Breast Cancer (2022) 29:437–449
https://doi.org/10.1007/s12282-021-01322-0

ORIGINAL ARTICLE

Quality of life improvement in breast cancer survivors affected by upper limb lymphedema through a novel multiperspective physical activity methodology: a monocentric pilot study

Giuditta Carretti[1] · Daniela Mirandola[1,2] · Francesca Maestrini[2] · Lisa Sequi[2] · Sara Germano[1] · Maria Grazia Muraca[3,4] · Guido Miccinesi[4] · Mirko Manetti[1] · Mirca Marini[1]

Received: 5 October 2021 / Accepted: 5 December 2021 / Published online: 13 January 2022

Abstract

Purpose Chronic lymphedema causes psychophysical sequelae jeopardizing quality of life (QoL) of breast cancer (BC) survivors, and lack of effective therapies represents a major challenge for healthcare professionals. Structured adapted physical activity (APA) may represent an effective strategy to attenuate cancer treatment-related impairments and improve QoL. Here, we describe the effects of a specific APA intervention based on a novel multiperspective methodology in counteracting lymphedema-related morphofunctional alterations and improving QoL of BC survivors.

Methods BC survivors with chronic moderate/severe lymphedema attending the Cancer Rehabilitation Center in Florence were assessed before and after 8-week APA. The protocol consisted of both APA specialist-supervised and self-leaded sessions using a tailor-designed proprioceptive board. Body mass index, bioimpedance parameters, indirect upper limb volume measurement, and ultrasonography were performed. Wrist flexion/extension and hand strength functional tests were also executed. QoL, depression/anxiety and pain intensity were evaluated by ULL27, HADS, distress thermometer and NRS questionnaires, respectively.

Results Although bioimpedance, ultrasound and volumetric measures remained mostly unchanged, wrist mobility, pain perception, depression, and QoL were all significantly ameliorated after APA.

Conclusions Our findings suggest that a multidisciplinary treatment approach involving APA professionals should be employed in the management of BC-related lymphedema to improve patient psychophysical outcomes and QoL.

Keywords Adapted physical activity · Breast cancer survivors · Cancer-related symptoms · Lymphedema · Patient-reported outcomes · Quality of life

Giuditta Carretti and Daniela Mirandola contributed equally to this work.

✉ Mirca Marini
mirca.marini@unifi.it

1 Department of Experimental and Clinical Medicine, Section of Anatomy and Histology, University of Florence, Largo Brambilla 3, 50134 Florence, Italy

2 The Italian League Against Tumors (LILT), 50126 Florence, Italy

3 Oncological Rehabilitation Centre (Ce.Ri.On.), 50139 Florence, Italy

4 Oncological Network, Prevention and Research Institute (ISPRO), 50139 Florence, Italy

Introduction

Breast cancer-related lymphedema (BCRL), which is one of the most dreaded and unfortunate breast cancer (BC) treatment outcomes, with risk proportional to the extent of axillary lymph node dissection and radiotherapy, results from lymphatic system obstruction or disruption [1–5]. BCRL risk estimates after treatment widely vary, with such a chronic condition occurring in up to 40% of BC survivors [6]. However, increasingly conservative surgical and radiotherapeutic approaches have decreased its incidence [7]. Sentinel-node sampling technique has also reduced the risk of BCRL onset [7]. Moreover, patient personal factors, such as obesity or high body mass index (BMI), can increase lymphedema risk, and infections or trauma may also trigger it [5].

BCRL is a chronic progressive syndrome characterized by swelling and multiple symptoms, due to abnormal protein-rich lymph fluid accumulation within the interstitial tissue localized in the arm, shoulder, breast, and/or adjacent thoracic quadrant [5, 8–10]. Lymphedema progresses in severity over time, from mild to severe edema, which can be associated with fibrosis and other complications such as cellulitis [10, 11]. Objective limb volume measurement is used to detect increased swelling and to monitor and record changes over time [12]. Limb volume can be estimated through water mass displacement methods or calculations derived from girth measurements [13, 14]. Volumetric measurements can be taken using a volumeter, while limb girths can be measured by placing a tape measure at different standard anatomical sites. Estimated volume is determined by summing segment volumes derived from the truncated cone formula [13, 14]. In particular, a circumference difference of 2 cm or higher at the same anatomic point between the affected and non-affected limb is considered as a clue for clinical diagnosis [3].

Lymphedema may appear gradually or suddenly, and its onset can occur months to years later from treatment [1, 5]. However, women treated for BC deal with a life-time risk of developing upper limb lymphedema that represents one of the most distressing long-term health problems [1, 5]. This condition can cause relevant physical and psychological consequences, negatively impacting quality of life (QoL) and compromising emotional wellbeing [2, 3]. Swelling can be accompanied by physical discomfort, pain/soreness, numbness, tingling, stiffness, impaired mobility of shoulder, arm, elbow, wrist, and/or fingers caused by decreased range of motion, fatigue, weakness, and heaviness of the affected limb. Psychological symptoms include anxiety, fear, depression, loss of body image and self-esteem, and decreased sexual drive.

Therefore, it is important not only understanding risk factors influencing BCRL, but also applying this knowledge to find preventative measures and diagnostic approaches to reduce morbidity and improve the overall QoL. This can be achieved by controlling the swelling, restoring affected limb functionality, and preventing potential complications. Of note, early treatment often leads to better results. Moreover, guidelines for BCRL prevention have been developed, but currently, there is no progress concerning the care of this chronic condition. Thus, management of lymphedema remains a major challenge for patients and health care professionals [5].

Strategies to manage BCRL are mainly non-pharmacologic, used alone or in combination with one another. However, these treatments seem not to offer a permanent reduction or recovery of upper limb swelling. Non-pharmacologic treatments involve various physiotherapeutic interventions such as complete decongestive therapy, manual lymphatic drainage, compression bandaging, and exercise [6, 15]. In addition, routine check-ups for lymphedema management, long-term physical therapy, and recurrent infections create financial and economic burdens affecting not only survivors but the health care system as well [6]. Regarding the exercise to prefer, the type based on repetitive movements seems to be more effective on musculoskeletal pump activation enhancing lymph flow and improving protein resorption, thus providing additional benefits to compression [9, 10]. In BCRL-affected women, slowly progressive weightlifting has shown to be safe and resulted in a decreased incidence of lymphedema exacerbations [10]. Physical activities and sport such as nordic walking, swimming and dragon boat are also recommended [10]. Nevertheless, possible benefits to the affected upper limb are not yet well established. Furthermore, aiming to address survivor psychosocial, as well as physical and functional concerns, a growing body of literature supports adapted physical activity (APA) as an effective intervention strategy [16–20]. In a previous pilot study, we described for the first time the effects of a specific adapted exercise on lymphedema management in BC survivors [21].

On these premises, here, we conducted a deeper investigation of the possible benefits of a specific multidimensional APA intervention aimed to reduce chronic moderate/severe BCRL and improve upper limb strength and mobility, as well as QoL. The protocol, based both on APA specialist-supervised and self-leaded sessions, was centered on a specific motor gesture performed using an innovative purpose-designed proprioceptive board named Hand-Walk.

Materials and methods

Study participants

A group of 88 survivors affected by BCRL was recruited at the Cancer Rehabilitation Center (Ce.Ri.On.) of Florence, Italy. On the basis of the inclusion criteria described hereafter, 43 subjects resulted eligible but 13 of them were not enrolled in the study due to different personal reasons (e.g., family problems, lack of time, transport difficulties). Sixteen out of the remaining 30 subjects (all women; mean ± SD age, 65.2 ± 8.6 years, range 53–77 years), in stable clinical conditions and after receiving a medical clearance by an oncologist, decided to take part in the proposed structured APA pathway, while the others 14 opted for a passive medical therapy offered by the Ce.Ri.On., consisting in acupuncture treatment. In particular, the protocol consisted in a supervised collective 8-week APA program integrated with home-based sessions of self-managed specific exercises performed using a tailored proprioceptive board, as detailed below. The eligibility criteria were: (1) presence of chronic moderate/severe upper limb BCRL following cancer-related axillary dissection clinically defined as a ≥ 3 cm difference of circumference measurement [16], taken at anatomical landmarks, between affected and non-affected upper limb and previously treated with standard physiotherapy protocol; (2) day and/or night elastic bandage application; (3) no other upper limb musculoskeletal disorders; and (4) no physical activity practice during the full study period. Exclusion criteria were the presence of lymphangitis, moderate/severe heart failure, known or suspected cancer recurrence, and lack of patient consent to take part in the study.

At baseline and after ending the structured APA intervention, all participants filled out several questionnaires such as the Upper Limb Lymphedema 27 scale (ULL-27) to evaluate health-related QoL [21–24], the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression [25, 26], the distress thermometer to rate psychological distress [22], and the numerical rating scale (NRS) to quantify back and shoulder pain intensity [23, 24]. Specifically, the ULL-27 questionnaire, which uses a scale consisting of 27 questions distributed across 3 domains (i.e., physical, psychological, and social), evaluates the QoL in 3 dimensions in subjects affected by upper limb lymphedema. Scores obtained in different dimensions are combined and elaborated to calculate the questionnaire total score (range 27–135 points). Getting high score of the scale means that lymphedema badly impacts the QoL of the individual [21–24]. HADS self-administered questionnaire is specifically developed to detect patient states of anxiety and depression and it is composed of two 7-item scales, one for anxiety and the other for depression [25, 27]. In addition, distress thermometer is a visual graphic scale consisting of 11 points with a range comprised between 0 (no distress) and 10 (extreme distress) [27]. Finally, NRS is a horizontal segmented numeric bar on which a respondent selects, on a 0–10 scale (0 = no pain and 10 = worst imaginable pain), the number that better quantify perceived pain intensity [16, 17].

The anthropometric measurements were taken in standardized way at baseline and after APA. Height and weight were matched to calculate BMI through the formula: weight divided by the square of height (kg/m^2). BMI categories were based on the World Health Organization classification. In addition, hip circumference was measured at the level of the widest circumference over the great trochanters, and waist circumference was taken midway between the lower rib and the iliac crest. Both circumferences must be measured, using a flexible but non-stretchable tape, on horizontal plane at the end of a gentle expiration performed by the subject in orthostatic position [28]. Moreover, body

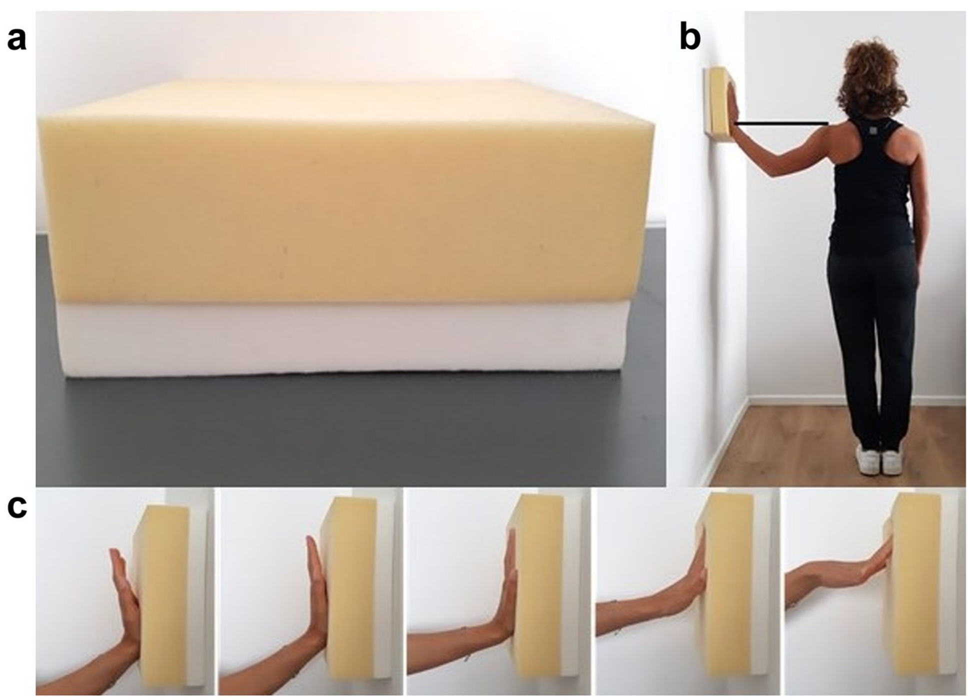

Fig. 1 **a** Details of Hand-Walk board peculiar composition. **b** Hand-Walk board wall placement and roll-up exercise start position. Orthostatic position beside the wall, feet together, perform a 90° lymphedema-affected upper limb abduction and place hand on Hand-Walk board paying attention to keep wrist joint at shoulder height and palm fully flat on the board, with slightly flexed elbow and extended wrist. **c** Detailed roll-up gesture sequence. Starting from the previously described position, perform the rolling movement by detaching hand palm from the board first and subsequently by pressing it slowly, from palm to fingertips, thus playing a complete wrist flexion. Keep on pressing fingertips against the board, and then conclude the pushing movement by completely removing hand from it. Get back to start position and cyclically repeat gesture sequence for three sets of 6/8 repetitions each

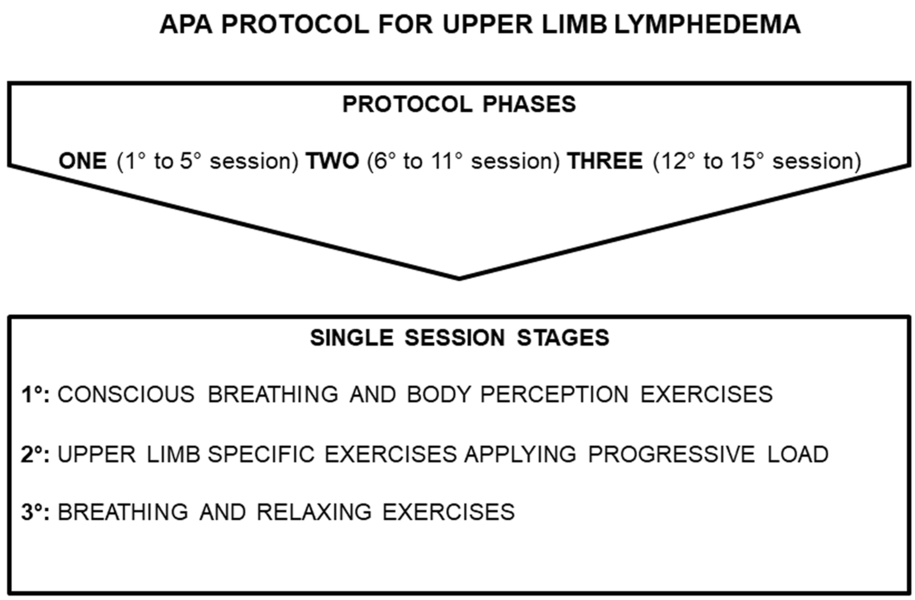

Fig. 2 Schematic diagram of adapted physical activity (APA) protocol for upper limb lymphedema

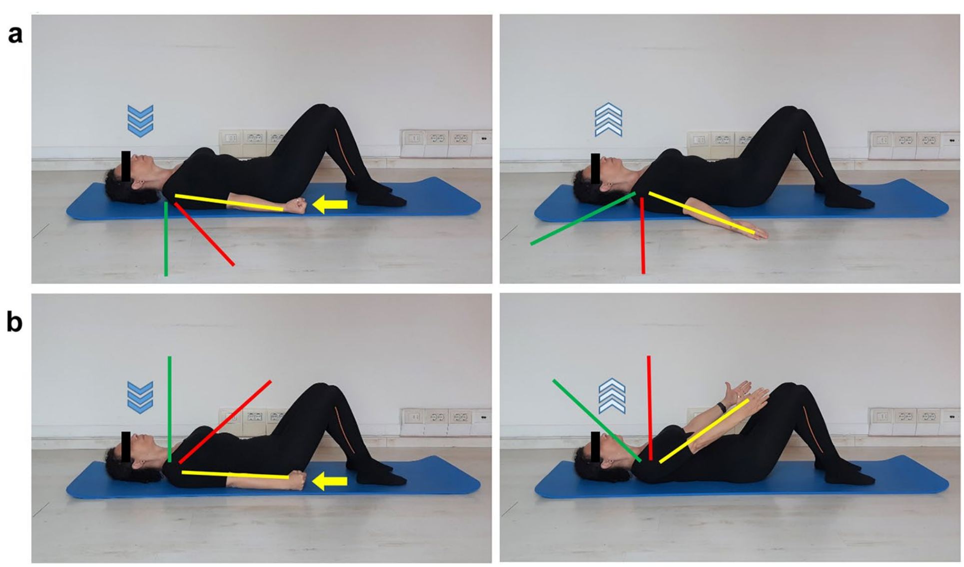

Fig. 3 **a** Progressive abduction and adduction of both upper limbs matched with hand finger flexion–extension executed on frontal plane. Supine position, flex both legs, set feet hip-width apart and rest straight arms by body sides with hand palms up. Inhale through the nose (light blue arrows) while closing hands in a fist (yellow arrow), exhale through the mouth (white arrows) while opening hands and perform upper limbs abduction on frontal plane until reaching a 45° angle (yellow lines) with respect to craniocaudal body axis. During abduction movement, focus on keeping both arms in touch with the floor without lifting them up. Starting from this reached position, repeat gesture until reaching a 90° angle (red lines) and, subsequently, until reaching the maximum upper limb range of abduction on frontal plane (green lines). Repeat the whole exercise sequence performing upper limb adduction, per decremental motion angles, until getting back to start position. Two sets of four total movements (abduction/adduction) each, 30-s recovery. **b** Progressive upper limb flexion and extension matched with hand finger flexion–extension executed on sagittal plane. Supine position, flex both legs, set feet hip-width apart and rest straight arms by body sides with hand palms down. Repeat previous exercise performing upper limb flexion on sagittal plane per stages, 45° (yellow lines), 90° (red lines) until reaching the maximum range of motion (green lines). Focus on playing inhalation (light blue arrows) during hand closure (yellow arrow) and exhalation (white arrows) during hand opening. Repeat the whole exercise sequence performing upper limb extension, per decremental motion angles, until getting back to start position. Two sets of four total movements (flexion/extension) each, 30-s recovery

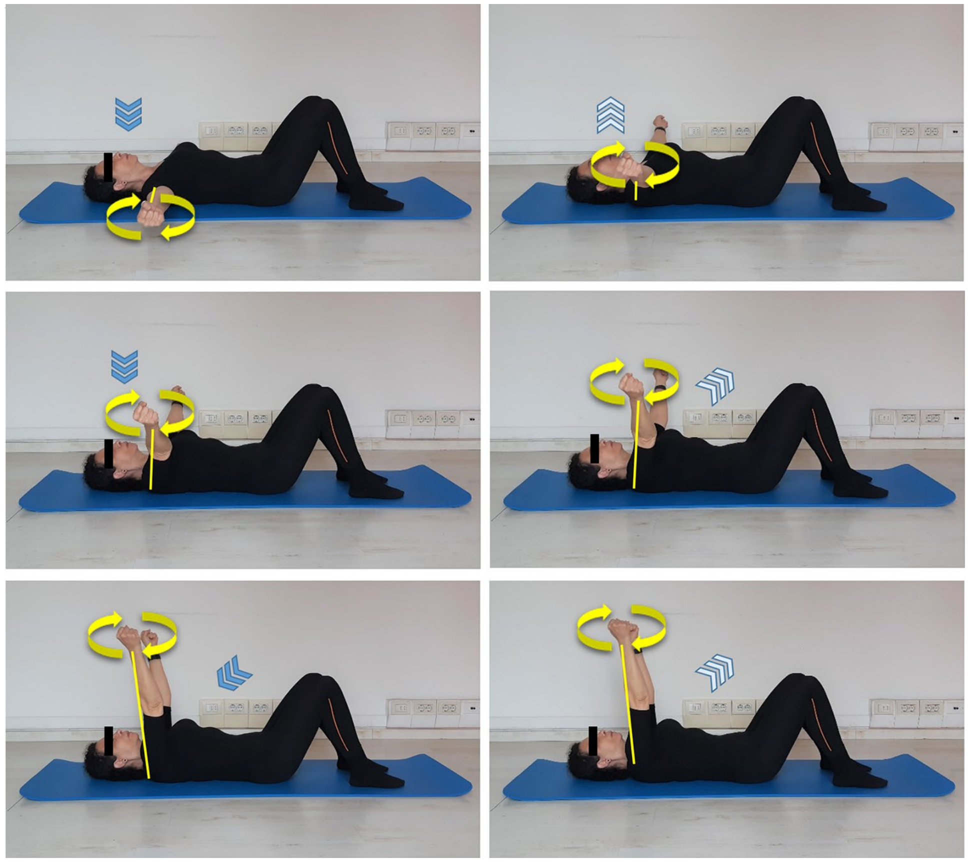

Fig. 4 Progressive circumduction of both upper limbs on transversal plane. Supine position, flex both legs, set feet hip-width apart and open both straight arms out at body sides on shoulders height with hand palms up. Inhale through the nose (light blue arrows) then exhale through the mouth (withe arrows), close hands in a fist and perform progressive upper limb circumduction on transversal plane (yellow lines and curved yellow arrows) until bringing arms in orthogonal position with respect to the floor. Starting from this reached position, inhale through the nose, open both hands, exhale through the mouth and perform upper limb circumduction reverse bound, until getting back to start position. Two sets of five repetitions, 30-s recovery

composition analysis (i.e., regional upper limb fat percentage and lean soft tissue mass, and total body intracellular and extracellular water) was determined by the multi-frequency segmental body composition analyzer Tanita MC-780 (Tanita Europe, Amsterdam, Holland) according to manufacturer instructions [29, 30]. To evaluate lymphedema status, bilateral circumferential measurements were taken using a tape measure at different anatomical levels. Based on these data, limb volumes were determined by summing each segment volume derived from the truncated cone formula [31, 32]. Circumferential measurements and ultrasonographic evaluations of soft tissue area structures were performed at 4 cm proximal to the wrist [31, 33, 34]. Wrist active flexion and extension were also evaluated by miniaturized inertial sensor (Moover, Sensor Medica, Montecelio, Rome, Italy) [35]. In addition, handgrip strength measured by dynamometry was considered as a further upper limb functionality parameter [21]. Finally, self-managed home-based specific upper limb exercises using the proprioceptive board were assessed through a self-reported diary, and a questionnaire (1–5 point scale) was administered to receive a feedback on the participant satisfaction about involving and performing the protocol [36]. A signed informed consent form was obtained from participants in accordance with the Declaration of Helsinki.

Structured physical activity protocol

The APA protocol, conceived, designed, and supervised by an adapted exercise specialist, consisted in 15 collective sessions which lasted 50 minutes each and were scheduled on 2 non-consecutive days per week. To achieve the main objectives of the protocol, that is BCRL sequelae reduction and consequent QoL improvement, group sessions were implemented by other ones individually performed and self-managed at home by each subject. Home sessions were scheduled two times per week on different days than collective sessions, preferably in the morning, and were focused on a specific upper limb motor gesture, called roll-up, which particularly involved metacarpophalangeal joint and wrist flexion–extension to boost lymphatic return, as previously described in detail [21]. Of note, this specific adapted exercise, consisting of sequential movements, made use of a tailored tool, named Hand-Walk, which was conceived and created drawing on the APA specialist expertise in oncological exercise field. It consisted in a proprioceptive board composed of two specific materials and purpose-designed for wrist, hand, and finger proprioception improvement through roll-up movement execution. Concerning its peculiar composition, the base layer (thin white part) was made of expanded polyethylene ETHAFOAM (105 kg\m^3 density, $-60/+80$ °C

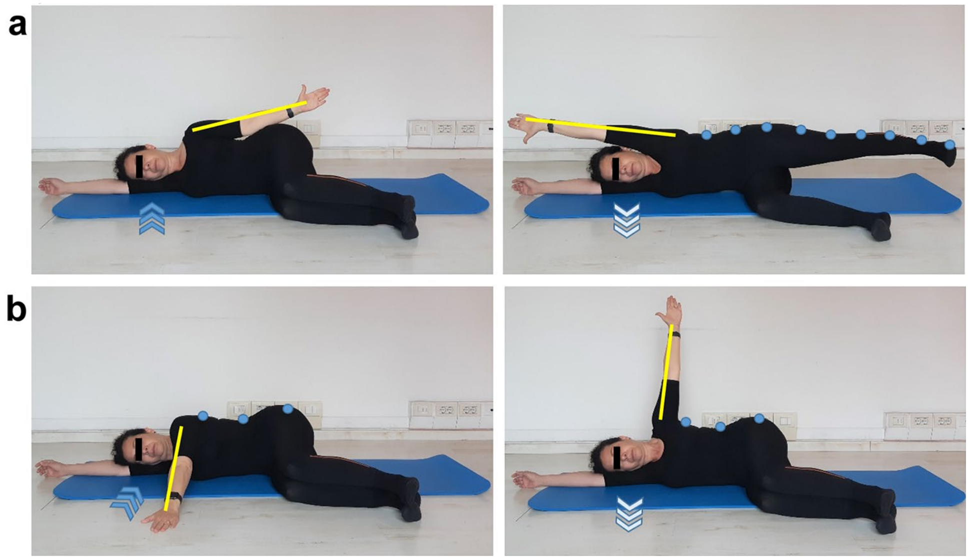

Fig. 5 **a** Upper limb abduction and adduction on frontal plane combined with lower limb extension on sagittal plane. Lateral decubitus, both legs, thighs and ankles flexed in 90° position. Place floor arm straight high on sagittal plane and rest head on it. Set top arm straight on body side with hand palm facing forward (yellow line). Inhale through the nose (light blue arrows), exhale through the mouth (white arrows) and perform upper limb abduction until reaching the maximum range of motion on frontal plane combined with the homolateral lower limb extension on sagittal one. Focus on keeping hip-knee-ankle alignment (light blue dots) during extension movement. Inhale through the nose and slowly get back to start position. Two sets of eight repetitions on each body side, no recovery. **b** Upper limb abduction and adduction on transversal plane. Lateral decubitus, both legs, thighs and ankles flexed in 90° position. Place floor arm straight high on sagittal plane and rest head on it. Set top arm straight in front of the body with hand palm touching the floor (yellow line). Inhale through the nose (light blue arrows) and push hand palm against the floor, then exhale through the mouth (withe arrows) and perform upper limb abduction on transversal plane until reaching the maximum range of motion. Focus on keeping shoulder-hip alignment (light blue dots) during movement. Inhale through the nose and slowly get back to start position. Two sets of eight repetitions on each body side, no recovery

service temperature and 110 kPa compressive strength), while the soft layer (thick yellow part), expressly designed to perform the roll-up exercise, was made of 100% polyurethane rubber (52 kg/m^3 ± 5% density) (Fig. 1a).

To promote subject adherence and active participation to the protocol, the first collective session was spent to clearly introduce the main objectives of the project, to explain Hand-Walk board purpose, and to customize and record its positioning measurements on the wall for each participant (Fig. 1b). In addition, APA specialist accurately showed and taught roll-up gesture (Fig. 1c), supervising and encouraging each subject to understand, perceive, and develop technical movement in a conscious way. To obtain a gradually improvement of body perception, coordination, postural control and strength, the whole protocol was structured in three phases. During the first phase (from 1st to 5th session) specific upper limb exercises, in basic supine decubitus position, were performed. The second phase (from 6th to the 11th session) comprised bodyweight exercises in seated, supine, and lateral decubitus position, and finally, during the third phase (from 12th to the 15th session) sensorimotor complexity and load were increased until introducing movements performed in orthostatic and quadruped position and using small fitness tools such as sponge balls and elastic bands. As shown in Fig. 2, each of 15 collective sessions was organized in 3 stages. The first stage was mainly focused on conscious breathing exercises and body perception/awareness, the second one on specific movements according to the major objectives and training progression purpose of the APA project, and the third one on breathing and relaxing exercises. Phase one of the protocol started with conscious breathing exercises, in supine decubitus position, initially focusing on global body perception and then on chest and abdominal areas perception and control (Fig. 2). All these exercises were performed applying an increasing difficulty level. The first aim of them was to simply perceive breath flow and body volumes and then, gradually, to control and direct it through the different respiratory body areas. Breathing control plays a key role in muscle chains contraction and release thus affecting global and segmental coordination, postural control, and strength improvement. Hence, during the entire protocol, participants were educated to inhale through the mouth and exhale through the nose, and to match the proper breathing phase to each movement stage, paying attention to correct any eventual postural compensation. In addition to respiratory focus, this first protocol phase was characterized by specific upper limb and core stability exercises, executed in supine decubitus position (Fig. 3).

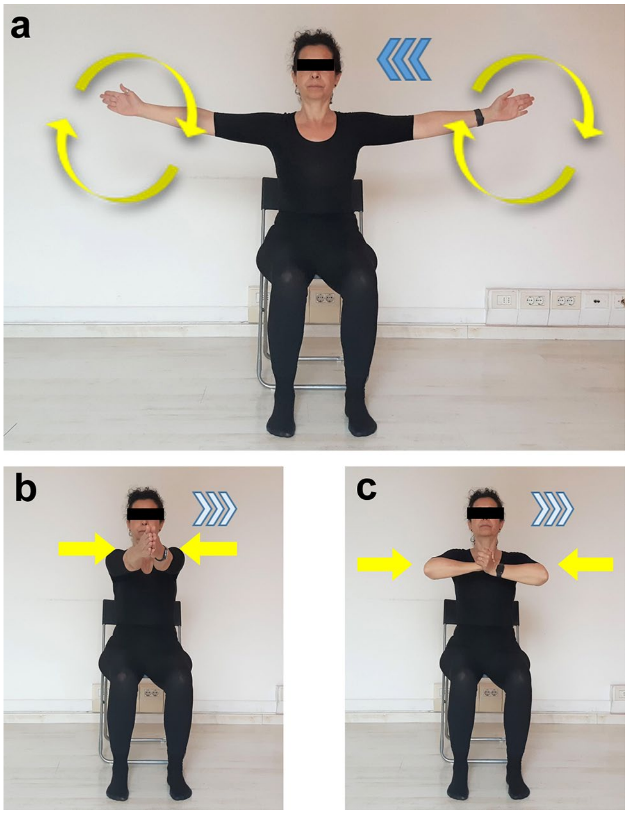

Fig. 6 Circumduction of both upper limbs on frontal plane combined with hand counterthrust. **a** Seated position on a chair without armrests, upper body straight, 90° flexed legs and thighs and feet slightly apart on the floor. Lift both straight arms out at body sides, on frontal plane, until reaching shoulders height, hand palms forward. Inhale through the nose (light blue arrows) and perform three clockwise upper limb circumduction. **b** Bring straight arms parallel in front of the body, join hand palms, exhale through the mouth (white arrows) and thrust hands one against each other (yellow arrows). Two sets of three repetitions clockwise and anti-clockwise, 30-s recovery. **c** Repeat previous exercise performing counterthrust with flexed upper limbs and joined hands in front of the chest (yellow arrows) while exhaling through the mouth (withe arrows). Two sets of three repetitions clockwise and anti-clockwise, 30-s recovery

By applying an incremental difficulty to sensorimotor control and motion angles, APA specialist aimed to increase upper limb, scapulothoracic and cervical mobility and to improve spine stability. Moreover, through exercises which involved and activated hand, arm, chest, shoulder, and neck muscle contraction, played a crucial drainage action, not only on axillary lymph nodes, but also on clavicular and cervical ones (Fig. 4).

The phase two of the protocol was centered on progressively increasing motor difficulty level and comprised exercises performed first in lateral decubitus position (Fig. 5) and then in seated position (Figs. 6 and 7), characterized by a significant involvement of coordination skills and focused on core stabilization.

Furthermore, during each collective session, subjects were asked to provide a verbal feedback regarding upper limb home workout performed using the purpose-designed tool, thus allowing APA specialist to investigate the specific exercise compliance.

To improve strength, coordination, mobility, proprioception, and whole-body conditioning, the third and last phase of the protocol was conceived applying an incremental difficulty both on motor gesture control and workout load. To achieve this aim, the APA specialist integrated and adapted the exercises executed in the previous phases, asking participants to perform them in seated, orthostatic (Figs. 8 and 9), and quadruped position.

Statistical analysis

All data are expressed as mean ± standard error of the mean (SEM), mean ± SD or percentage. A paired Student's *t*-test was used to compare the baseline vs. post-APA scores. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the statistical package STATA 11.

Results

Sixteen BC survivors, aged 65.2 ± 8.6 years, took part in the structured APA protocol. Participant characteristics at baseline are summarized in Table 1. Of note, according to BMI value (BMI ≥ 25), approximately 90% of subjects were overweight or obese (Table 1).

Data concerning body composition of all study participants assessed by anthropometry and bioimpedance analysis at baseline and after 8-week APA intervention are reported in Table 2.

In particular, anthropometric parameters and bioimpedance measurements were not significantly different between baseline and after APA intervention, as well as the ultrasound and volumetric measures remained mostly unchanged after APA (Tables 2 and 3).

Focusing on functional tests, a significant improvement in wrist mobility was observed after the APA protocol, though hand strength was only slightly increased without reaching the statistical significance (Table 3). In addition, NRS score changes reported by the study participants revealed a significant decrease in lymphedema-affected upper limb and lumbar pain perception at post-APA respect to the baseline ($p = 0.0198$ and $p = 0.0438$, respectively). Moreover, a trend toward an improvement in pain perception of dorsal spine tract was observed post-APA (Table 4).

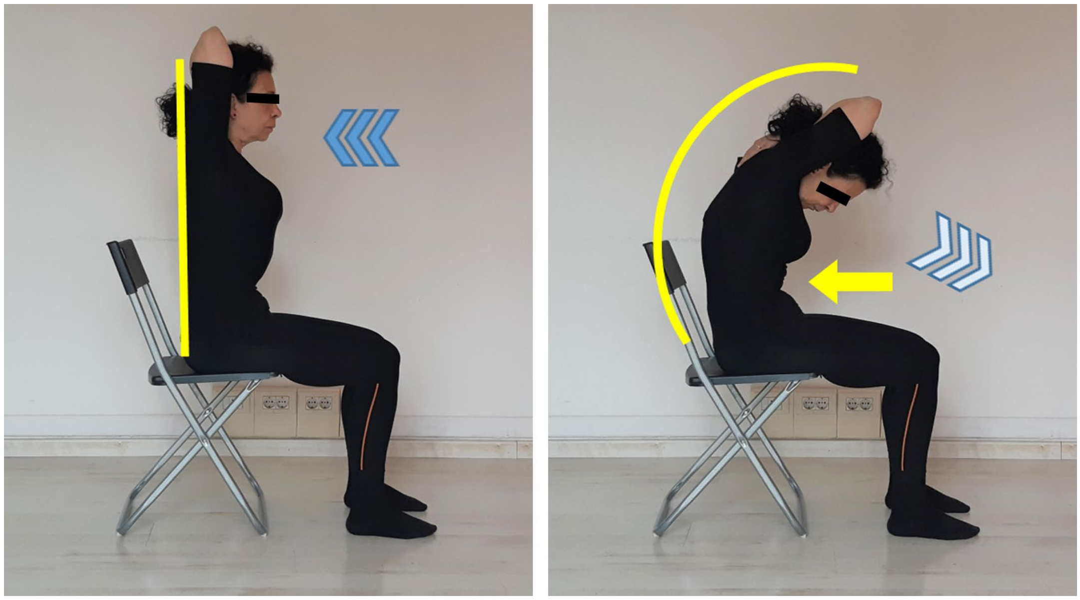

Fig. 7 Scapular abduction with flexed upper limbs overhead. Seated position on a chair without armrests, upper body straight (straight yellow line), 90° flexed legs and thighs and feet slightly apart on the floor. Lift both arms, flex them keeping elbows opened at head sides and place hand palms on neck. Inhale through the nose (light blue arrows), exhale through the mouth (white arrows) while getting elbows closer to each other thus allowing a slight scapular abduction. Perform a pelvic retroversion (yellow arrow) increasing dorsal kyphotic curve (curved yellow line) during abduction movement. Inhale through the nose and slowly get back to start position. Two sets of eight repetitions each, 30-s recovery

Fig. 8 Upper limb thrust against the wall in frontal orthostatic position. Stand up facing the wall, parallel feet slightly apart, spine in neutral position. Flex arms in front of the body and place hand palms on the wall at shoulders height (yellow line). Inhale through the nose (light blue arrows), exhale through the mouth (white arrows) and perform a light hand thrust against the wall. Inhale and slide both hands upward on the wall (yellow arrow), then exhale and perform hand thrust once again. Repeat the exercise until completely extending upper limbs and reaching the maximum height/range of motion. Starting from this reached point, repeat exercise progressively getting back to start position. Two sets of two repetitions, 60-s recovery

Fig. 9 Upper limb thrust against the wall in lateral orthostatic position. Stand up beside the wall, parallel feet slightly apart, spine in neutral position. Place hand palm on the wall at shoulder level (horizontal yellow line). Inhale through the nose (light blue arrows), exhale through the mouth (white arrows), and perform a light hand thrust against the wall. Inhale and slide hand upward on the wall (yellow arrow), then exhale, and perform hand thrust once again. Repeat exercise until completely extending upper limb (yellow line) and reaching the maximum height/range of motion. Starting from this reached point, repeat exercise progressively getting back to start position. Two sets of two repetitions for each upper limb, 60-s recovery

Table 1 Baseline characteristics of study participants

Variables	Participants ($n = 16$)
Age, mean ± SD (range)	65.2 ± 8.6 (53–77)
BMI, mean kg/m^2 ± SEM	32.04 ± 3.2
BMI category, %	
< 25 (normal weight)	6.2
25–29.9 (overweight)	31.4
≥ 30 (obese)	62.4
Breast surgery, %	
Quadrantectomy	58.8
Modified radical mastectomy	23.5
Mastectomy with breast reconstruction	17.7
Operated side, %	
Right	43.8
Left	56.2
Adjuvant treatments, %	
Chemotherapy	68.7
Radiotherapy	25.0
Endocrine treatment	81.0

BMI body mass index, *SD* standard deviation, *SEM* standard error of the mean

As far as the assessment of self-reported questionnaires is concerned, ULL27 questionnaire results indicated a significant improvement in the overall QoL after our APA protocol (Table 5).

Focusing on ULL27 three dimensions, significant positive changes were found for physical functioning and social components, while no difference between baseline and post-APA was detected for psychological component score (Table 5). Furthermore, a trend toward improvement in the anxiety component of the HADS questionnaire was observed post-APA, whereas depression state was significantly lower at the ending of the APA intervention (Table 5). Finally, a slightly decrease in the distress thermometer was also found post-APA (Table 5).

Good adherence, assessed using self-reported diary, was observed in self-managed home-based specific upper limb exercises using the proprioceptive board (68.75% of participants).

Concerning the assessment of participant satisfaction about involving and performing the protocol, post-APA data showed that BC survivors considered the structured APA protocol a positive and effective experience (4.6 points). In addition, women reported perceiving an improvement in upper limb functionality and edema reduction (4.4 and 3.8 points, respectively).

Table 2 Mean scores of anthropometric and bioimpedance measurements of breast cancer survivors ($n = 16$) at baseline and after 8-week adapted physical activity (APA) intervention

Variables	Baseline Mean (SEM)	Post-APA Mean (SEM)	*p*-value*
BMI, kg/m^2	32.04 (3.2)	31.50 (3.6)	0.1123
Waist circumference, cm	95.97 (10.81)	94.60 (11.78)	0.1193
Hip circumference, cm	109.25 (9.12)	109.10 (9.57)	0.1237
Bioimpedance measurements			
Upper limb fat mass, %	1.78 (0.24)	2.19 (0.45)	0.3783
Upper limb lean mass, %	3.03 (0.12)	3.05 (0.12)	0.5655
Total body intracellular water, %	20.46 (0.87)	20.79 (0.87)	0.2525
Total body extracellular water, %	17.57 (0.66)	17.52 (0.68)	0.4716

BMI body mass index, *SEM* standard error of the mean

*Student's *t*-test for paired data

Table 3 Mean scores of both ultrasound and volumetric measures and functional tests of affected upper limb at baseline and after 8-week adapted physical activity (APA) in all study participants ($n = 16$)

Variables	Baseline Mean (SEM)	Post-APA Mean (SEM)	*p*-value*
Upper limb volume, mL	3992.20 (295.6)	3971.40 (280.7)	0.6412
Ultrasonographic evaluation, mm			
Hand	0.65 (0.11)	0.64 (0.1)	0.8137
Mid forearm	1.11 (0.14)	1.10 (0.1)	0.8117
Elbow	0.52 (0.08)	0.48 (0.05)	0.1634
Half arm	0.71 (0.06)	0.71 (0.04)	0.9437
Wrist flexion, °	72.16 (3.8)	82.81 (1.4)	0.0108
Wrist extension, °	58.95 (2.9)	64.33 (1.9)	0.0097
Hand grip test, kg	24.07 (1.9)	24.85 (1.6)	0.4354

SEM standard error of the mean

*Student's *t*-test for paired data

Table 4 Perception of pain score values at baseline and post-adapted physical activity (APA) protocol

Variables	Baseline Mean (SEM)	Post-APA Mean (SEM)	*p*-value*
Perception of pain (NRS)			
Upper limb pain	3.92 (0.7)	2.78 (0.7)	0.0198
Cervical pain	4.21 (0.9)	4.01 (0.7)	0.7359
Dorsal pain	3.85 (0.9)	2.35 (0.8)	0.1034
Lumbar pain	6.14 (0.6)	5.00 (0.7)	0.0438

NRS Numerical Rating Scale, *SEM* standard error of the mean

*Student's *t*-test for paired data

Discussion

BCRL is a major side effect and a complication from BC surgery and radiotherapy, causing chronic lymphedema in the upper limb [39]. The consequent malfunctioning lymphatic system, which delays lymphatic drainage, causes an abnormal tissue protein increase resulting in chronic inflammation, fibrosis, pain, and limited range of motion [37]. In addition, this unremitting and potentially disabling condition leads to functional disabilities and mental disturbances, such as anxiety, depression and emotional distress [37, 38]. At present, many BCRL treatment options are available, though none of them seems to offer a permanent reduction or resolution of upper limb swelling [21, 38]. In particular, manual lymphatic drainage, included in complex decongestive therapy, is designed to reduce swelling by promoting lymphatic drainage [37]. Of note, nonpharmacologic treatments, such as acupuncture, massage, and exercise, have been shown to be helpful for BCRL management [9, 21, 38–40]. Specifically, the exercise involving affected upper limb muscles, joints and motor skills may be beneficial in the control of edema [9, 10, 21, 38, 41].

In this context, our study focuses on the effectiveness of an innovative structured 8-week APA protocol targeted to BC survivors to manage chronic moderate/severe upper limb BCRL. In detail, our tailored intervention was based on supervised group sessions combined with home-based self-managed exercises employing a proprioceptive tool

Table 5 Mean scores of quality of life, anxiety/depression status and distress thermometer questionnaires of breast cancer survivors ($n = 16$) at baseline and post-adapted physical activity (APA) intervention

Variables	Baseline Mean (SEM)	Post-APA Mean (SEM)	*p*-value*
Quality of life (ULL-27)			
Total score	35.78 (4.76)	27.38 (3.37)	0.0104
Physical dimension	37.14 (5.86)	27.02 (4.45)	0.0119
Psychological dimension	39.28 (4.38)	38.52 (2.90)	0.8421
Social dimension	26.78 (5.89)	12.85 (4.59)	0.0048
Anxiety/depression status (HADS)			
Anxiety	6.40 (1.17)	5.4 0 (1.10)	0.2170
Depression	6.66 (0.82)	5.06 (0.65)	0.0210
Distress thermometer	3.21 (0.6)	3.01 (0.5)	0.6301

HADS Hospital Anxiety and Depression Scale, *SEM* standard error of the mean, *ULL-27* Upper Limb Lymphedema 27

*Student's *t*-test for paired data

purposely designed to promote upper limb lymphatic return, thus favouring lymphedema reduction and improving both upper limb functionality and QoL of BC survivors. Previous studies evidenced that, although volume alterations may not be noticeable, patients affected by lymphedema can have significant QoL impairments [42]. Additionally, there is no evidence of a direct correlation between volume change severity and subjective outcomes. Patients with relatively minor volume variation can face heavy and stressful psychosocial and/or physical challenges anyway [42]. According to these data, albeit affected upper limb ultrasound imaging and volume measurements remained mostly unchanged after APA, our results highlight a significantly decreased pain perception in the upper limb affected by lymphedema accompanied by a significant improvement of wrist mobility, thus notably contributing to QoL recovery. In particular, based on our findings on upper limb volumetric and functional parameters pre- and post-APA protocol, we can hypothesize that the applied exercise methodology may be effective in improving arm functionality even on a short term, while for a significant lymphedema reduction a longer intervention might be needed. Concerning wrist mobility increase, well- known as a crucial autonomy parameter, our results highlight the importance of the utilization of a customized tool, such as Hand-Walk board, to optimize and fasten training outcomes on a specific body segment. Of note, after our APA protocol completion, the ULL-27 total score was remarkably improved. In particular, physical functioning and social components displayed a significant enhancement, though the psychological component score was unchanged. However, it is noteworthy that depression was significantly reduced post-APA intervention, as well as emotional distress was slightly improved. It is well known that these patients exhibit an excess of psychological sequelae and low levels of psychosocial adaptation with respect to the general population [43]. In accordance with previously reported findings [10, 16, 27], it appears that practicing physical activity with a teamwork approach can promote social interaction skills among BC survivors.

Overall, our findings should be interpreted in the context of study limitations which are mostly represented by the relatively small sample size, and the lack of randomization and control group. In this regard, it should be considered that our investigation was conceived within the frame of a structured pathway recently proposed by Ce.Ri.On. featuring either acupuncture or APA support in BCRL management at the individual's choice. However, despite the aforementioned limitations, this monocentric pilot study has also some strengths worth mentioning. Indeed, it is remarkable that the tailored methodology applied in our APA protocol encouraged subject active participation and body awareness, along with resulting into a functional recovery of upper limb affected by chronic lymphedema and overall QoL improvement. In addition, since there is an evident lack of literature regarding specific exercise methodology for oncological patients, and tailored APA protocols need to be designed and leaded on small groups to properly respond to subjective needs and ensure participant safety, our study was structured as a small-scale preliminary trial to investigate and test training load/dosage and effectiveness of APA addressed to BC survivors affected by BCRL. Moreover, by accurately teaching roll-up gesture, consisting in a sequential flexion–extension of wrist and metacarpophalangeal joints with a pushing phase recalling the muscular foot pump [16, 44, 45], and customizing Hand-Walk board positioning, the APA specialist aimed to encourage women to acquire a conscious body control and perception, hence providing them a concrete tool for autonomous motor gesture control. Our multidisciplinary team knowledge and expertise, both in APA and oncological fields, granted a global patient management that was deeply appreciated by the participants, as testified by the good protocol adherence and satisfaction reported in the individual diaries/questionnaires. Furthermore, owing to a detailed description of our specific protocol and Hand-Walk material composition and practical utilization, we are confident that the present study can make a concrete contribution to the research area of APA tailored to BC survivors, in particular allowing the protocol reproduction in future studies, such as multicentric investigations enrolling a larger sample.

Lastly, it must be mentioned that during our APA protocol practice no adverse events related to the exercise intervention were recorded, thus highlighting its suitability both in conceptualization and application.

Conclusions

Since pluridimensional needs, lack of resolutive therapies as well as positive effects of regular physical activity on psychophysical wellbeing are widely demonstrated in BC survivors, a tailored APA protocol may represent a successful strategy to counteract cancer treatment-related sequelae with an overall improvement of QoL [16–20, 38]. The encouraging results of our preliminary study strengthen the necessity of including qualified APA specialists in multidisciplinary patient care teams to guarantee a global and effective approach for BCRL management.

Acknowledgements The authors are most grateful to the women who took part in the study, and to Mr. Alessandro Sarti (Ortopedia Fiorentina Srl, Florence, Italy) for manufacturing of Hand-Walk proprioceptive board.

Author contributions Conceptualization, DM, MGM and MM (Mirca Marini); methodology, DM, MGM and MM (Mirca Marini); formal analysis, GC, DM, FM, LS, SG and GM; investigation, GC, DM, FM, MM (Mirko Manetti) and MM (Mirca Marini); data curation, GC, DM, MM (Mirko Manetti) and MM (Mirca Marini); writing—original draft preparation, GC, MM (Mirko Manetti) and MM (Mirca Marini); writing—review and editing, GC, DM, FM, LS, SG, MGM, GM, MM (Mirko Manetti) and MM (Mirca Marini); supervision, MM (Mirca Marini); funding acquisition, MM (Mirca Marini). All authors have read and agreed to the published version of the manuscript.

Funding This research was supported by MIUR (Ministry of Education, University and Research, Italy)-University of Florence funds (ex 60%; Grant number: MIRCAMARINIRICATEN21) granted to M.M. (Mirca Marini).

Declarations

Conflict of interest The authors declare no conflict of interest.

Institutional review board statement The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ISPRO Review Board (approval number: 137/2016- cdc 755; approval date: 12 April 2017).

Informed consent statement Written informed consent was obtained from all study participants.

References

1. Thomas-MacLean R, Miedema B, Tatemichi SR. Breast cancer-related lymphedema. Women's experiences with an underestimated condition. Can Fam Physician. 2005;51:246–7.
2. Fialka-Moser V, Korpan M, Varela E, Ward A, Gutenbrunner C, Casillas JM, Delarque A, Berteanu M, Christodoulou N. The role of physical and rehabilitation medicine specialist in lymphoedema. Ann Phys Rehabil Med. 2013;56:396–410.
3. Saleh HA, Rageh TM, Alhassanin SA, Megahed MA. Upper limb lymphedema related to breast cancer therapy: incidence, risk factors, diagnostic techniques, risk reduction and optimal management. Int Surg J. 2018;5:3633–9.
4. Rebegea L, Firescu D, Dumitru M, Anghel R. The incidence and risk factors for occurrence of arm lymphedema after treatment of breast cancer. Chirurgia (Bucur). 2015;110:33–7.
5. Fu MR. Breast cancer-related lymphedema: symptoms, diagnosis, risk reduction, and management. World J Clin Oncol. 2014;5:241–7.
6. Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. Gland Surg. 2018;7:379–403.
7. Rockson SG. Lymphedema after breast cancer treatment. N Engl J Med. 2018;379:1937–44.
8. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. J Clin Oncol. 2008;26:5689–96.
9. Kwan ML, Cohn JC, Armer JM, Stewart R, Cormier JN. Exercise in patients with lymphedema: a systematic review of the contemporary literature. J Cancer Surviv. 2011;5:320–36.
10. Grada AA, Phillips TJ. Lymphedema: diagnostic workup and management. J Am Acad Dermatol. 2017;77:995–1006.
11. Singh B, Disipio T, Peake J, Hayes SC. Systematic review and meta-analysis of the effects of exercise for those with cancer-related lymphedema. Arch Phys Med Rehabil. 2016;97:302-15.e13.

12. Armer JM, Stewart BR. Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. Lymphology. 2010;43:118–27.
13. Sander AP, Hajer NM, Hemenway K, Miller AC. Upper-extremity volume measurements in women with lymphedema: a comparison of measurements obtained via water displacement with geometrically determined volume. Phys Ther. 2002;82:1201–12.
14. Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper-extremity volume estimates: comparison of calculated volume derived from girth measurements and water displacement volume. Phys Ther. 2003;83:134–45.
15. Zoberi K, Tucker J. Primary care of breast cancer survivors. Am Fam Physician. 2019;99:370–5.
16. Mirandola D, Miccinesi G, Muraca MG, Sgambati E, Monaci M, Marini M. Evidence for adapted physical activity as an effective intervention for upper limb mobility and quality of life in breast cancer survivors. J Phys Act Health. 2014;11:814–22.
17. Mirandola D, Miccinesi G, Muraca MG, Belardi S, Giuggioli R, Sgambati E, Manetti M, Monaci M, Marini M. Longitudinal assessment of the impact of adapted physical activity on upper limb disability and quality of life in breast cancer sur-vivors from an Italian cohort. Support Care Cancer. 2018;26:329–32.
18. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst Rev. 2012;8: CD008465.
19. Pennington KP, McTiernan A. The role of physical activity in breast and gynecologic cancer survivorship. Gynecol Oncol. 2018;149:198–204.
20. Mirandola D, Monaci M, Miccinesi G, Ventura L, Muraca MG, Casini E, Sgambati E, Manetti M, Marini M. Long-term benefits of adapted physical activity on upper limb performance and quality of life in breast cancer survivors. J Funct Morphol Kinesiol. 2017;2:38.
21. Mirandola D, Monaci M, Miccinesi G, Muraca MG, Papi F, Manetti M, Sgambati E, Marini M. Effects of a specific adapted upper limb exercise on lymphedema in breast cancer survivors: a pilot study. Gazzetta Medica Italiana Archivio per le Scienze Mediche. 2018;177:204–11.
22. Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. Support Care Cancer. 2005;13:904–11.
23. Stasi E, Bartoletti R, Aloisi D, Launois R, Alliot F. Upper limb lymphedema QoL (ULL27) traduzione e adattamento transculturale in lingua italiana. Giornale Italiano di Linfologia. 2012;1:5–14.
24. Vatansever AK, Yavuzşen T, Karadibak D. The reliability and validity of quality of life questionnaire upper limb lymphedema (ULL-27) Turkish patient with breast cancer related lymphedema. Front Oncol. 2020;10:455. https://doi.org/10.3389/fonc.2020.00455.
25. Costantini M, Musso M, Viterbori P, Bonci F, Del Mastro L, Garrone O, Venturini M, Morasso G. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. Support Care Cancer. 1999;7:121–7.
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
27. Mirandola D, Franchi G, Maruelli A, Vinci M, Muraca MG, Miccinesi G, Manetti M, Marini M. Tailored sailing experience to reduce psychological distress and improve the quality of life of breast cancer survivors: a survey-based pilot study. Int J Environ Res Public Health. 2020;17:4406.
28. Gadekar T, Dudeja P, Basu I, Vashisht S, Mukherji S. Correlation of visceral body fat with waist–hip ratio, waist circumference and body mass index in healthy adults: a cross sectional study. Med J Armed Forces India. 2020;76:41–6.
29. Leszczak J, Czenczek-Lewandowska E, Przysada G, Baran J, Weres A, Wyszyńska J, Mazur A, Kwolek A. Association between body mass index and results of rehabilitation in patients after stroke: a 3-month observational follow-up study. Med Sci Monit. 2019;25:4869–76.
30. Saran M, Czyżewski Ł, Wyzgał J, Pacek A, Szarpak Ł. Comparative analysis of arterial stiffness and body composition in early and late periods after kidney transplantation. Transplant Proc. 2018;50:1829–33.
31. Megens AM, Harris SR, Kim-Sing C, McKenzie DC. Measurement of upper extremity volume in women after axillary dissection for breast cancer. Arch Phys Med Rehabil. 2001;82:1639–44.
32. Wiser I, Mehrar BJ, Coridd M, Kenworthy E, Cavalli M, Encarnacion E, Dayan JH. Preoperative assessment of upper extremity secondary lymphedema. Cancers (Basel). 2020;12:135. https://doi.org/10.3390/cancers12010135.
33. O'Toole J, Jammallo LS, Skolny MN, Miller CL, Elliott K, Specht MC, Taghian AG. Lymphedema following treatment for breast cancer: a new approach to an old problem. Crit Rev Oncol Hematol. 2013;88:437–46.
34. Hwang JH, Lee CH, Lee HH, Kim SY. A new soft tissue volume measurement strategy using ultrasonography. Lymphat Res Biol. 2014;12:89–94.
35. Faisal AI, Majumder S, Mondal T, Cowan D, Naseh S, Deen MJ. Monitoring methods of human body joints: state-of-the-art and research challenges. Sensors (Basel). 2019;19:2629. https://doi.org/10.3390/s19112629.
36. Sylvia LG, Bernstein EE, Hubbard JL, Keating L, Anderson EJ. Practical guide to measuring physical activity. J Acad Nutr Diet. 2014;114:199–208.
37. Seo D, Lee S, Choi W. Comparison of real-time ultrasound imaging for manual lymphatic drainage on breast cancer-related lymphedema in individuals with breast cancer: a preliminary study. Phys Ther Rehabil Sci. 2020;9:43–8.
38. Eaton LH, Narkthong N, Hulett JM. Psychosocial issues associated with breast cancer-related lymphedema: a literature review. Curr Breast Cancer Rep. 2020;25:1–9.
39. Cassileth BR, Van Zee KJ, Yeung KS, Coleton MI, Cohen S, Chan YH, Vickers AJ, Sjoberg DD, Hudis CA. Acupuncture in the treatment of upper-limb lymphedema: results of a pilot study. Cancer. 2013;119:2455–61.
40. Yao C, Xu Y, Chen L, Jiang H, Ki CS, Byun JS, Bian W. Effects of warm acupuncture on breast cancer-related chronic lymphedema: a randomized controlled trial. Curr Oncol. 2016;23:e27–34.
41. Cormie P, Pumpa K, Galvão DA, Turner E, Spry N, Saunders C, Zissiadis Y, Newton RU. Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. J Cancer Surviv. 2013;7:413–24.
42. Coriddi M, Dayan J, Sobti N, Nash D, Goldberg J, Klassen A, Pusic A, Mehrara B. Systematic review of patient-reported outcomes following surgical treatment of lymphedema. Cancers (Basel). 2020;12:565. https://doi.org/10.3390/cancers12030565.
43. Symvoulakis EK, Anyfantakis DI, Lionis C. Primary lower limb lymphedema: a focus on its functional, social and emotional impact. Int J Med Sci. 2010;7:353–7.
44. Uhl JF, Gillot C. Anatomy of the veno-muscular pumps of the lower limb. Phlebology. 2015;30:180–93.
45. Ricci S, Moro L, Antonelli IR. The foot venous system: anatomy, physiology and relevance to clinical practice. Dermatol Surg. 2014;40:225–33.