[c]	75.0 %	41.8 %	0.43
Taxane	40.0 %	50.0 %	1.0[c]	100.0 %	47.1 %	0.25[c]	50.0 %	48.4 %	1.0[c]	100.0 %	42.9 %	0.20[c]
Radiotherapy	69.2 %	84.0 %	0.35[c]	77.8 %	87.5 %	0.77[c]	60.0 %	89.2 %	0.23[c]	100.0 %	88.1 %	1.0[c]
Boost	66.7 %	35.4 %	0.14[c]	42.9 %	34.3 %	0.97[c]	66.7 %	31.8 %	0.53[c]	0	32.2 %	0.43[c]
Staging			0.55[c]			0.57[c]			0.26[c]			0.07[c]
I	54.5 %	64.1 %		55.6 %	66.7 %		40.0 %	69.4 %		75.0 %	69.2 %	
II	45.5 %	31.5 %		33.3 %	29.5 %		60.0 %	26.4 %		0	27.7 %	
III	–	4.3 %		11.1 %	3.8 %		0	4.2 %		25.0 %	3.1 %	
Venipuncture	23.1 %	6.3 %	0.13[c]	0	3.8 %	1.0[c]	0	2.7 %	1.0[c]	0	3.0 %	1.0[c]
BP on at-risk arm	7.7 %	5.3 %	1.0[c]	22.2 %	12.5 %	0.77[c]	0	1.4 %	1.0[c]	0	3.0 %	1.0[c]
Seroma	53.8 %	40.0 %	0.52[c]	22.2 %	6.3 %	0.30[c]	0	4.1 %	1.0[c]	0	1.5 %	1.0[c]
Infection	15.4 %	9.5 %	0.86[c]	11.1 %	5.0 %	1.0[c]	0	4.1 %	1.0[c]	0	1.5 %	1.0[c]
Axillary web syndrome	38.5 %	21.1 %	0.30[c]	0	12.5 %	0.57[c]	0	2.7 %	1.0[c]	0	0	–
Reduced range of movement	53.8 %	26.3 %	0.09[c]	33.3 %	8.8 %	0.10[c]	0	5.4 %	1.00[c]	0	4.5 %	1.0[c]
Injury to at-risk arm	15.4 %	1.1 %	0.04[c]	0	1.3 %	1.00[c]	0	8.1 %	1.00[c]	0	9.0 %	1.0[c]

MFU month follow-up, *BMI* body mass index, *LND* lymph node dissection, *SLND* sentinel lymph node dissection, *ALND* axillary lymph node dissection

[a] Independent samples t test

[b] Mann-Whitney U Test

[c] Chi-square analysis

with 1.00 (IQR 4.2) for those without (p=<0.0001). These findings were not significant at 6, 9 or 12 MFU; however, sample sizes were very small (n=7, n=3, n=3, respectively) as most PICC lines were redundant post-chemotherapy. There were no significant differences in PVD between these groups.

Follow-up

Any of the participants that reached the CM or BIA cut-offs at any of the assessment time points (3, 6, 9 or 12 months) were referred to the specialist lymphoedema team for further assessment and management. Over the course of the study, a total of 31 participants were identified by either CM or BIA and referred on. Several of these lymphoedema therapists brought it to the research teams' attention that some patients, when re-assessed, were below cut-offs or near baseline measurements. As a result, we were able to obtain follow-up information for 27 of the 31 participants that were referred. The mean time from referral to being assessed by a lymphoedema specialist was 4.8 weeks (±20.1). At their first lymphoedema assessment, 14/27 (51.8 %) patients' measurements had returned to approximate baseline/below cut-off. These patients were monitored by the lymphoedema team. We were able to further follow up on 10/14 patients and at their 6-month review with the lymphoedema team. Six of these patients

continued to have no evidence of lymphoedema, three had been treated for lymphoedema and one patient declined follow-up assessment.

Discussion

To our knowledge, this was the first prospective BCRL screening programme to examine feasibility within a clinical setting. We also investigated the efficacy of single frequency BIA (10-U increase from baseline values or outside the normal range of +10U) compared to CM (≥5 % volume increase from baseline) in identifying early BCRL and factors associated with lymphoedema development.

High recruitment (85.7 %) and retention (83.8 %) rates indicate that breast cancer survivors are interested and value such a programme. Common reasons for declining or withdrawing from the study were related to time and travel. We aimed to accommodate participants with convenient follow-up assessments, and this is perhaps one reason that a high retention rate was achieved. It further highlights that screening programmes could be incorporated within patient pathways. Programmes introduced as part of routine care can increase acceptance among breast cancer survivors [31].

It is difficult to evaluate our uptake and attrition as similar studies have often failed to report these [27, 28]. However, Kilbreath and colleagues [32] utilised BCRL screening as part of the design of their intervention RCT and reported retention rates of 88 %. A prospective observational study [7] reported recruitment and retention rates of 85.1 and 74.9 %, respectively. Based on these figures, our study compares favourably. In terms of eligibility, 23.8 % of those screened were excluded. These exclusions may not all be valid in clinical practice, and thus, more patients could benefit from screening. This notwithstanding, due to safety issues, BIA cannot be used in patients with a cardiac device or metal implant and, due to fluid fluctuations, may not be reliable in patients with renal or heart failure and pregnant women.

Participants' baseline volume measurements (total PVD −0.3 %, IQR 5.4 %, range −9.7 % to 9.9 %) and L-Dex scores (0, IQR 5.1, range −9.7 to 9.9) were diverse and reiterate the importance of pre-surgical quantification of inter-limb variance in achieving an accurate and early diagnosis of BCRL [28, 32]. Few participants in our study had zero PVD between arms or indeed BIA score at baseline. Thus, using our PVD and BIA cut-offs without baseline comparisons would risk a large percentage of participants being undiagnosed or misdiagnosed, both of which could have significant implications on quality of life and psychological well-being. However, it is uncertain as to whether or not it is possible to obtain true baseline values. Physiologically, it is conceivable that metastatic spread to the axillary lymph nodes could disrupt lymphatic drainage prior to surgery. Our findings suggest that this is feasible as 16.5 % of participants had a total PVD of between 5 and 10 % at baseline and 13.7 % had L-Dex scores between 5 and 10 U. While further exploration is warranted, two recent studies indicate that pre-surgical inter-limb differences are mainly related to limb dominance and not that of cancer side or level of nodal involvement [32, 33].

Overall, BCRL incidence was 31.6 %, with just over one third reporting subjective symptoms. Based on PVD, incidence rates were 28.6 and 11 % for BIA. Studies using similar PVD cut-offs have reported incidence rates of 20.7–67.7 % [7, 34]. In terms of BIA, rates have ranged from 33 to 40 % [8, 26]. A systematic review and meta-analysis detailed the huge variation by study design, measurement method, surgery and study location [10]. The authors report an incidence rate of 21.4 % from prospective cohort studies and incidence rates of 15.9 % for those diagnosed by BIA and 14.8 % for those identified by CM.

We considered both segmental and total PVD in assessing lymphoedema which may explain our higher incidence rate. Our findings demonstrate that BCRL can be present in isolation in distal or proximal segments which may not be identified if only calculating total PVD. Stout et al. [35] echo our findings and acknowledge that using total PVD may not be sufficiently sensitive for screening purposes. Likewise, lymphoscintigraphy has demonstrated that drainage pathways do not run in a direct, progressive manner and that segmental variations exist [36]. Future studies and clinicians should consider these findings.

In our study, of the 28 participants that were identified with PVD, 8 (28.6 %) of these patients were also identified by BIA. Similarly, other studies report varying degrees of detection. Hayes et al. [37] found that of the cases identified by BIA, only 35 % were detected using CM. Similar findings were reported in a later study [8]. These studies however did not obtain baseline measures, which, as previously outlined, is imperative for an accurate diagnosis [9, 28]. Box et al. [26] found BIA to have a 67 % detection rate compared to limb volume difference. In terms of advocating one measurement technique over another, our findings should be considered with care, as our study did not take into account upper limb dominance. We recognise this as a limitation of our study when comparing the two measurement techniques for BCRL screening, especially as BIA does account for dominance.

Our findings further show that distal, proximal and total PVD are not significantly correlated with BIA. Fu and colleagues [38] did find that BIA and CM were correlated, but the authors did not control for BMI or age, even though they report that L-Dex scores showed positive trends with BMI. Within their study, the authors acknowledge that there is no existing data to support the sensitivity and specificity of BIA using an L-Dex score of greater than +10 as a diagnostic cut-

off point, and this criterion misses 34 % of true BCRL cases [38]. However, while lowering the L-Dex cut-off to greater than +7.1 (approx impedance ratio of 1.108 or a cut-off point approximately equivalent to the mean +2 SD), BIA was able to identify 80 % of true lymphoedema cases but still produced false negatives for 20 %. It should however be highlighted that this cross-sectional study compared healthy females, cancer survivors at risk of BCRL and those diagnosed with BCRL; thus, no baseline data was available for each group which is a major limitation of their findings. Additionally, the BCRL cohort was only eligible if treated for lymphoedema at least 6 months prior to enrolment. It is recognised that BIA may not be suitable for assessing established lymphoedema due to the changes that can occur within the tissues [38]. Furthermore, the authors compare BIA with CM as the reference/gold standard. As with our study, it should be highlighted that a gold standard approach for BCRL identification and screening has yet to reach consensus. Additional research is highly warranted to explore the discrepancies outlined in our study and those by Fu et al. [38] to establish the best screening tool, measurement protocol and CM and BIA cut-offs that are reliable for early-stage detection and screening. Future studies should also explore the impact PICC line insertions in the contra-lateral arm may have on the BIA results and thus establish if our findings are noteworthy. PICC line insertions can cause phlebitis and inflammation within the tissues [39] and could explain the high percentage of cases that went undetected by BIA.

Our sample size was not large enough across time points to enable a regression analysis of BCRL risk factors. However, patients with lymphoedema had significantly higher BMI; higher proportions had a recent injury to the ipsilateral arm and more lymph nodes excised. Although these findings were not consistent across time points, they have been reported elsewhere. A meta-analysis of treatment-related risk factors found that ALND significantly increases patients' risk of developing BCRL [40]. Like us, many studies have reported high BMI/obesity as a BCRL risk factor [6, 10, 38, 41–43].

We were able to follow-up on 27 participants who were identified as having BRCL and referred on from our study to a specialist lymphoedema service. Just over half (n=14) of these patients had returned to approximate baseline measurements or below cut-offs when assessed by a lymphoedema therapist. Information was available for ten of these patients at their 6-month specialist review, and six continued to have no evidence of lymphoedema. It is reported that the majority of BCRL cases present within the first year [7, 8]; however, our findings suggest that a large proportion of these may be transient. Kilbreath and colleagues [32] conducted a secondary analysis of an intervention RCT whereby patients at risk of lymphoedema were randomised into an exercise programme or a control. They found that 15 participants had elevated extracellular fluid at 3 MFU, but only 8 remained elevated at 9 MFU and only 4 at 15 MFU. Similarly, a longitudinal study by Hayes et al. [8] found that 58 % had transitory lymphoedema, while other research found 23 % to experience mild lymphoedema that was transient in nature [44]. In all three studies, percentages of participants had received an intervention, and in two, participants did not have pre-surgical measurements [8, 44]. Considering the methodological issues in the aforementioned studies and as we were not able to follow up on all participants and over a longer period of time, further research is warranted to investigate the nature of lymphoedema in the first-year post-surgery and establish the incidence of true lymphoedema cases.

Although BCRL is defined as a chronic, progressive condition, our results and that of existing evidence [8, 32, 44] demonstrate that for some, oedema within the first-year post-surgery may be temporary and fluctuate as part of the natural treatment process. Taxane-based chemotherapy has been documented to cause generalised swelling [28]. These findings thus contest our thinking and further complicate BCRL screening, diagnosis and treatment. Giving a patient a diagnosis of BCRL is not to be taken without due consideration as the diagnosis itself and the subsequent management can impact greatly on quality of life and cause psychological distress [5, 6, 45]. Nonetheless, a delayed diagnosis could have a more significant bearing on overall quality of life, and treatment outcome as lymphoedema that has progressed beyond an early stage can often require more intensive management. Again, the best approach has yet to be established.

Conclusion

A screening programme is acceptable by breast cancer patients within the first-year post-surgery. However, we are still some way from fully understanding the natural behaviour of BCRL within this timeframe and how this should be managed as well as definitive risk factors. As it stands, we are yet to agree a definition of what constitutes early-stage lymphoedema as well as the best screening tool. Ours was a feasibility study with relatively small numbers, and dominance was not accounted for using CM. Larger well-designed research methodologies are required to explore this further. Addressing these issues will significantly progress our knowledge, clinical diagnosis and treatment of BCRL.

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Conflict of interest The authors declare that they have no conflict of interest and confirm that they have control of all primary data and agree to allow the journal to review the data if requested.

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