Quality of life interventions in breast cancer survivors: state of the art in targeted rehabilitation strategies

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Abstract

Breast cancer (BC) is the most common malignant tumor and the most prevalent cause of mortality in women. However, the improvement in early diagnosis and in the clinical management through effective adjuvant therapies results in a progressive increase of long-term BC survivors, leading to a higher incidence of treatment-related disabling complications, such as BC related lymphedema, axillary web syndrome, persistent pain after BC treatment, cancer treatment-induced bone loss, aromatase inhibitor-induced arthralgia, and cancer related fatigue. All these pathological conditions might have a detrimental impact on health-related quality of life (HRQoL) experienced by BC survivors. In the recent past, HRQoL has been considered as one of the main outcomes to define the good success of oncological rehabilitation interventions. Therefore, we aimed to describe the role that oncological rehabilitation might play as "quality of life intervention" in terms of recovering function, improving independence in activities of daily living, reducing disability, and increasing HRQoL in BC survivors. Taken together, the present review emphasized that this complex scenario should require a precision medicine approach in order to provide a more effective decision-making and an adequate treatment compliance by patients affected by BC sequalae.

Keywords: breast cancer, rehabilitation, quality of life, breast cancer related lymphedema, lymphedema, cancer related fatigue, fatigue, bone loss, axillary web syndrome, pain

1. Introduction

Breast cancer (BC) is the most common malignant tumor and cause of mortality in women [1], and the American Cancer Society estimates that 276,480 new cases of invasive breast cancer will be diagnosed in women and 42,170 women will die from BC in the United States of America in 2020 [2]. However, in the recent past, the improvement in early tumor diagnosis and the effectiveness of adjuvant therapies resulted in a progressive increase of long-term survivors, with a significant decline in the BC death rate (by 40% since 1989) [1,3].

On the other hand, the increased survival rate led to a higher incidence of treatment-related disabling complications including breast cancer related lymphedema (BCRL) [4-6], axillary web syndrome (AWS) [7-8], persistent pain after breast cancer treatment (PPBCT) [9], cancer treatment-induced bone loss (CTIBL) [10], aromatase inhibitor-induced arthralgia (AIA) [11], and cancer related fatigue (CRF) [12-13].

Despite often neglected in common clinical practice, these conditions have detrimental effects on patients' health status, definitely leading to a high burden of psychological suffering, functioning impairments, and poor health-related quality of life (HRQoL) [14].

In the last decades, HRQoL has been considered as one of the main outcome measures in both clinical and research setting to define the success of oncological and subsequent interventions [14-15]. Thus, under the umbrella of "quality of life interventions" stand a constellation of different therapeutic approaches aiming at the management of several pathological conditions related to both active therapeutic oncological treatments and the tumor itself that hinders cancer patients' HRQoL. However, the poor HRQoL experienced by BC survivors is the result of a more or less severe degree of disability and functioning impairment produced by all these pathological sequelae.

In this context, rehabilitation interventions mainly act on functioning recovery and disability reduction obtaining sideways an increase in HRQoL (see Figure 1). Thus, the concept of "quality of life interventions" that hint at a simple HRQoL improvement intervention could be expanded to the

concept of Oncological Rehabilitation which comprises a wider set of procedures and fields of action better framing the complex management of BC survivors.

2. Breast cancer related lymphedema

BCRL is an insidious and progressive pathological condition consisting of localized inflation of lymph, interstitial fluids and proteins in the subcutaneous tissue. BCRL genesis is mainly related to a negative imbalance between lymph production and reabsorption and occurs by a direct lymphatic invasion of the tumor itself, and/or after surgery (including axillary lymph-node dissection) and radiotherapy [4,6,16-20].

BCRL is considered as an important health issue affecting approximately 20% of BC survivors [18] within 24 months from surgery, albeit a few cases do occur also after several years since surgical and radiotherapy interventions [21].

The risk of developing BCRL is related to several etiopathogenic factors [6]. Lymphadenectomy is the leading cause of BCRL, followed by radiation treatment, extensive mastectomy, low socio-economic status, family and working responsibilities, surgical intervention at the dominant side of the body, and a high body mass index [4,6,22-24]. Moreover, it has been shown that patients undergoing both extensive axillary dissection and radiotherapy have a greater risk of developing lymphedema [4]. The main BCRL clinical features are an increased upper limb volume commonly associated with cutaneous alteration, discomfort or even pain, limitation in shoulder range of movement (ROM), strength and upper limb function and psychological sequelae affecting self-perception [7-8,23-26]; taken together all these pathological manifestations lead to an extremely poor HRQoL in these women.

Early detection of BCRL is mandatory to plan prompt and effective rehabilitation treatment. Starting from clinical evaluation, the cornerstone of BCRL diagnosis and follow-up is the upper limb volume evaluation [4]. Several methods have been proposed over the last years, albeit the most

used in the clinical practice are: circumferential method (CM) [27-28], water displacement (WD) [28-29], and the three-dimensional laser scanner (3DLS) [5,30-31].

More in detail, the CM is mostly adopted in the common clinical practice and is based on the measurement of specific arm circumferences to calculate the upper limb volume, assuming its shape might be considered as a truncated cone solid [32]. However, it has been dramatically questioned the sensitivity of this technique considering the arm gibbousness commonly reported in BCRL patients [28,30,32]. On the other hand, WD is considered the "gold standard" among the volume measurement techniques to assess the upper limb volume, but it is not commonly used in real-life practice due to relatively complex and time-consuming procedures, and contraindication for patients with skin lesions [28-29]. Lastly, 3DLS is an instrumental tool able to digitally reconstruct the upper limb to non-invasively assess its volume, with emerging evidence on accuracy, reliability, and reproducibility in BCRL women [5,30-31].

Taking into account the remarkable burden of BCRL clinical manifestations, starting from an adequate diagnosis, it is imperative to find efficient treatment strategies of treatment. In particular, complex decongestive therapy (CDT) is a multicomponent treatment aimed at reducing the degree of lymphedema and consolidating the results achieved in BCRL patients [33]. CDT includes manual lymphatic drainage (MLD), therapeutic exercise, skincare to prevent infection, compression, and bandaging treatment [34]. Therapeutic exercise has a key role for BCRL; more in detail, aerobic exercise, stretching, and physical activities as yoga and pilates are indicated for the treatment of BCRL [35-36]. Particularly, Resistance exercise could be considered as safe, not worsening the upper limb swelling, and might be performed with adequate intensity by BC survivors with significant improvement in terms of both objective (e.g. ROM, muscle strength, and reduced upper limb volume) and subjective parameters (e.g. HRQoL) [37]. Other rehabilitation interventions could be used for lymphedema volume reduction, including compression sleeves and bandaging techniques, which are also useful for the prevention of further swelling, whereas they could not exert a direct action in reducing the tissue thickness [38].

3. Axillary web syndrome

AWS is a common sequela of BC surgery, characterized by the presence of visible and/or palpable web of string-like structures (i.e. fibrotic cords) extended through the subcutaneous tissue of the axilla region [39]. AWS incidence is commonly underestimated due to due to a lack of agreement regarding the diagnostic criteria, and it is probably one of the less investigated sequelae affecting BC survivors. Moskowitz et al. [40] firstly assessed AWS and reported an incidence rate of 6% in BC women after axillary lymph-node dissection (ALND), while a recent systematic review [41] showed that AWS incidence could range from 6 to 85.4%. The mean time of AWS development was considered at around 2 weeks after the surgery with an estimated spontaneous resolution time of 3 months [40]. However, in a retrospective study recently published by our group [8], we reported a prevalence of 29.4% of AWS in a sample of 177 women referred to an Oncological Rehabilitation Unit after BC surgery.

AWS commonly occurs after ALND, but also after axillary lymphadenectomy for melanoma staging or other conditions as massive axillary lymphadenopathy, infections and trauma [40,42]. The etiopathogenesis of AWS is still controversial and involves the sclerosis of veins and lymphatic vessels as a consequence of surgical tissue insult leading to sustained inflammation, thrombosis and lastly fibrosis [43]. This condition, also known as cording, is clinically characterized by a visible and/or palpable web of string-like structures (i.e. cords) localized at the subcutaneous level of the site of surgery [40]. This fibrotic mass consists of a single fibrotic band or multiple thin cords [42], or in some cases, it could be shaped as a subcutaneous nodule simulating a metastasis [44]. AWS patients commonly experience a limited ROM of the shoulder which negatively affects their HRQoL, especially during arm abduction [45-46].

The main diagnostic criteria are clinical and consist of the visual and palpatory identification of the fibrotic cords (number and localization). However, in some cases, it is important to adequately

distinguish AWS and Mondor's disease, a rare condition characterized by superficial thrombophlebitis, through local ultrasound assessment [7].

AWS treatment is complex and heterogeneous and directly involves the patient through education, home-performed exercises, and lifestyle interventions. It is important to highlight that AWS, although it is commonly a self-limiting disease, should be promptly treated to prevent shoulder ROM limitations, chronic pain and poor HRQoL [42]. In this context, rehabilitation has a key role in terms of soft tissue and scar manual treatment, upper limb mobilization and muscle stretching. Moreover, it has been also shown that a combination with MLD might result also in a reduction of BCRL, a very common concomitant condition in BC survivors [47]. Lastly, some new therapeutic approaches have been proposed over the last years, such as percutaneous needle cord disruption with fat grafting and Xiaflex or collagenase Clostridium histolyticum intralesional injection to the cording [48].

4. Persistent pain after breast cancer treatment

Chronic pain in cancer patients is a major health issue boosting disability and negatively affecting the HRQoL in this subject. Chronic pain management after cancer treatment plays a key role in the oncological rehabilitation scenario, with crucial implications in terms of both rehabilitative protocol feasibility and outcomes in BC survivors.

One of the most disabling conditions in BC survivors is PPBCT, defined as the presence of pain after a surgical procedure that lasts more than the usual healing time of 3 months [49]. More in detail, PPBCT prevalence in BC women treated with surgery is 29.8%, 27.3% after radiotherapy, and 21.8% after combined treatments [9]. These patients commonly complain of pain localized to the axilla, medial upper arm, thorax, and surgical scar [50] and PPBCT seems to be related to anxiety, stress, and depression [51], being the most important predictor of a low-grade quality of life after BC surgery [52].

To date, the precise etiopathogenesis of PPBCT is still unclear, although nerve fibers damaged during surgery or as a consequence of radiations and chemotherapies seems to play a main pathophysiological role in PPBCT genesis [53]. Indeed, nerve injury-induced neuropathic pain is one of the most common causes of post-surgical persistent pain, particularly after thoracic and breast surgery reaching a prevalence of 66 and 68% respectively [54]. Furthermore, the site of the tissue trauma is characterized by a chronic inflammatory process sustained by a consistent local release of cytokines, bradykinin, prostaglandins and histamine [55]. This inflammatory milieu results in a peripheral sensitization leading to the reduction of the threshold necessary to generate an action potential at the neuronal level [56]. ALND, radiotherapy, younger age, and high body mass might represent risk factors for the development of PPBCT [57-58]. However, the strongest association was found with ALND, which leads to an increase of 21% in the risk of PPBCT [9].

Being PPBCT a complex and multifactorial condition, its management should only be multidisciplinary involving both pharmacological and non-pharmacological approaches, such as physical therapies [59]. The main pharmacological agents used to treat PPBCT are analgesics, opioids, and non-steroid anti-inflammatory drugs. Moreover, anti-depressive agents such as amitriptyline and venlafaxine but also neuroleptic agents as levetiracetam and gabapentin have been tested in PPBCT without providing any evidence in pain and depression relief [59].

Considering the non-pharmacological approaches, the main rehabilitative interventions aimed at improving HRQoL are physical exercise, including active and passive mobilization, stretching exercises, myofascial relaxation, and shoulder ROM improvement [60]. Although these rehabilitative interventions improved shoulder mobility, their efficacy on pain relief is still debated [61]. More in detail, the myofascial technique is effective in reducing persistent arm pain in BC survivors at 3 months after surgery [62]. In this respect, the efficacy data on longer follow-up studies are expected.

5. Cancer treatment-induced bone loss

CTIBL refers to a clinical condition characterized by the development of secondary osteoporosis due to adjuvant therapies, such as tamoxifen and aromatase inhibitors (AIs), to reduce the proliferative effects of estrogens in BC patients [63-65]. Unfortunately, these drugs promote bone resorption [66] and lead to a decrease in bone mineral density and an increase in fragility fractures risk with a consequent disability and poor HRQoL [67]. CTIBL is a growing health issue in BC women, with crucial implications in the long-term management of these women [68-69]. According to CITBL pathophysiology, the magnitude of bone loss is related to the rapidity and severity of the estrogen deficiency [70], and AIs lead to a significantly higher risk of fragility fractures compared to tamoxifen (odds ratio = 1.47) [71].

Several positions and statements have been recently published about CITBL diagnosis and treatment. An adequate assessment of bone health through the lumbar spine and femoral dual-energy x-ray absorptiometry is highly recommended in BC women treated with AIs [72]. Indeed, BC women undergoing AIs should also perform an adequate physical examination, and an assessment of their risk of developing incident fractures in the next 10 years, through the Fracture Risk Assessment Tool.

The multifactorial therapeutic approach to CITBL includes lifestyle changing (e.g. stopping smoking and drinking alcohol), adequate physical activity, correct diet, and calcium and vitamin D supplementation [73]; among the several pharmacological treatments proposed to treat CITBL, oral bisphosphonates (i.e. alendronate and risedronate), zoledronic acid, and denosumab are considered as the first-line therapies [68-69].

6. Aromatase inhibitor-induced arthralgia

As previously discussed, AIs are commonly used as adjuvant therapy in women affected by hormone receptors-positive BC [63-65]. These pharmacological therapies could last for several years and might induce, apart from CITBL, as a frequent side effect, the AIA [74]. The prevalence of this pathological condition is variable, ranging from 20% [75] up to 74% [76], with a pooled

value showed in a meta-analysis of 46% [77]. AIA is reported as a huge burden by BC survivors and might compromise their HRQoL, leading also to treatment non-compliance [74].

The main pathophysiological mechanisms underpinning AIA are estrogen deficiency, which has been considered for a long time the main cause, and autoimmunity [78]. Estrogens indeed provide a beneficial effect on bone and cartilage health in terms of both inflammation reduction and tissue tropism. In this regard, estrogen-based therapy decreases joint pain and radiological knee osteoarthritis [79], meanwhile estrogen deficiency promotes an inflammatory milieu through the increased secretion of pro-inflammatory cytokines [80]. AIA is commonly described as joint pain and stiffness mainly localized in hand, wrist, and knee [77].

Few studies investigated AIA development risk factors and low body mass index (BMI), taxane-based chemotherapy and worst cancer stage were mainly related to AIA occurrence [81]. AIA management is a challenging issue for physicians and involves both pharmacological and non-pharmacological interventions [82]. More in detail, several therapies have been used for treating AIA, including prednisolone, etoricoxib, duloxetine, bisphosphonates, calcitonin, testosterone, thymosin, and diuretics; however, to date, there is still a limited evidence on these interventions [82].

Among non-pharmacological approaches, physical exercise seemed to be effective in decreasing AIA, as showed by a recent study reporting a reduction in joint pain of 29% after 1 year after a physical exercise protocol, whereas women treated with usual care had an increase of 3% of AIA symptoms [83]. More in detail, the exercise training protocol included both resistance training and aerobic exercise, performed at home and a gym with supervision, for 150 minutes per week over a year [83]. Lastly, non-conventional approaches to treat AIA have been investigated and among these the most promising seemed to be acupuncture, already effective also in general pain management; however, to date, its effectiveness in reducing AIA and joint pain in BC survivors is still debated [84].

7. Cancer related fatigue

CRF is defined by the National Comprehensive Cancer Network as “a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [85]. CRF prevalence is approximately 40% up to 90% in cancer survivors [86] and patients affected by CRF complain about physical and mental stiffness, idleness, stress, inactivity, short-term memory loss and reduced learning capacity and concentration [87]. CRF is commonly referred to as the most distressing symptom in BC survivors, both during and after active treatment with a detrimental effect on HRQoL [12, 88-89]. CRF etiology is still poorly understood and the main factors underpinning its pathogenesis are mitochondrial dysfunction and chronic low-grade inflammation, with a consequent increase of reactive oxygen species production [90-91]. Moreover, several risk factors have been identified, including sleep disturbance, emotional stress, anxiety, physical inactivity, high BMI, extensive surgery, chemotherapy, and radiotherapy [12,89].

Being CRF a complex and multifaceted condition with relevant disabling implications, an early diagnosis is crucial and should be performed with both unimodal (e.g. Visual Analog Scale, Brief Fatigue Inventory, and Cancer-related Fatigue Distress Scale) and multimodal tools (e.g. Multidimensional Fatigue Inventory, Functional Assessment of Cancer Therapy-Fatigue Subscale Instrument and the Multidimensional Fatigue Symptom Inventory), to explore all the domains underlying this complex phenomenon [92].

To date, several therapeutic interventions have been proposed to treat CRF in BC survivors [93-94], including also lifestyle improvements and behavioral therapy, as increasing sleep time [95]. Moreover, a healthy and balanced nutrition, including an adequate intake of vitamins, proteins, carbohydrates, and minerals, should be recommended in CRF patients to provide a correct energy intake aimed at reducing CRF [92]. Moreover, diets rich in antioxidants are proved to be related to a lower prevalence of CRF and a recent study highlighted the efficacy on CRF reduction and sleep

improvement of a 3 months “fatigue reduction diet”, rich in fruit, vegetables, whole grains, and omega-3 fatty acid-rich foods in BC survivors compared with a standard diet [96].

However, to date, physical exercise is the most effective intervention to reduce the negative impact of CRF on BC survivors [13,97]. Several systematic reviews and meta-analysis showed an improvement of CRF symptoms in cancer survivors treated with physical exercise, increasing both physical and HRQoL during and after treatment [98-100]. Among different types of exercise, evidence suggests that aerobic and resistance exercises are the most effective in reducing CRF in BC patients [101-102], and a physical exercise protocol consisting of 40 minutes per session, 3 sessions per week for more than 28 weeks seems to exert the greater beneficial effect to reduce fatigue [100].

Lastly, yoga is considered as a supportive intervention for decreasing CRF, reducing sleep disturbance, and improving HRQoL in BC patients, as reported by a recent meta-analysis [103]. Similarly, even though with less consistent evidence, also mind-body therapies like Qigong and TaiChi showed a significant reduction of CRF, depression, and sleep disturbance in BC survivors [104].

8. Conclusions

Thanks to the increasing effectiveness of the screening programs and treatment protocols, the number of people who die of BC has progressively declined. In this scenario, caregivers are expected not only to prolong their patients’ life but also to preserve and improve their HRQoL. BC “survivorship” comprises the continuum from initial diagnosis through the rest of the patient’s life, evocate different issues and feelings to different individuals. The goal of HRQoL interventions is to return to the QoL before the initial diagnosis of BC. We would like to emphasize that this complex scenario requires a precision medicine approach for a more effective decision-making and also treatment compliance.

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MI and AdS contributed equally to this work as first authors; Study conceptualization and design: MI, AdS, NF; Literature research: AdS, EC, SC, MB; Writing manuscript: MI, AdS; Critical revision: NF; Supervision: MI, CC, NF; Revision and approval of the final draft by all the authors.

List of abbreviations

3DLS: three-dimensional laser scanner

AIA: aromatase inhibitor-induced arthralgia

AIs: aromatase inhibitors

ALND: axillary lymph-node dissection

AWS: axillary web syndrome

BC: breast cancer

BCRL: breast cancer related lymphedema

BMI: body mass index

CDT: complex decongestive therapy

CM: circumferential method

CRF: cancer related fatigue

CTIBL: cancer treatment-induced bone loss

HRQoL: health-related quality of life

MLD: manual lymphatic drainage

PPBCT: persistent pain after breast cancer treatment

ROM: range of motion

WD: water displacement

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Figures legend.

Figure 1. Quality of life strategies in breast cancer survivors.