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LETTER TO THE EDITOR

Prospective surveillance for breast cancer-related lymphedema (PROTECT)

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Background

Breast cancer-related lymphedema (BCRL) is a progressive condition caused by damage to the lymphatic system [1] and affects one in three patients following axillary lymph node dissection [2]. The early phase of BCRL involves accumulation of extracellular fluid without fibrosis (subclinical), that later progress to irreversible intradermal fibrosis (chronic)[3]. Risk factors for BCRL include obesity and body weight gain [4,5]. It can be associated with feeling of heaviness, inferior quality of life and emotional distress [6] and when chronic require continuous treatment with compression garments [7–9]. Clinical guidelines [10–14] recognize the importance of early detection and management of BCRL to allow simpler treatment and better clinical outcomes and highlight the need for research into development and testing of programs that enable surveillance of survivors at-risk [13–15]. However, in Denmark there is no national streamlined approach for measurement and management of BCRL likely due to paucity of research evidence into effective, scalable, and accessible surveillance programs.

Prospective surveillance and early management (PS) programs are suggested to improve early detection and treatment of BCRL and prevent progression of the condition [16]. Such programs include pre-surgery and ongoing post-surgery assessments to detect BCRL and if detected, to provide early treatment [17,18]. Two small trials (total $n = 106$) suggest a preventative effect of PS programs versus usual care (relative risk 0.31; 95%CI 0.10 to 0.95) [16] and a larger trial suggest that PS using bioimpedance spectroscopy (BIS) is ideal to allow early detection of BCRL [19], however, robust controlled trials are needed to confirm the effect [16].

To date, all research has focused on PS programs delivered as hospital-based surveillance afforded by therapists. However, such programs risk increasing the inequity of health among survivors. It is therefore important to ensure that patients with a wide representation of education levels, income, living arrangements and comorbidity can access and participate in PS programs. Furthermore, the main barriers for implementing this approach in publicly funded healthcare are access to trained healthcare professionals, access to sophisticated measurement tools to identify BCRL, and the associated cost of long-term surveillance for a large at-risk population. These barriers highlight the need to consider other delivery strategies, such as a self-management approach, to increase the reach and equity of access to surveillance programs.

To improve reach and lower the costs of PS programs, we developed self-management BCRL surveillance resources [20], demonstrated them to be feasible and acceptable to include in hospital-based programs [21] and able to support survivors in performing measurements of own arm circumference at home in a reliable and valid manner [20,21]. These resources include a brief video to allow people to learn to perform self-measurements of arm circumference along with an inexpensive tape measure that allows for hand-free measurements.

This trial examines if a self-managed PS program reduce the prevalence of chronic BCRL compared to usual care. The purpose of this manuscript is two-fold, namely, to report: a) the trial protocol; and b) preliminary feasibility data.

Methods

Design

This is a multicenter single-blind randomized controlled trial with a parallel cohort of patients with breast cancer comparing the outcomes of prospective surveillance (PS) versus

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usual care (UC) and low-risk (LR) cohort at 24-months after surgery for breast cancer (Figure 1, Supplementary file 1 and 2).

Recruitment

Patients with planned surgery for breast cancer at five University Hospitals in Denmark, are informed about the study at the time of diagnosis by the nurses and receive written information. Study staff (nurses or physical therapists) then contact patients, who are interested in participating and provide detailed information, screen for eligibility, and book a pre-surgery baseline visit. Strategies to ensure adequate recruitment include monthly updates to recruiting breast surgery departments along with financial compensation for the time spent with recruitment.

Eligibility criteria

1) ≥18 years; 2) planned surgery for breast cancer; 3) understands Danish. Exclusion criteria: 1) previous surgery for breast cancer; 2) preexisting lymphedema; 3) pacemaker; 4) pregnancy; 5) conditions known to cause swelling (i.e. thrombosis in the arms).

Allocation

Following surgery, participants with ≥6 axillary lymph nodes removed are randomized 1:1 to PS or UC *via* computer-based randomization using variable block sizes and stratified by hospital. Participants with <6 lymph nodes removed are ineligible for randomization and allocated to a LR cohort. Study staff contact all participants by telephone, perform the randomization, and inform about allocation.

Intervention

PS participants perform prospective surveillance and receive early intervention, if BCRL is detected. Participants receive a package including a video of how to perform measurements of own arm circumference and tools for self-measurement. Participants perform self-measurements at five points along

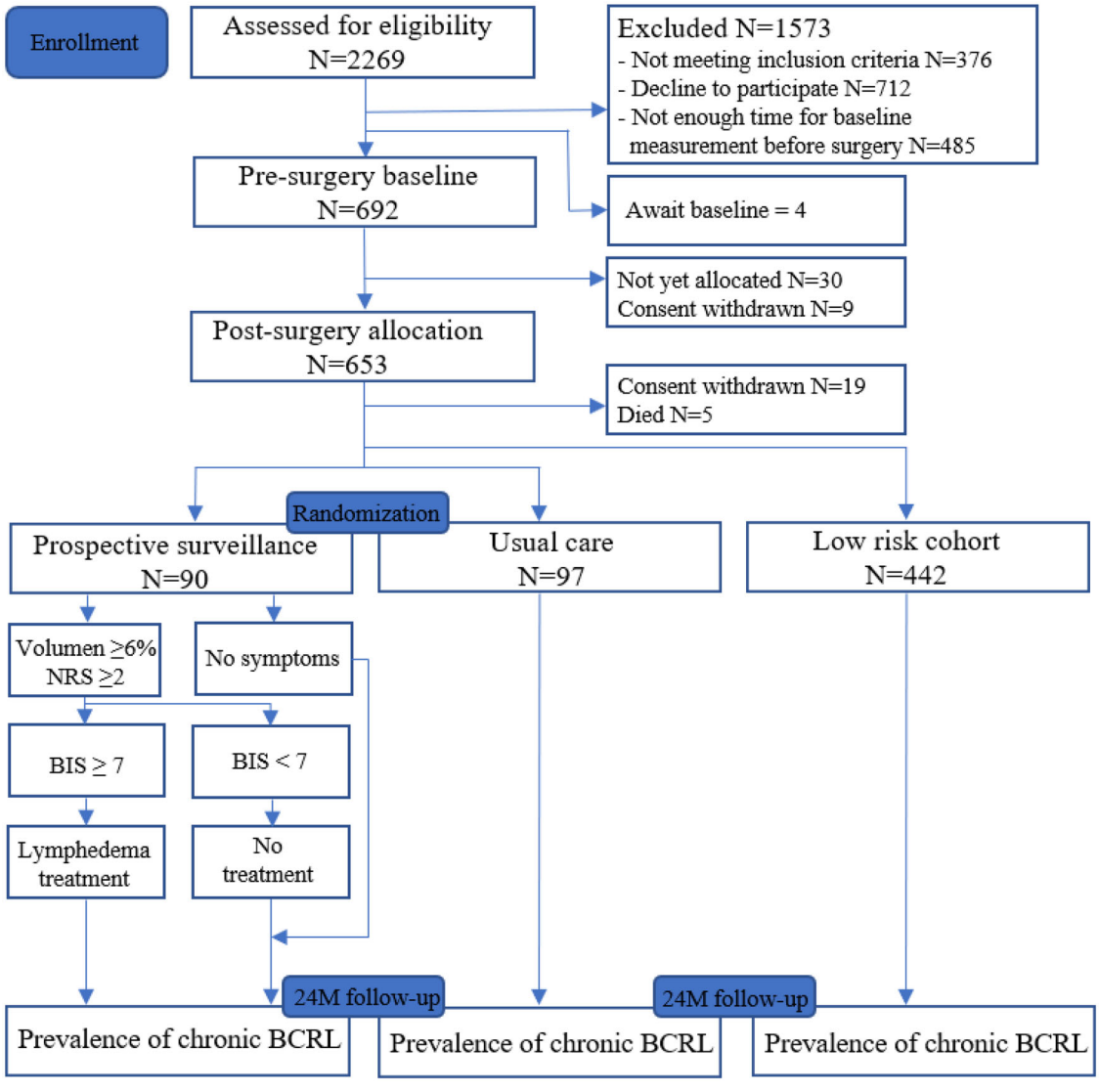

Figure 1. Flow chart.

the arm at home every three months (Supplementary file 3) and report these along with sign and symptoms of BCRL (heaviness, tightness, and swelling reported on the 0–10 Numeric Rating Scale (NRS)).

A participant with an increase from pre-surgery in arm volume of ≥6% by self-measurement, which is the minimal detectable change[21], or symptoms of BCRL ≥2 NRS [22], is seen for a BIS measurement at the hospital of surgery. A participant is considered having subclinical BCRL, if an increase in lymphedema index (L-DEX) ≥7 from pre-surgery measured by BIS is identified [23,24]. The participant is then referred to a lymphedema therapist at the hospital and provided an off-the-shelf compression sleeve and glove, if hand swelling is present (ccl2 flat knit or circular knit) to be worn 10 h/day for four weeks along with a recommendation to use the arm for daily activities and maintain regular physical activity [14]. Following the four-week compression period, participants are re-measured using BIS to evaluate response. Participants with resolved BCRL discontinue wearing daily compression, continue the 3-months surveillance program, and may be re-referred if needed. Adherence to wearing compression along with adverse events are tracked. Participants who do not respond to off-the-shelf compression receive complex decongestive therapy (CDT).

Participants who are unable to perform self-measurement can have help from a spouse or family member or are offered hospital-based BIS measurements every three months for the duration of the study. We hypothesize that 80% will be able to perform self-measurement[21].

UC and LR cohort

These participants will not receive prospective surveillance. The UC and LR participants will follow the usual post-operative care including follow-up with the surgeon, municipality-based rehabilitation, and referral to hospital-based lymphedema treatment, if BCRL is detected. BCRL treatment usually consists of CDT with bandaging, manual lymph drainage, and fitting of custom-made compression garment.

Sample size

Sample size calculations were targeted to have 80% statistical power in a prospective analysis followed by a log-rank test with 5% significance level. We hypothesize that PS would reduce the prevalence of chronic BCRL by 50% compared to UC [16]. A prevalence of BCRL of 30% in the UC group is anticipated [2], and 15% loss to follow-up. On this basis, 250 randomized participants are needed.

Outcomes

The primary outcome is prevalence of chronic BCRL at 24 months post-surgery. A binary outcome (y/n) defined as BIS ≥10 from pre-surgery or outside normal range ±10[25].

Secondary outcomes are: 1) time-to-treatment. For PS, this will be calculated as the time from surgery to first elevated L-DEX which triggers immediate treatment. For UC and LR, this will be calculated as the time from surgery to BCRL diagnosis, and time from diagnosis to BCRL treatment; 2) health-related quality of life measured by the EuroQol 5-Domaine Questionnaire [26]; 3) arm function measured by the QuickDASH Questionnaire [27].

Explorative outcome are: 1) skeletal muscle mass and fat mass from: a) baseline to post- neoadjuvant chemotherapy (NACT) for participants who receive NACT; and b) baseline to 24 months post-surgery for all participants; and 2) emotional functioning measured by the subscale from the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)[28].

Feasibility outcomes are recruitment rate, attrition, proportion of PS participants who perform self-measurements, and perceived worry about performing self-measurements.

Procedures

All data is collected through electronic data capture (REDCap®). Baseline measurements are completed following written consent at pre-surgery by nurses or physical therapists and include BIS measurements, height, body weight, self-measurements of arm circumference and completion of patient-reported outcomes. Participants who receive NACT are offered an additional assessment post-NACT and prior to surgery with BIS and self-measurements. The PS participants perform self-measurements at 3, 6, 9, 12, 15, 18, 21 months post-surgery [25]. All participants complete questionnaires at 6, 12, 18 and 24 months, and BIS measurement and self-measurement at 24 months (Supplementary file 4). Clinical and treatment variables are obtained from the medical records. Participants who fail to complete the questionnaire receive a reminder and are offered to complete the questionnaire by telephone. The study staff, who perform the end of study measurement, and the statistician will be blinded to group status. The lymphedema therapists and participants are not blinded to allocation due to the nature of the intervention.

Statistical analysis

All participants will be followed from time of inclusion until death or end of follow-up, whichever comes first. The occurrence of BCRL will be treated as the main event of the analysis. Participants who die will be censored out of the analysis, while multiple imputation will be used to obtain data for participants who discontinue the trial prior to final assessment. Cox regression models will be applied to estimate the effect of intervention on the risk of BCRL. As an explorative analysis, we will examine demographic factors (i.e. education) and clinical factors (i.e. BMI, cancer stage and treatment) as effect modifiers of our outcomes.

Ethics

The Capital Region Ethics Board has considered that ethical approval is not required as the trial is categorized a quality improvement project (ID 20055674). The Helsinki Declaration

Table 1. Participant characteristics.

	All $n = 629$	PS $n = 90$	UC $n = 97$	LR Cohort $n = 442$
Age (years), mean (SD)	61.1 (11.2)	60.5 (12.5)	59.7 (13.3)	62 (11.1)
Sex (female), *n* (%)	627 (99.7)	90 (100)	97 (100)	440 (99.5)
Site, *n* (%)				
Aarhus University Hospital	87 (13.8)	12 (13.3)	12 (12.4)	63 (14.3)
Copenhagen University Hospital, Rigshospitalet	150 (23.8)	19 (21.1)	18 (18.6)	113 (25.6)
Herlev/Gentofte Hospital	186 (29.6)	26 (28.9)	29 (29.6)	131 (29.6)
Zealand University Hospital, Roskilde	111 (17.6)	17 (18.9)	18 (18.6)	76 (17.2)
Odense University Hospital	95 (15.1)	16 (17.8)	20 (20.6)	59 (13.3)
BMI, mean (SD)	27.0 (5.5)	27.6 (5.2)	28.2 (6.8)	26.6 (5.2)
Living alone, *n* (%)	173 (28.1)	29 (33.0)	30 (31.9)	114 (26.3)
Missing, *n* (%)	13 (2.1)	2 (2.2)	3 (3.1)	8 (1.8)
Education, *n* (%)				
No education	4 (0.6)	0 (0)	0 (0)	4 (0.9)
Primary school	38 (6.1)	7 (7.9)	5 (5.3)	26 (6.0)
High school	8 (1.3)	1 (1.1)	1 (1.1)	6 (1.4)
Vocational education 2–3 y	220 (35.5)	32 (36.0)	39 (41.0)	149 (34.2)
Undergraduate education 3–4 y	225 (36.3)	32 (36.0)	34 (35.8)	159 (36.5)
Graduate education >4 y	122 (19.7)	16 (18.0)	15 (15.8)	91 (20.9)
Other	3 (0.5)	1 (1.1)	1 (1.1)	1 (0.2)
Missing, *n* (%)	9 (1.4)	1 (1.1)	2 (2.1)	6 (1.4)
Family income yearly, *n* (%)				
100.000–250.000kr	70 (11.9)	17 (20.7)	11 (12.2)	42 (10.1)
250.000–400.000kr	116 (19.7)	15 (18.3)	16 (17.8)	84 (20.1)
400.000–550.000kr	111 (18.8)	11(13.4)	21 (23.3)	79 (18.9)
550.000–700.000kr	84 (14.2)	6 (7.3)	17 (18.9)	61 (14.6)
700.000–850.000kr	55 (9.3)	9 (11.0)	5 (5.6)	41 (9.8)
850.000–1.000.000kr	53 (9.0)	7 (8.5)	4 (4.4)	42 (10.1)
>1.000.000kr	101 (17.1)	17 (20.7)	16 (17.8)	68 (16.3)
Missing, *n* (%)	39 (6.2)	8 (8.9)	7 (7.2)	24 (5.2)
Ethnicity, Danish, *n* (%)	563 (91.5)	76 (92.7)	88 (92.6)	395 (91.4)
Missing, *n* (%)	14 (2.2)	2 (2.2)	2 (2.1)	10 (2.3)
Smoking, *n* (%)	70 (11.3)	8 (9.0)	11 (11.6	51 (11.7)
Missing, *n* (%)	10 (1.6)	1 (1.1)	2 (2.1)	7 (1.6)
Comorbidity, *n* (%)	248 (40.1)	37 (41.6)	44 (46.3)	167 (38.4)
Missing, *n* (%)	10 (1.6)	1 (1.1)	2 (2.1)	7 (1.6)
Thoughts about performing self-measurement for lymphedema				
I am able to measure my arms at home				
Strongly disagree		1 (1.3)		
Disagree		1 (1.3)		
Slightly disagree		1 (1.3)		
Neural		5 (6.3)		
Slightly agree		0 (0.0)		
Agree		23 (28.8)		
Strongly agree		49 (61.3)		
Missing, *n* (%)		10 (11.1)		
I think that measuring my arms at home every 3 months will increase my worry about developing lymphedema				
Not at all		43 (53.8)		
A little		12 (15.0)		
Neutral		17 (21.3)		
Quite a bit		6 (7.5)		
Very much		2 (2.5)		
Missing, *n* (%)		10 (11.1)		

PS: Prospective surveillance and early management group; UC: usual care group; BMI: Body Mass Index; Kr: Danish kroner; y: years; SD: standard deviation.

is followed for all aspects of the study including for data handling and protection of participant rights. The core research team (BSR, CJ, SJ) will have access to the final dataset, and findings will be disseminated as widely as possible.

Results

As of March 21st, 2023, 2269 patients have been screened, and 1893 met the eligibility criteria (Figure 1). Of these, 712 patients declined participation mainly due to lack of energy ($N = 513$), and for 485 patients, there was not time to schedule a baseline assessment before surgery. To date, 692 patients have consented to participate (recruitment rate 37%), and 28 (4%) have withdrawn. To date, 653 have been allocated to PS ($N = 90$), UC ($N = 97$), or LR cohort ($N = 442$). Participants have a wide representation of level of education and income, about 30% live alone, and 40% have comorbidities in addition to breast cancer (Table 1). Among PS participants, six are unable to perform self-measurements and receive hospital-based surveillance, and eight report that self-measurement would increase their worry about developing BCRL quite a bit or very much.

Discussion

PROTECT is the first trial to purposefully deliver prospective surveillance in multiple modes (self-managed or hospital-

based) with the ambition to not increase inequity in access to PS programs. Introducing PS with pre-surgery assessment into Danish University Hospitals seems feasible based on recruitment rate and low attrition. By integrating self-measurement resources, this surveillance program optimizes reach, uptake, and adherence to surveillance. This is illustrated by the wide representation of the sociodemographic characteristics of participants and still 93% of PS participants perform self-measurements every three months, and 91% consider it to not increase their worry about developing BCRL. However, about 700 patients declined participation mainly due to lack of energy. This is a high number yet expected, as patients are informed about the study at the time of diagnosis and thus overwhelmed with the situation, information overload, and decisions around treatment. We speculate that if BIS measurement was part of routine care at the breast surgical departments, patients would not need to decide on participation until two months after surgery and thus fewer would decline participation or be excluded due to lack of time.

With the anticipated growth in the number of patients with breast cancer, development and testing of evidence-based programs is imperative to reduce the high number of patients who develop chronic BCRL. The preliminary data reported here suggest that this program is clinically feasible and accessible for survivors, and thus scalable if documented effective. This may pave the way for reducing the burden of BCRL and improving quality of life for breast cancer survivors.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The preliminary data reported here can be requested from the corresponding author following completion of data sharing agreements.

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