EXERCISE REHABILITATION IN BREAST CANCER

Breast cancer is the most common cancer in women worldwide, and the probability of an arbitrary woman being diagnosed with breast cancer during her lifetime is about 10-13%. (1); among these women, 38% were diagnosed more than 10 years ago.

Because of its high incidence and relatively good prognosis, breast cancer is the most prevalent cancer among women in the world. However, breast cancer is still the leading cause of cancer-related death among women in many developed countries, and is the most common cause of death of women aged 40–60 years (1). Breast cancer mortality rates have declined, possibly due to earlier detection, improvements in surgical resection, radiation, and systemic therapies (2). Thus, as more patients survive breast cancer, the number of women living with long-term side effects also increases (2).

CLINICAL PRACTICE

Today, three screening tests are routinely in use for detection of breast cancer: mammography, physical breast exam, and breast self-exam. When a breast tumor is detected, a more detailed examination can be done (mammogram and/or ultrasound and/or MRI (Magnetic Resonance Imaging). The final diagnosis is performed by microscopic examination of fine-needle aspirations (cytology) or a biopsy (histology) (3). Even though the routines related to breast cancer diagnosis are efficient, patients may have to wait several weeks before treatment. This delay waiting period may impose additional psychological challenges for the woman.

Treatment options of breast cancer patients and morbidities.

Breast cancer treatment involves multiple medical disciplines. The treatment depends on the patients age, menopausal status as well as disease stage and pathological features; type, tumor grade, multifocal receptor status, and family predisposition (3). Disease stage is determined by tumor size, the number and location of lymph nodes involved, and the presence or absence of distant metastatic disease. The treatment consists of local treatments such as surgery and radiotherapy, systemic treatment such as chemo and hormone therapy, and monoclonal antibodies (4;5).

Surgery

Surgical procedures have been modified during the last decades (6). With *radical mastectomy* (Halsteds method), major side effects occurred (extensive and frequent arm and shoulder morbidities). It was therefore replaced by m*odified radical mastectomy* in the 1970-80's. Postsurgical side effects were reduced without increase in local relapses or decreased survival rates. Breast conserving treatment was then developed. Randomized studies showed that only removing the tumour (lumpectomy) and a rim of normal surrounding breast tissue were as safe as modified radical treatment, if the patient was treated with postoperative radiotherapy to the whole breast (7;8).

Axillary lymph node dissection (ALND) is now done in less than 50 % of the patients due to sentinel lymph node biopsy (SLNB) (9;10). The status of the axilla is one of the most important prognostic factors in breast cancer. Subsequent decisions on supplementary treatment depend on how much lymph nodes are affected as well as other patient and tumour characteristics.

Mastectomy is still recommended for patients with large tumours and for patients when irradiation is contraindicated. Other factors may need to be taken into account as well when consider mastectomy (e.g. genetic factors and high risk of relapse) (3). For these patients, breast reconstruction can be performed concomitantly with mastectomy or at a later time.

Systemic (neo) adjuvant treatment
Systemic therapy is indicated for patients with high and intermediate risk of cancer recurrence. In most cases systemic treatment is given shortly after surgery (adjuvant), e.g. endocrine- and/or chemotherapy; some patients also receive monoclonal antibody therapy, e.g. trastuzumab (Herceptin). In some cases, chemotherapy is given before surgery (neoadjuvant) to try to shrink the tumour (down-stage) to make surgical removal possible. The type of chemotherapy or monoclonal antibody treatment is selected based on the type, size, and grade of the tumour and the molecular characteristics and involvement of lymph nodes in the axilla. Other combinations of chemotherapies can be given depending on tumour characteristics. Endocrine therapy is only given to patients after histologically proven estrogen (ER) and/or progesterone (PgR) receptors(3,11).

Side effects of regular treatment
Several health problems/side effects may develop following breast cancer diagnosis and treatment (presented in Table 1). Side effects can follow surgery, either ALND or SLNB, but are less common and often less severe following SLNB (9). Common side effects are temporary or permanent numbness of the skin on the inside of the upper arm, temporary or long-term limitation of arm and shoulder movements, and swelling of the breast and arm called lymphedema. Lymphedema is the most sig-nificant of these side effects and may develop into a permanent health problem. Significant lymphedema is reported in 10-50 % of women who have had axillary lymph node dissection and approximately 5-20 % of women who have had sentinel lymph node biopsy. Lymphedema may result in cosmetic deformity, loss of functionality, physical discomfort, recurrent episodes of erysipelas, and psychological distress. Pain is reported by 12 - 51% of patients 1 year after treatment (12), most frequently due to nerve injuries during surgery; the treatment is often pharmacological.
Early side effects due to radiation can include irritation, rubor in the skin during radiation treatment, and tiredness resulting in reduced physical activity. The majority of skin reactions disappear a few weeks after treatment is completed. Late side effects can include slightly darker skin in the treated area and continued sensitivity to sun exposure. Later development of teleangectasis, skin- and lung fibrosis may occur. If the axilla has been irradiated, there is an increased risk of reduced mobility of the shoulder, lymhedema, especially after ALND and when several lymph nodes have been affected (13). Pulmonary sequela as radiation pneumonitis (incidence 2-29%) is rarely of clinical consequence.

Side effects of chemotherapy shows individual variation and is also depending on the type of drug used (14). Common acute side effects are: alopecia (hair loss), nausea, fatigue, increased risk of weight gain, increased risk of infection, and temporary effects on bone marrow with lower blood counts, especially white blood cells (leucocytes).

The most common side effect of endocrine therapy is weight gain, symptoms of menopause, hot flashes, and vaginal dryness.. Some drugs may cause an increased risk of osteoporosis and bone fractures (15).

Cardiac toxicity is a concern in breast cancer survivors (14). There is known for a long time that anthracyclines cause acute and chronic cardiotoxicity. However, the cardiotoxic effects of radiation therapy, hormonal therapy (including tamoxifen and the aromatase inhibitors), and chemotherapy with taxanes and trastuzumab treatment have emerged more recently (3;11;14). A single breast cancer patient may receive anthracyclines, trastuzumab and radiotherapy before commencing hormonal therapy (14).
One major consequence of breast cancer and associated treatments is weight gain. Physical inactivity has also been observed as a consequence of various breast cancer treatment modalities (2). There is some

studies that show an association between weight gain and increased breast cancer recurrence and mortality (16;17).

Common long term side effects and consequences after breast cancer are listed in table 1.

Table 1. Long term side effects and consequences after breast cancer treatment Problem type	**Side effects related to the disease**	**Side effects related to treatments**	**Type of treatment**
Fatigue **Depression**	**X**	**x**	**Chemotherapy** **Endocrine therapy** **Irradiation**
Lymphedema	**X**	**x**	**Surgery** **Irradiation**
Shoulder movement impairments	**X**	**x**	**Surgery,** **Axillary dissection** **Irradiation**
Weight gain	**x**		**Chemotherapy** **Endocrine therapy** **Hormone therapy**
Cardio-respiratory	**x**		**Chemotherapy** **Irradiation** **Monoclonal antibodies**
Skeletal **Bone marrow** **Osteoporosis**	**x**		**Chemotherapy** **Endocrine therapy (Aromatase Inhibitors)**
Pain	**x**	**x**	**Surgery** **Chemotherapy**
Slightly increased risk of thrombosis (blood clot)	**x**		**Chemotherapy** **Endocrine therapy**

REHABILITATION OF BREAST CANCER PATIENTS

Rehabilitation is a process in which different caregivers use a combination of their specific treatment modalities. In the following paragraphs we will therefore describe the most common modalities.

Physiotherapy

Physiotherapy for breast cancer patients is based on the same principles as for other patient groups, although they have some special problems related to their cancer and its treatment. Physiotherapy uses both passive and active stimuli in prevention, treatment and rehabilitation. It involves careful examination of the musculoskeletal system and the application of knowledge, stimuli, and skills.

Impaired shoulder function and development of arm lymphedema, i.e. an arm volume difference between the arms of >150 ml or circumferential arm difference of >2 cm, are common side effect of treatment for early breast cancer. Therefore, complications following cancer treatment, such as lymphedema, scar adherence, pulmonary complications, range of motion, and muscle strength, are of major importance.
Water displacement, circumference measurement, and tissue tonometry are important methods used to evaluate the status of lymphedemous limbs. Goniometers and dynanometers are used to measure the range of motion and muscular force/endurance, respectively.
The American College of Sports Medicine (ACSM) roundtable on exercise guidelines for cancer survivors describes that exercise during and after cancer treatment is safe and can help patients improve their physical capacity and quality of life (18). The ACSM guidelines indicate specific exercise programs oriented towards impairments associated with disease and medical treatment (18). Strength exercise does not have any negative effects on an existing SL (19); instead, it has beneficial effects such as improvement of strength (20) and lower exacerbation rates (21). However, these recommendations do not include any information about the prevention of SL in breast cancer patients.

They showed that exercise in the form of progressive resistance training as well as combined exercise therapies consisting of physiotherapy, physical therapy, MLD, stretching, massage, and/or kinesiotherapy are safe and might have a preventive effect.

In the past, physicians believed that cancer patients must avoid exercise (18), and literature indicating that exercise can cause or exacerbate lymphedema still exists (22). However, the present review revealed that 5 out of 8 trials reported significant preventive effects of resistance training and exercise on SL incidence. Park et al. (23) investigated the incidence and risk factors of SL(secondary lymphedema) in breast cancer patients. They demonstrated that women who exercised regularly, performed preventive self-care, and received information about the possible appearance of a lymphedema before local treatment had a lower risk of developing lymphedema. Proposed mechanisms included that exercise promotes the contractility of the skeletal muscles and subsequently provides primary pump mechanisms for lymph and venous drainage (24,25).

Besides radiation and the number of surgically removed lymph nodes (30), overweight also contributes crucially to the development of SL (26–28). In the study by Sagen et al. (29), a significant risk increase was observed in patients with a body mass index of >25 kg/m2 ($p = 0.005$). Shaw et al. (31) also referred to the relationship between overweight/obesity and the development of lymphedema (32). According to Bicego et al. (24), further risk factors include obstruction, trauma, and inflammation (33). Physical inactivity results in a decrease in lymph circulation. Physical exercise maintaining or improving the ‘range of motion’ of the shoulder therefore seems to be an effective and preventive measure. Additional benefits include improved muscle strength/fitness and maintenance of body weight.
Further, Ahmed et al. (22) recommend that breast cancer patients should perform strength training of the upper body because this does not promote the risk or symptoms of lymphedema. Besides, Sagen et al. (29) recommend that patients with axillary lymph node dissection continue to exercise without restriction in daily living. In addition, considering early exercise intervention in women with breast cancer is important and necessary (34). The studies by Ahmed et al. (22) and Schmitz et al. (40) show that progressive strength training can generate a preventive effect. Combined exercise therapy can result in similar effects (35-37). Exercise additionally supports muscular pump function and should be performed at a moderate level of intensity and with a small number of repetitions. The application of MLD seems to have prophylactic effects only in combination with exercise, and current data does not show any evidence for MLD as a single primary prophylactic method (38). To guarantee the safe and effective performance of the exercises, the support of a certified exercise therapist during the first months of the exercise training is also advised
(39).

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