Herlev og Gentofte Hospital

# Clinical Study Protocol

## Exercise in older women with breast cancer during systemic therapy – a randomized controlled trial

The study is one of five studies included in the TOLCA project "Translational and clinical research focused on OLder patients with CAncer aiming to improve patient survival and quality of life".

## Indholdsfortegnelse

## Synopsis

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| **Title** | Exercise in older women with breast cancer during systemic therapy – a randomized controlled trial. |
| **Introduction** | Although cancer is predominantly a disease of the elderly, older cancer patients are underrepresented in clinical trials. Aging itself is associated with limitations in physical function, reduced reserve capacity, a poorer resilience to physiological stressors, and an increased burden of comorbidities. A diagnosis of cancer and its accompanying treatments can lead to numerous symptoms and side effects, physical disability, psychological distress and increased health care needs. The interplay between age-related and cancer-related declines in health increases vulnerability and the risk of development of short and long-term disability. Research has shown that exercise training has several beneficial effects in cancer patients and survivors both during and after anti-cancer treatment. However, older patients have often been underrepresented in these studies, and only few exercise-based intervention studies have specifically focused on older cancer patients. Breast cancer is a malignancy associated with aging. Research projects that investigate the effect of interventions that may reduce symptoms, maintain physical function, and optimize QOL are wanted.<br><br>The TOLCA Breast Cancer Exercise study will be conducted similar to the ongoing PACE-MOBIL-PBL study regarding physical therapy. |
| **Design** | TOLCA Breast Cancer Exercise study is a two-armed 1:1 randomized controlled study in older patients with breast cancer treated with adjuvant or first-line palliative systemic therapy. |
| **Target population** | Older patients with breast cancer who are treated with adjuvant or first-line palliative systemic therapy. |
| **Number of Centers and setting** | Single center. Department of Oncology and Department of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital. |
| **Objectives** | To investigate the effect of an exercise-based intervention on physical function and capacity, cancer-related symptoms and side-effects, depression and anxiety, quality of life, body composition, treatment tolerance and toxicity, inflammation, hospital admissions, and survival. |
| **Selection Criteria** | **Inclusion criteria**:<br>• Be operated for primary breast cancer within 12 weeks or<br>• Be diagnosed with locally advanced or metastatic breast cancer. Be treated with adjuvant or first-line palliative therapy defined as chemotherapy ± HER2 directed treatment, ± antihormonal treatment, antihormonal treatment ± HER 2, directed treatment ± CDK 4/6 inhibitor.<br>• Be ≥ 70 years of age at the time of signing the informed consent form<br>• Have an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2<br>• Be able to speak and read Danish, and to provide a signed informed consent form |

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| | **Exclusion criteria**; patients with:<br>• Any physical condition that hinder the execution of physical exercise training<br>• Other types of cancer<br>• Documented and uncontrolled brain metastases that hinder participation in an exercise-based trial, based on the referring oncologist's assessment<br>• Dementia, psychotic disorders, or other cognitive diseases or conditions that hinder written consent<br>• Unstable medical disease or history of serious or concurrent illness; any medical condition that might be aggravated by exercise training or that cannot be controlled, including, but not restricted congestive heart failure (NYHA class III-IV), unstable angina pectoris, implantable cardioverter defibrillator (ICD), or myocardial infarction within 6 months, based on the referring oncologist's assessment<br><br>In patients with documented bone metastases:<br>• A bone metastatic burden or location that poses a risk of injury in the performance of exercise training, as assessed by the referring oncologist |
| **Study arms** | Included patients will be randomized 1:1 to an intervention group and a control group.<br><br>Patients in the intervention group will receive standard care and a 12-week exercise-based intervention comprised of:<br>1. Supervised and group-based exercise training at the hospital setting two times a week. Each session will last approximately 60 minutes<br>2. Home-based walking with activity tracker assessment. Evaluation and goal-setting in relation to activity (step counts) will be conducted once weekly<br>3. Serving of a protein supplement (protein drink or bar) after each supervised training session<br><br>Patient in the control group will receive standard care. |
| **Baseline data and endpoints** | **Baseline data**<br>• Demographic and patient-reported data: data on civil status, working status, education, smoking, alcohol consumption, weight loss before and after cancer diagnosis, and physical activity<br>• Clinical and medical data: diagnosis, treatment, performance status (ECOG), comorbidity, including Charlson comorbidity score.<br><br>**End-points**<br>• Physical function and capacity: 30-second chair stand test (30s-CST) **(primary outcome)**, 6-minute-walk-test (6MWT), hand grip strength (HST), 6- and 10-meter gait speed, measured at normal and maximal gait speed (6MGS & 10MGS) and stair climb test (SCT).<br>• Feasibility measures: recruitment rate, attrition, retention, and adherence<br>• Patient reported outcomes: patient reported performance status (ECOG), EORTC Quality of Life Questionnaire (EORTC-QLQ-C30 |

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| | & BR23), the Hospital Anxiety and Depression Scale (HADS), and M.D. Anderson Symptom Inventory (MDASI)<br>• Physical activity: step counts, distance, and energy consumption measured with an activity tracker<br>• Treatment tolerance and toxicity: completion of scheduled therapy, dose-reductions, discontinuations, toxicity (according to the National Cancer Institute Common Toxicity Criteria for Adverse Events v4)<br>• Body measures and composition: weight, height, body mass index (BMI), and body composition measured by bioimpedance assessment and DXA scans<br>• Inflammatory biomarkers: C-Reactive Protein (CRP), Interleukin 6 (IL-6), YKL-40, GDF11 and GDF15.<br>• Hospital admissions: numbers, causes, length of hospitalizations and contact to the Emergency Room (ER) with falls.<br>• Mortality/survival |
| **Number of patients / sample size** | No prior studies have reported the minimal clinically important difference in the 30s-CST in older patients, or in cancer patients. However, based on results from a prior study focusing on patients with osteoarthritis, a clinically important change in the 30s-CST was set at 2.6 repetitions. Based on results from other studies focusing on patients with advanced cancer, a standard deviation (SD) of around 3 in 30s-CST was reported. To be able to detect a change of 2.6 repetitions in the between group difference at the 12-week assessment, and to obtain a type I error rate of 5% and a power of 90%, a sample size of 29 patients per study arm will be needed. To account for an expected dropout rate of approximately 40%, we decided to increase this number to a group size of 50. Hence, a total of 100 patients will be included in the study. |
| **Statistical Analysis** | Feasibility measures will be reported as numbers and percentages. Reasons for declining participation will be analyzed descriptively with numbers and percentages of patients declining for various reasons. Baseline characteristics will be calculated for all patients included (total), and separately for the intervention group and the control group. For all quantitative variables, the median number and interquartile range (IQR) will be calculated, and for nominal variables the number and percentage distribution will be calculated. Results from physical tests, blood test, body measures, and questionnaires will be reported as means and standard deviations (SD) or as median and IQR, as appropriate. Change over time in ordinal categorical values will be evaluated by a trend test using logistic regression. In-group and between- group differences in continuous-level data, will be performed using a repeated measurement analysis. Survival analyses will be conducted with Kaplan-Meier method, competing risk analyses and Cox regression analyses. The significance level of all tests is set a $p < 0.05$, and analyses will be carried out in SAS or R by Zoltan Szallasi (DTU) in collaboration with the study group. |
| **Publication of results** | Positive, negative, or inconclusive results from the TOLCA-Breast Cancer Exercise study will be published in relevant international peer-reviewed journals. Co-authorship for the upcoming publications will be offered to members of the project group or other collaborators based on contributions to the current work, and in accordance with the Vancouver recommendations. |

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| **Potential risks and disadvantages** | There are a few potential risks and disadvantages for patients in the intervention groups, including exercise injuries and discomfort in performing the exercise program. However, risks and disadvantages are limited. If a patient reports any discomfort or incidence of injury during the intervention, the safety and further program-continuation for the patient will be discussed in the research group, and in consultation with the patient and the responsible physician. Data on adverse events will be collected systematically throughout the intervention period.<br>Body composition will be assessed for all included patients at baseline and after 12 weeks using DXA technology. At each of the two DXA scans patients will be exposed to a small radiation dose of approximately 3 µGY (= 0.003 mSv). |
| **Scientific statement** | The TOLCA - Breast Cancer Exercise study is expected to involve low risk of adverse events and discomfort for patients involved. It is the project group's assessment that it is necessary to carry out the current research project to gain important knowledge about the effect and feasibility of exercise-based intervention as a rehabilitative approach to older patients with breast cancer. The project group estimates that the TOLCA-Breast Cancer Exercise intervention will maintain or increase physical function levels, reduce symptoms and side effect, increase tolerance to oncological treatment, and improve psychological well-being and QOL in older patients with breast cancer and that the expected benefits of the intervention exceeds the estimated limited risks for patients involved. |

## Generel information

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| Primary investigator | Ida Lundager, PhD student<br>Department of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital Herlev Ringvej 75, 2730 Herlev, Denmark<br>Telephone: +45 38689570<br>Email: ida.katrine.lundager@regionh.dk |
| Medical responsibility | Dorte Nielsen, Professor, MD, PhD, DMsc. Department of Oncology, Herlev and Gentofte Hospital |
| Project group | • Anders Vinther, MSc in Physiotherapy, PhD. Department of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital<br>• Carsten B. Juhl, MSc in Physiotherapy, PhD. Department of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital<br>• Hanne F. Skall. Department of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital<br>• Marta Kramer Mikkelsen, RN, MHSc, PhD-student. Department of Oncology, Herlev and Gentofte Hospital<br>• Cecilia Lund, MD, PhD. Departments of Medicine and Oncology, Herlev and Gentofte Hospital<br>• Julia S. Johansen, Professor, MD, DMSc. Departments of Oncology and Medicine, Herlev and Gentofte Hospital<br>• Dorte Nielsen, Professor, MD, PhD, DMSc. Department of Oncology, Herlev and Gentofte Hospital<br>• Anne Polk, MD, PhD-student. Department of Oncology, Herlev and Gentofte Hospital<br>• Stig E. Bojesen, Professor, MD, PhD, DMSc. Department of Clinical Biochemistry, Herlev and Gentofte Hospital |
| Statistician | • Zoltan Szallasi, Professor, PhD. Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark (DTU) |
| Collaborators | • Charlotte Suetta, Clinical associate professor, MD, PhD, Department of Clinical Medicine, Rigshospitalet |
| Funding | The TOLCA-Breast Cancer Exercise study is financially supported by a grant from the VELUX Foundation. The VELUX Foundation will be mentioned in all written and oral presentations and publications. The VELUX Foundation will not have any role in the conduction of the study design or protocol, data collection, interpretation of data, or in the drafting or approval of coming publications. |
| Time schedule | Project preparation: April 2018 – May 2018<br>Recruitment and intervention: August 2018 – December 2020 |

## List of abbreviations

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| **ACSM** | American College of Sports Medicine |
| **ADL** | Activities of daily living |
| **BC** | Breast cancer |
| **BMI** | Body mass index |
| **BI** | Bioelectrical impedance |
| **CCI** | Charlson comorbidity index |
| **CG** | Control group |
| **CRAG** | Cancer & Aging Research Group |
| **CRP** | C-reactive protein |
| **DXA** | Dual-energy X-ray absorptiometry scan. |
| **EORTC** | European Organization for Research and Treatment of Cancer |
| **EORTC QLQ-C30 evt. suppleret med BR23** | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- C30 |
| **ECOG** | Eastern Cooperative Oncology Group |
| **ER** | Estrogen receptor |
| **ESPEN** | European Society for Clinical Nutrition and Metabolism |
| **EWGSOP** | European Working Group on Sarcopenia in Older People |
| **5-FU** | 5-fluorouracil |
| **GFR** | Glomerular filtration rate |
| **HADS** | Hospital Anxiety and Depression Scale |
| **HCP** | Health care professional |
| **HR+** | Hormone receptor positive |
| **HST** | Handgrip strength test |
| **HER2** | Human epidermal growth factor receptor 2 |
| **ICF** | Informed consent form |
| **IG** | Intervention group |
| **IL-6** | Interleukin 6 |
| **IQR** | Interquartile range |
| **MDASI** | M.D. Anderson Symptom Inventory |
| **M:I ratio** | Mortality to incidence ratio [1-(mortality/incidence)] |
| **PA** | Physical activity |
| **PRPS** | Patient reported performance status |
| **PROM** | Patient-reported outcome measure |
| **PRT** | Progressive resistance training |
| **PS** | Performance status |
| **RM** | Repetition maximum |
| **SCT** | Stair Climb Test |
| **SD** | Standard Deviation |
| **SMART** | Specific, measurable, achievable, realistic/relevant and time-based. |
| **TP** | Thymidine phosphylase |
| **QOL** | Quality of life |
| **30s-CST** | 30-second chair stand test |
| **6MGS** | 6-meter gait speed |
| **10MGS** | 10-meter gait speed |
| **6MWT** | Six-minute-walk-test |

# 1. Introduction

Although the risk of cancer increases with age, and the number of older cancer patients is expected to rise in the coming years (1-4), research on older cancer patients and survivors has been limited (3, 5). In Denmark, approximately 65% of all cancers are diagnosed among patients ≥ 65 years of age, and the number of incident cancers is expected to increase with 30% towards 2030 solely because of the increasing elderly population (6). Before discussing the impact of cancer disease in older individuals, it is necessary to describe the normal aging process and psychosocial factors related to aging.

## 1.1 The aging process

The age at which a person is considered being 'elderly' or 'older' varies in the literature and currently no definitive consensus exists. Age above 65 years has traditionally been chosen as the 'cut-off' as it represents the age of retirement in many Western countries. Aging involves a continuum of changes in function, biological, psychological and social structures that vary depending on individual differences in genetic factors. It must be empathized that older people represent a widely heterogeneous group and that chronological age does not accurately describe the capacity, resources and functioning of an older person. In a biological view, aging involves physiological changes in the organisms that lead to a decline of biological functions and the ability to adapt to metabolic stress. The biological changes involve a decrease in cardiac function and capacity due to reduced muscle strength, vascular stiffness, increased ventricular wall thickness, atherosclerosis, and loss of elasticity of the vessel walls (7). The respiratory tract undergoes structural and functional changes which are often associated with a decrease in lung function, limited regeneration and an enhanced susceptibility to infections and pulmonary diseases (8). Despite large variation among individuals, aging is also associated with a decline in kidney function, including a decreased renal blood flow and glomerular filtration rate (GFR), which makes drug excretion more problematic (9). In the gastrointestinal tract, age-related physiological changes (e.g. decrease in gastric acid and functional absorption, alterations in gastric motility and gastrointestinal hormones) may significantly alter the absorption and metabolisms of nutrients and medications, and thereby places older persons at a major disadvantage when they are exposed to weakness or disease (10). The aging process typically involves changes in the body composition with an increase in fat mass and a decrease in muscle mass. Evidence suggests that age-related loss of muscle mass starts in the fifth decade with an annual rate of up to 1-2%, and mainly influences the lower body skeletal muscle mass (11, 12).Loss of muscle mass is accompanied by an even faster deterioration of muscle strength (13).With age, the bones deteriorate in composition, structure and function. Increased bone resorption and reduction in bone formation leads to a fall in bone mineral density, and increased risk of osteoporosis and bone fractures (14). Aging also has an effect on immunity, with evidence indicating that the cell-mediated immunity consistently displays age-related declines in function (15). The reduction of reserve capacity in bone

marrow that occurs with aging deduces the ability to respond to stressors such as infections or blood loss (15, 16). Comorbidity, defined as the occurrence of two or more medically diagnosed diseases, increases with age and heightens the risk of disability and mortality (17, 18). Furthermore, the use of multiple drugs for multiple diseases, also known as polypharmacy, leads to an increased risk of drug interactions, adverse drug reactions, and poor adherence (19). The aging process also entails cognitive and psychosocial changes. Despite significant heterogeneity among older individuals, cognitive changes are recognized as a normal part of the aging process, and some cognitive abilities such as memory, processing speed, and conceptual reasoning decline over time(20). Social structures and roles also change with aging because of multiple factors and events such as retirement, limited social network, loss of family members or close friends, decreased functional ability, and increased dependency(21).

### 1.2 Cancer and aging

Aging itself is associated with limitations in physical function, reduced reserve capacity, a poorer resilience to physiological stressors, and an increased burden of comorbidities (17, 22). A diagnosis of cancer and its accompanying treatments can lead to numerous symptoms and side effects, physical disability, psychological distress and increased health care needs (23). The interplay between age-related and cancer-related declines in health increases vulnerability and the risk of development of short and long-term disability (24, 25). Compared to older individuals without a history of cancer, older cancer patients and survivors suffer from a greater incidence of limitations in activities of daily living (ADL), reduced quality of life (QOL), lower self-rated health, and higher prevalence of geriatric syndromes such as depression, falls and osteoporosis (26, 27). Research suggests that older cancer patients derive benefits to chemotherapy similar to the benefits derived by younger patients (28-30). However, older cancer patients are at increased risk of chemotherapy toxicity due to age-related physiologic changes, e.g. decreased stem-cell reserves, reduced ability to repair cell damage, and progressive loss of body protein (31). Furthermore, comorbidities and their associated treatments increase risk of chemotherapy toxicity even further (31). Recommendations from an expert group meeting in 2016 concluded that rehabilitation services should be offered early to older cancer patients to optimize tolerance to cancer treatment, minimize toxicity, and improve outcomes (32).

### 1.3 Sarcopenia and cancer cachexia

Loss of muscle mass and strength is a part of the normal aging process, and is often referred to as ‘sarcopenia’. In accordance with an European consensus report, sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and muscle strength (33). Sarcopenia has multiple contributing factors including aging process itself, insufficient nutrition, sedentary lifestyle or bedrest, and chronic diseases and certain medical drugs. Sarcopenia that occurs solely due to aging is

typically referred to as ‘primary sarcopenia’, while the term ‘secondary sarcopenia’ is used to describe sarcopenia that is caused by other factors such as cancer or other chronical diseases (33). Sarcopenia may be responsible for functional impairment, increased risk of falls, and loss of independence in the elderly population (34). The clinical diagnosis of sarcopenia is made from the presence of low muscle mass in combination with low muscle function (either low muscle strength or performance), and can be diagnosed with different validated measurement techniques (33). Besides sarcopenia, ‘cachexia’ is another depleting syndrome that causes weight loss and muscle wasting due to an underlying disease. Cachexia is an important complication among cancer patients, particularly in advanced-stage cancer. Cancer cachexia is “a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment” (35). The pathophysiology of cancer cachexia is complex and includes a combination of reduced energy intake, hormonal alterations, and abnormal metabolism and inflammation. Cancer cachexia is clinically defined as loss of more than 5% of stable body weight over the past 6 months, or loss of more than 2% of body weight in patients who are already showing depletion according to Body Mass Index (BMI) (BMI $<20 kg/m^2$) or according to skeletal muscle mass (sarcopenia) (35). Differentiation between cachexia and sarcopenia can be difficult as loss of muscle mass is an important feature of cachexia, and therefore most cachectic subjects will also be sarcopenic, whereas most sarcopenic subjects are not considered cachectic (36). Prior studies have identified cachexia and sarcopenia as contributors to impaired physical functioning (37), reduced tolerance to anti-cancer treatment (38-40), higher symptom burden (41), reduced QOL (41, 42), and increased mortality (39, 43-46) among patients with cancer. Therefore, it is of upmost importance to focus on prevention, identification and treatment of cancer cachexia and sarcopenia in clinical practice. However, research has shown that cancer cachexia and sarcopenia are rarely recognized or managed actively by physicians (41, 47). Furthermore, older cancer patients may be at particular risk of cachexia and sarcopenia due to age-related declines in physical reserves, sedentary life-style, insufficient nutrition and comorbidities(48). Evidence suggests that regular exercise training, increased activity level, and sufficient energy and protein intake are effective strategies in the prevention and treatment of sarcopenia, which also have been shown as promising interventions in the prevention and treatment of cancer cachexia (49-51). According to recently published guidelines for nutritional care in cancer patients from the European Society for Clinical Nutrition and Metabolism (ESPEN), body resources and physiological decline in cancer patients are endangered by a complex pattern of physical and functional derangement (52). Therefore, strategies to prevent and treat malnutrition, sarcopenia and cachexia among cancer patients should optimally comprise a comprehensive approach, including nutritional advice/therapy,

counseling and guidance to optimize symptom management, and physical rehabilitation/exercise training (52).

## 1.4 Exercise training

Exercise training is a strengthening multi-effect strategy that has the capacity to work across multiple organ systems. Research has shown that exercise training (e.g. aerobic training, resistance training, and balance and flexibility exercises) is safe and beneficial to perform for older people. The beneficial effects include increased muscle mass and strength, aerobic capacity, functional mobility and ADL function, balance and reduction of falls, improved QOL, and reduction of depressive symptoms (53-56). Also, evidence suggests that exercise training alone or in combination with nutritional interventions have some effect on the prevention and treatment of age-related sarcopenia (57, 58). The effects of exercise interventions have also been widely investigated among cancer patients. Research has shown that exercise training is effective in the prevention or reduction of symptoms and side effects from cancer disease and treatment (59). Several intervention studies have investigated effects of exercise training in cancer patients both during and after oncological treatment, and a myriad of beneficial effects have been documented, including reduced levels of fatigue, and improved aerobic capacity, muscular strength, physical functioning and QOL (60-62). However, older patients have often been underrepresented in these studies, and only few exercise-based intervention studies have specifically focused on older cancer patients (63). Among the few studies that investigated the effects of exercise interventions in older cancer patients, most focused on older patients with early-stage breast, prostate and colorectal cancer in the post-operative treatment period, and excluded patients in active oncological treatment. Especially, research investigating the effect of exercise training in older cancer patients with advanced-stage disease is lacking (63).

## 1.5 Breast cancer

Breast cancer is the most frequent cancer among women and is a major cause of cancer-related deaths worldwide. It is estimated that more than 1.67 million new cases of breast cancer occurred worldwide in women in 2012 (65). Breast cancer accounts for approximately 522,000 deaths in the world each year, which makes it the 5th most common cause of cancer-related death today in women and men combined (64). In 2030 breast cancer is expected to be the 5th leading cause of cancer-related death (65). Every year approximately 5000 women are diagnosed with breast cancer in Denmark (68; NORDCAN 2011-2015; Cancerregisteret Årsrapport 2016).

At diagnosis, more than 90% of patients present with early breast cancer defined as local disease amenable for curative surgery. Depending on patient age, menopausal status and tumor characteristics such as size, grade of malignancy, lymph node status, estrogen receptor (ER) and human epidermal

growth factor receptor 2 (HER2) expressions, approximately 90% of patients with early breast cancer are offered systemic adjuvant treatment. This includes some or all of the following; anti-estrogen, anti-HER2 treatment and chemotherapy (69). The hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer subtype is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers (70).

Overall, adjuvant chemotherapy decreases risk of recurrence and improves survival, but the absolute benefits in patients with a low risk of recurrence may be small. Therefore, the decision to offer chemotherapy must consider risk factors of the disease as well as patient age and comorbidities. Adjuvant chemotherapy is standard for patients with triple-negative breast cancer and HER2-positive breast cancer. Chemotherapy treatment decision-making for women with ER-positive, HER2-negative breast cancers is more complicated, owing to the variation in prognosis among women with ER-positive, HER2-negative tumors, the effectiveness of adjuvant endocrine therapy at reducing recurrence, and the variable sensitivity of ER-positive tumors to chemotherapy treatments. For such patients, the decision to administer chemotherapy is based on an assessment of the composite risk of recurrence and likely benefit of treatment based upon patient age, tumor lymph node status, size, grade, lymphovascular invasion, and the results of a gene expression profile such as PAM50. In Denmark, standard adjuvant chemotherapy consists of three series of epirubicin + cyclophosphamide (every 3 weeks) and 3 series of paclitaxel (every week) (66). Patients with HER2-positive disease receive trastuzumab 600 mg s.c every three weeks in combination with paclitaxel and continuing for 12 months. Risks of chemotherapy include acute toxicities including fatique, nausea, vomiting, hair loss and myelosuppression. Immunosuppression associated with chemotherapy may also lead to severe infections in some. Taxanes are associated with neuropathy, which generally resolves weeks to months after treatment, but may be incomplete in severe cases. Longer-term toxicities also include the risks of cardiotoxicity associated with anthracyclines and the rare risk of chemotherapy-related leukemia (67). Risk of trastuzumab include flue like symptoms immediately after injections and cardiotoxicity.

About 3-10% of the patients will have distant metastases at the time of diagnosis and the risk of loco-regional or metastatic relapse after treatment for early breast cancer is approximately 20% (71-73). Despite new treatments arising during the past decades metastatic breast cancer remains a largely incurable disease. After documentation of distant metastases, the median survival is approximately 2 years with a 5-year mortality of approximately 80% (73-75). Increased survival and quality of life are therefore the primary goal of treatment for these patients. The goals of treatment of metastatic breast cancer are to prolong survival and improve quality of life by reducing cancer-related symptoms. In order to achieve these goals, an individualized approach is needed since no one strategy can be applied for all women. In Denmark, the following strategies are applied: 1) Patients with hormone receptor-negative

HER2- negative breast cancer is offered chemotherapy. In general, sequential use of single-agent chemotherapy is used as sequential single-agent treatment is often less toxic and results in similar overall survival compared with combination chemotherapy (76); 2) Patients with symptomatic hormone receptor-positive breast cancer, in whom endocrine therapy is unlikely to result in a prompt clinical response. These include patients with rapid disease progression following more than one endocrine therapy (i.e., endocrine-resistant disease) and patients with a large tumor burden involving visceral organs and threatening organ function; and 3) Patients with HER2-positive disease will receive chemotherapy in combination with HER2-directed treatment (73).

The majority of patients with breast cancer have ER-positive disease, and in the case of recurrence, they will primarily develop metastases to the bones and lymph nodes. In addition, there is often a long disease-free interval. Postmenopausal patients with metastatic breast cancer, who have ER-positive and HER2-negative tumors, are primarily offered endocrine treatment with an aromatase inhibitor or fulvestrant, possibly in combination with a CDK4/6 inhibitor. Patients who are premenopausal are offered ovariel suppression in combination with an aromatase inhibitor or fulvestrant in combination with CDK4/6 inhibitors.

CDK4/6 inhibitors are recommended in addition to endocrine treatment in first-line treatment in patients with PS 0-1 (68).

The choice of first line chemotherapy takes into account several factors in an effort to individualize therapy as much as possible as there is no ideal sequence of treatments that can be applied to all patients. It is likely that patients with metastatic breast cancer will receive many (if not all) available treatments throughout the course of their disease.

For HER-2 negative patient who has been previously exposed to adjuvant chemotherapy the preferred regimen will most often be capecitabine. The drug is an orally fluoropyrimidine carbamate that is enzymatically-activated to 5-fluorouracil (5-FU) preferentially by thymidine phosphylase (TP) in the liver and tumor tissue (77). Capecitabine for metastatic breast cancer has been shown to be well tolerated and efficient as both first- and second-line therapy (77, 78). Capecitabine is approved for metastatic breast cancer in combination with docetaxel after failure of prior anthracycline treatment, or as monotherapy in patients' resistant to both taxanes and anthracyclines (79). Side effect its primary toxicities are hand-foot syndrome and diarrhea, and it can be used in settings of mild hepatic dysfunction. It causes very little alopecia or neuropathy.

For HER-2 negative patient who had not received adjuvant chemotherapy the preferred regimen will depend on performance status, tumor burden and patient's preferences. The most used regimens are doxetaxel or capecitabine (see above) (54). Taxanes are among the most active agents for metastatic breast cancer. Docetaxel is associated with a significant risk of fluid retention, which is reduced by

premedication. Side effects include alopecia, neuropathy and myalgia, myelosuppression, febrile neutropenia, edema, and gastrointestinal toxicities. Therapies that target HER2 have become important agents in the treatment of metastatic breast cancer and have altered the natural course of HER2-positive breast cancer. Because the use of HER2-directed therapy improves survival for patients with HER2-positive metastatic breast cancer, such patients receive HER2-directed therapy as first- and later-line treatment (69). In HER-2 positive patients the preferred treatment regimen is vinorelbine in combination with trastuzumab and pertuzumab (66). The treatment regimen is reasonably well tolerated with toxicities consistent with the known safety profiles of the individual agents. Common side effects for vinorelbine include: nausea, vomiting, fatigue, and constipation whereas pertuzumab may be associated with heart problems, diarrhea, and rash or itching.

### 1.5.1 Exercise training in patients with breast cancer

Exercise training for older patients with breast cancer is a relatively unexplored research field. It is indicated that physical activity after breast cancer diagnosis is associated with better survival (70, 71). Physical activity is safe and effective in improving health-related QOL as well as physiological, behavioral and physical outcomes among breast cancer survivors (71). Only a small number of minor adverse events have been reported and no evidence of harmful or negative effects of physical activity interventions among women diagnosed with breast cancer have been found (71).

Several exercise interventions among patients with breast cancer receiving adjuvant therapy consist of resistance training or a combination of resistance- and aerobic training (72-81). These exercise interventions reduce fatigue (74, 77) and symptoms of depression (74) and improve QOL (73, 76, 77) for patients with breast cancer receiving adjuvant therapy. Furthermore, exercise interventions have a positive effect on minimizing decline in cardiorespiratory fitness and improve muscle strength (75, 76, 79), physical function, bone mineral density, sleep (82), and shoulder range of motion (75, 82). Resistance training in patients with breast cancer during adjuvant chemotherapy significantly reverses sarcopenia and dynapenia (72).

Slimmer, fitter and younger (premenopausal) breast cancer patients receiving chemotherapy are more likely to benefit from a higher dose of exercise intervention than their counterparts. This indicates that age, menopausal status, obesity, past exercise experience and fitness level should be taking into account when exercise is prescribed to cancer patients (76).

The exercise interventions mentioned above all include patients with breast cancer with a mean age of approximately 55 years. Very few trials have examined the effect of exercise among older breast cancer patients undergoing treatment (83, 84). One trial has examined the effect of yoga training compared to

routine physical therapy (n = 20) (83). Both types of exercise seemed to have a positive effect on QOL (83). Therefore, research exploring exercise training in combination with oncological treatments for older breast cancer patients is needed.

## 2. Study rationale and aim

Older cancer patients are underrepresented in clinical trials, including trials within exercise training in combination with oncological treatments. Nevertheless, the older cancer population is the largest group of cancer patients, and their number is rapidly growing. With a mean age around 65 years at diagnosis, breast cancer is associated with aging. Interventions that reduce symptoms, maintain physical function and optimize QOL are essential. Since few previous studies have investigated the effect of an exercise-based intervention specifically focused on older patients with primary or advanced-stage breast cancer during chemotherapy, the primary focus of the current study is to investigate the effect and feasibility of such an intervention. Hence, the aim of the present "TOLCA - Breast Cancer Exercise" study is to investigate the effect of a 12-week exercise-based intervention, comprised of a supervised and group-based resistance training program, an individualized and home-based walking program in older patients (≥ 70 years) newly diagnosed with primary, locally advanced or metastatic breast cancer who are undergoing treatment with adjuvant or first-line palliative systemic therapy.

## 3. Research questions and hypotheses

### 3.1 Research questions

1. Can the exercise-based intervention increase or maintain physical function levels in older patients with breast cancer during treatment with adjuvant or first-line palliative systemic therapy?
2. Is it feasible and safe to recruit and engage older patients diagnosed with breast cancer in the exercise-based intervention during treatment with adjuvant or first-line systemic therapy?
3. Can the exercise-based intervention reduce symptoms and side-effects in older patients with breast cancer during treatment with adjuvant or first-line systemic therapy?
4. Can the exercise-based intervention improve QOL and psychological wellbeing among older patients with breast cancer during treatment with adjuvant or first-line palliative systemic therapy?
5. Can the exercise-based intervention affect circulating biomarkers of inflammation in older patients with breast cancer during treatment with adjuvant or first-line palliative systemic therapy?

6. Are circulating levels and changes in inflammatory biomarkers associated with the development of cancer cachexia, sarcopenia, and other changes in body composition in older patients with breast cancer during treatment with adjuvant or first-line palliative systemic therapy?

### 3.2 Study hypotheses

We hypothesize that the exercise-based intervention will maintain or increase physical function levels, reduce symptoms and side effects, improve QOL and psychological wellbeing, and prevent weight loss and muscle wasting in patients with breast cancer during treatment with adjuvant or first-line palliative systemic therapy. We predict that recruitment of older patients with breast cancer might be challenging because of treatment-related side-effects, symptom burden, and age-related factors that affect these patients. Also, as prior exercise-based intervention studies targeted patients with advanced stage cancer during systemic therapy treatment have experienced considerable attrition rates, we expect that a certain percentage of drop-outs during the intervention period will be inevitable. However, we believe that an intervention specifically targeted the special needs of older patients with breast cancer treated with adjuvant or first-line palliative therapy can be integrated in both the hospital and home setting, will make the intervention feasible and effective.

## 4. Design and methods

### 4.1 Design

TOLCA – Breast Cancer Exercise is a prospective two-armed randomized controlled trial of a 12-week exercise intervention in older patients (≥70 years) with breast cancer who are treated with adjuvant or first-line palliative systemic therapy.

### 4.2 Recruitment of patients

Patient will be recruited from the Department of Oncology, Herlev and Gentofte Hospital. Potentially suitable patients will be identified and screened by oncologists to find eligible participants. The screening procedure aims at confirming that inclusion criteria are met (4.3), and that none of the exclusion criteria are present (4.4). The oncologist will inform eligible patients about the possibility to participate in the TOLCA – Breast Cancer Exercise study. Patients who are interested in participation will hereafter be informed, and potentially recruited and randomized by the primary investigator Ida Lundager. Before the information, by the primary investigator, is given to the patient, patients are informed about the possible to have an assessor. Patients will be informed both verbally and in writing about the TOLCA – Breast Cancer Exercise program, perceived benefits, risks, and safety precautions, and about their personal rights in entering the trial. The information will be given to the patients in

undisturbed settings at outpatient department of oncology. After all information have been delivered and understood, patients will be informed about their right for time to consider participation in the study (a minimum of 24 hours). Hereafter, informed consent forms (ICF) will be signed and collected from patients who want to participate in the trial. Included patients will receive a copy of the signed ICF.
Due to ethical considerations, and challenges with significant information load, patients will first be approached and informed about the TOLCA – Breast Cancer Exercise trial after the first treatment dose of either adjuvant or first-line palliative systemic therapy.

### 4.3 Inclusion criteria

Patients must:

- Have undergone surgery for primary breast cancer within 12 weeks or
- Be diagnosed with locally advanced or metastatic breast cancer
- Be treated with adjuvant or first-line palliative therapy with chemotherapy ± HER2 directed treatment, ± antihormonal treatment, antihormonal treatment ± HER 2, directed treatment ± CDK 4/6 inhibitor
- Be ≥ 70 years of age at the time of signing the ICF
- Have an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2
- Be able to speak and read Danish, and to provide a signed ICF

### 4.4 Exclusion criteria

Patients with:

- Any physical condition that hinder the execution of physical exercise training
- Other type of cancer
- Documented and uncontrolled brain metastases that hinder participation in an exercise-based trial, based on the referring oncologist's assessment
- Dementia, psychotic disorders, or other cognitive diseases or conditions that hinder formal consent
- Unstable medical disease, condition, or history of serious or concurrent illness; any medical condition that might be aggravated by exercise training or that cannot be controlled, including, but not restricted to congestive heart failure (NYHA class III-IV), unstable angina pectoris, implantable cardioverter defibrillator (ICD), or myocardial infarction within 6 months, based on the referring oncologist's assessment

In patients with documented bone metastases:

- A bone metastatic burden or location that poses a risk of injury in the performance of exercise training, as assessed by the referring oncologist

## 4.5 Stratification at randomization

Patients included in the study will be randomized 1:1 to the intervention group and control group. As cancer stage and performance status are expected to influence the outcomes of interest, stratification will be performed at randomization. Patients will be stratified at randomization based on:

- Cancer stage and treatment.

Randomization and stratification will be performed through the randomization module in REDCap.

## 4.6 Intervention

### *4.6.1 Exercise intervention*

Patients in the intervention group will receive usual care and the exercise-based intervention. Based on recommendations from the Cancer and Aging group NCU U13 (63), this intervention will be initiated early after cancer diagnosis. Focusing on a group of older patients with breast cancer and treated with adjuvant or first-line palliative systemic therapy several factors have been considered in targeting the intervention, including the debilitating symptoms and side-effects, age-related physical limitations and comorbidities, and the rapid physical decline seen among patients with advanced cancer. The overall focus of the TOLCA – Breast Cancer Exercise intervention lies on maintaining muscular strength, physical function and mobility. In addition to the PRT, an individualized light to moderate intensity walking program, based on step counts, will be developed for each patient with the aim of avoiding inactivity and to keep patients active on days when they are not engaged in the PRT program. The exercise-based intervention is composed in a way that allows individualization based on each patients' physical state, psychosocial state, and motivation throughout the intervention period. Patients included in the intervention group will receive a 12-week exercise-based intervention composed of the following components:

1. **Supervised and group-based exercise program**: Patients in the intervention group will participate in the supervised exercise program two times a week, and each session will last approximately 60 minutes. The exercise program consists of warm-up exercises, including exercises for balance and flexibility (15 minutes), a program of PRT that comprises seven resistance training exercises targeting the large muscle groups (chest press, low row, hamstring curls, knee extension, leg press, abdominal crunches, back extensions) (35 minutes), and stretching and relaxation (10 minutes). In

week 1-2, patients will be introduced to the PRT and the program will be initiated with high repetition numbers and low load. The intensity is progressed during the intervention period from two to three sets with a load corresponding to 15 to 8 repetition maximum (RM) (the load that can be lifted to 15 and 8 repetitions, respectively, using proper technique as assessed by the physiotherapist). This model of PRT is in accordance with the recommendations from the American College of Sports Medicine (ACSM) (85). The progression will be tailored to each individual patient regarding potential comorbidities and physical limitations, and will be closely monitored by the responsible physiotherapist. In patients with documented bone metastases, a very conservative approach to progression will be taken, which involves very small increments in resistance. The supervised exercise training will take place at the Department of Occupational Therapy and Physiotherapy at Herlev and Gentofte Hospital, and will be led by an experienced physiotherapist. When entering the project, all patients will receive a 'replacement training program' that includes a few effective exercises for the major muscle groups and can be performed at home. If a patient for unforeseen reasons cancels a group-based training session during the intervention period, the patient will be recommended to perform the exercises in the replacement-program instead. All patients will be thoroughly introduced to these replacement exercises when entering the study.

2. **Individualized walking program** based on step counts (pedometer assessment). After randomization, patients in the intervention group will receive an activity tracker and will be asked to wear it for three consecutive days. Based on each patient's starting point (a mean of the three pre-measured days), preferences and motivation, an individualized walking program will be conducted to increase or maintain the level of activity. Goal-setting in relation to step counts will be set once weekly in collaboration between each patient and the primary investigator (Ida Lundager). Even though the overall aim is to increase activity level/step counts during the intervention, it is also possible to maintain or even reduce the step-goals in some weeks if an increase is not realistic due to physical or psychosocial reasons, or if patients are already sufficiently active. Each patient will receive a booklet at the introduction meeting with information and advice about walking, and goal-setting and evaluation schemas for the 12-week intervention. Evaluation and goal-setting will be conducted once a week before or after the supervised training session, or by telephone (based on patients' preferences). Patients will also be asked about their beliefs and confidence about reaching their next goal (self-efficacy rating).

3. **Nutritional supplement after supervised exercise session:** a nutritional supplement (protein bar or protein drink) will be given to patients immediately after the supervised exercise training session at the hospital setting.

The TOLCA – Breast Cancer Exercise intervention is illustrated in Table 1.

**Table 1. Components of the multimodal TOLCA – Breast Cancer Exercise intervention**

| | **Supervised exercise training** | **Nutritional supplement** | **Home-based walking** |
|---|---|---|---|
| **Content** | • Warm up<br>• Exercises for balance<br>• Exercises for flexibility<br>• Progressive resistance training<br>• Stretching<br>• Relaxation | Protein drink or protein bar (~ 200-300 calories, 12-18 grams of protein). | Walking/activity based on step counts from the activity tracker. Individualized goal-setting and evaluation once weekly. |
| **Frequency** | 2 times a week, for 60 minutes per session. | 2 times a week after supervised training session. | Continuously over the 12-week intervention. Evaluation and goal-setting once weekly. |
| **Setting** | Dept. of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital. | Dept. of Occupational Therapy and Physiotherapy, Herlev and Gentofte Hospital. | Home-setting.<br>Evaluation and goal-setting will be conducted at the hospital setting or by telephone (based on patients' preferences). |

### *4.6.2 Theoretical framework*

The elements of exercise training in the TOLCA – Breast Cancer Exercise study are designed in accordance with Danish and international basic principles and recommendations for exercise training in healthy individuals, healthy older individuals, cancer patients, and older cancer patients (82, 85, 86). Both Danish and international guidelines emphasize the importance of adapting exercise training to both cancer site, symptoms and side effects, and with consideration for each individuals' health status, physical limitations, and comorbidities (82, 86). Focusing on older cancer patients, Danish recommendations specifically underline that exercise interventions should focus on maintaining mobility and physical function (86). With an overall purpose of empowering and activating patients involved, goal-setting will be incorporated as an element in the intervention (home-based walking program). Goal setting is widely recognized as an effective method to achieve behavioral changes and enhance self-efficacy in people (87). In the rehabilitation setting it is generally agreed that goals must

be specific, measurable, achievable, realistic/relevant and timed-based (SMART). Furthermore, goal-setting should be carried out through a continuous process that involves planning, evaluation and reassessment, in collaboration between the patient and HCP (88, 89).

### 4.7 Study assessments and data collection

The following assessments and data collection will be performed:

1. Clinical data and medical outcomes: data on diagnosis, time of diagnosis, treatment regime, performance status (ECOG) (Appendix 1), and comorbidities (assessed by Charlson comorbidity index (CCI) (90) will be registered and assessed from medical records. Risk of systemic therapy toxicity (toxicity score) will be calculated using the Cancer & Aging Research Group (CARG) toxicity score with data from medical records and patient questionnaire (28).

2. Demographic and patient-reported data: data on civil status, working status, education level, smoking habits, alcohol consumption, weight loss before and after cancer diagnosis (kg/percent), and physical activity level before cancer diagnosis and current will be collected through patient questionnaire (Appendix 2).

3. Physical function: To measure physical capacity and lower extremity strength, the 30-second Chair Stand Test (30s-CST) will be used **(primary outcome).** The 30s-CST is a widely used physical measure, especially among older people and those with significant weakness, and is regarded as a prerequisite for functional independence (91).The 30s-CST has also been used and tested in cancer patients (92). Using a chair with a seat of 45 cm above the floor, patients will be instructed to sit in the middle of the chair with their back straight, arms crossed over the chest, and both feet resting flat of the floor (93). The correct technique will be demonstrated for patients before assessment. On the instructor's signal patients will be asked to stand straight and then return to the seated position as many times as possible in 30 seconds. A modified version of the 30s-CST, where patients are allowed to use armrests, can be used in patients who are not able to rise from a chair without using their arms. Use of the modified version will be registered, and will be carried out in accordance with the test manual (93). The 30s-CST has proved to be a valid and reliable method in measuring lower body strength among healthy community-dwelling older adults (91). Physical performance will also be assessed with a 6-meter gait speed test (6mGS) and 10 meter gait speed test (10mGS) at normal and maximal gait speed (94). Gait speed is a suitable measure to use in the clinical evaluation and rehabilitation setting when focusing on older individuals, as it is easy to administer, and has documented predictive value for health-

related outcomes such as functional and cognitive decline, falls, hospitalization, independence, and mortality (94, 95).To measure physical capacity and endurance, the six-minute-walk-test (6MWT) will be used. The 6MWT measures the distance an individual can walk over a total of six minutes on a hard and flat surface. It was originally developed for use in frail older patients, but it has been used and validated in a variety of chronic diseases and populations (e.g. cardiac, cancer and pulmonary patients) (96, 97). Prior studies have demonstrated that the 6MWT is a reliable and valid measure of physical capacity and endurance in older adults and in cancer patients, and that the test may have prognostic value among cancer patients (98, 99). To measure physical function of the upper-body, the handgrip strength test (HST) will be used. Handgrip strength will be measured using a hand-held Jamar dynamometer and with three attempts performed for each hand. Measurements of grip strength with the Jamar dynamometer have evidence for good reliability and validity (100). Patient will be sitting down during the assessment with their elbow flexed at 90º. The best measure in the strongest hand will be used as test score. Research has shown that handgrip strength may be independently associated with functional capacity, QOL and survival in patients with advanced cancer (101). To measure lower extremity muscle power a stair climb test (SCT) will be used. The patient will climb a flight of stairs (20 steps) as fast as possible. The best of three trials will be used as test score. Leg power is an influential factor in the mobility performance of older adults (102). The SCT is a clinically relevant measure of lower extremity power among older adults and is associated with more complex modes of testing power (103). All physical tests will be conducted by blinded physiotherapists.

4. Feasibility measures: feasibility of the intervention will be evaluated as acceptability, attrition and adherence. Acceptability will be measured as the number of eligible patients who agree to participate in the study. Also, reasons for refusing participation will be registered and evaluated. Attrition is the number of patients who do not complete the study (drop-outs). For each component of the intervention (supervised exercise, protein supplement after exercise sessions, and walking program) adherence to the intervention will be assessed. Safety (adverse event) and tolerability will be evaluated at every training session and at the weekly evaluation of the walking program.

5. Patient-Reported Outcomes Measures (PROMs): Patient reported performance status (PRPS) will be assessed using ECOG PS (Appendix 1). PS is a known and common-used prognostic tool for assessment and decision making in oncology and palliative settings. Evidence suggests that

patients are reliable assessors of their own performance status, and that PRPS is a predictor of cancer-related outcomes (104). To measure symptom burden, M.D. Anderson Symptom Inventory (MDASI) will be used (Appendix 3). MDASI is a multi-symptom PROM to assess the severity of symptoms and the interference with daily living as assessed by cancer patients based on the last 24 hours (105). MDASI consists of 13 core symptom items representing symptoms that have been found to have the highest frequency and/or severity among cancer patients with various cancers and treatment types, and 6 interference items representing commonly experienced symptom interference with daily activities (105). To assess QoL the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and the breast cancer specific module QLQ-BR23 (EORTC QLQ-C30 & BR23) will be used (Appendix 4). EORTC QLQ-C30 comprises 30 items, is designed to be cancer specific, and consists of six functional scales (physical, role, cognitive, emotional, social functioning, and global QOL) and symptom scales (fatigue, nausea/vomiting, sleep disturbance, constipation, diarrhea, appetite loss, dyspnea) (69, 106). EORTC QLQ-C30 is developed in a way that is appropriate for self-administration and for use across a range of cultural setting. To assess symptoms of depression and anxiety, the Hospital Anxiety and Depression Scale (HADS) will be used (Appendix 5). HADS comprises a total of 14 items and is designed to measure general anxiety and depression by self-administration (107).

6. Physical activity: Data of steps counts will be assessed daily for patients in the intervention group. Data of walked steps, distance and energy consumption for all patients (intervention group and control group) will be assessed in a 3-days period both before and after the intervention period (at baseline and 12-week post-intervention). Data on physical activity will be measured with an activity tracker.

7. Chemotherapy tolerance: data on completion of scheduled chemotherapy, dose-reductions, treatment discontinuations, toxicity (according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4) will be registered from medical records.

8. Body composition: data on weight, height, BMI, and body composition will be registered. Weight, height and BMI will be assessed using standard procedures (no shoes, light clothing). Body composition will be assessed by whole-body dual-energy x-ray absorptiometry scan (DXA) and by bioelectrical impedance (BI) assessment. The DXA technology is a special type of X-ray that is based on a three-component model that determines fat-free-mass, body fat, bone

mass, and bone mineral density (111). DXA is acknowledged as a valid method to evaluate body composition, and it is frequently used both in research and in the clinical setting (111, 112). However, all available single methods for the assessment of body composition have their limitations. Focusing on DXA, it has previously been questioned whether the validity is affected by patients' hydration status, and, prior studies have also shown that the validity may be impaired in very lean or in very obese persons (112, 113). Therefore, assessment of body composition will be supplemented with BI assessment. BI is a portable, easy-to-use, and non-invasive method to estimate body composition (114). BI measures the resistance of different body tissues to the flow of a low-level electrical signal which is sent through the body. The electrical flows at a different rate through the various body tissues, which allows for the analyses of estimated body fat percentage, fat mass, fat-free mass, muscle mass, body water, and bone mass (114). The validity of BI measures of body composition can be affected by several factors, including body position, distribution of body fat, skin temperature, and dietary intake (112, 115). Incidence of cancer cachexia will be determined as loss of more than 5% of stable body weight over the last 6 months, or loss of more than 2% of body weight in patients with BMI < 20kg/m$^2$ or in patients with sarcopenia (35). Incidence of sarcopenia will be determined by the consensus criteria from the European Working Group on Sarcopenia in Older People (EWGSOP), and will determined by exact cut-off value representing incidence of both low muscle mass and low muscle function (performance or strength) (33).

9. Biomarkers: Results from prior studies have shown that inflammation is a critical component of cancer development and progression (116, 117). Inflammation has also been linked to important clinical outcomes, such as cancer-related fatigue and cancer cachexia (43, 118). Although not yet fully elucidated, it also seems that exercise training may have the potential to affect tumor-specific and anti-cancer treatment outcomes through regulations of inflammatory processes and functions (119). Loss of skeletal muscle mass (sarcopenia) is an independent prognostic factor predicting poor outcome in a wide range of cancers (108). In recent years, there has been an increased focus on the possible importance of growth differentiation factor 11 (GDF-11) and growth differentiation factor 15 (GDF-15) for the development of sarcopenia. GDF-11 and GDF-15 belong to both the TGFβ family shown via the ActRII/ALK4/5 signaling pathway to inhibit skeletal muscle growth. High levels of GDF-11 and GDF-15 have been shown to be associated with frailty and increased comorbidity in older subjects and, quite recently, also shown to be up-regulated in cancer and related to the muscle loss seen in conjunction with cancer and cachexia (109, 110). Data on biomarkers will be collected and registered as an exploratory translational

part of the study (see detailed description in section 4.8). Included patients must give their separate informed consent to participate in the biomarker study. Patients who refuse to participate in the biomarker study will still be allowed to participate in the TOLCA – Breast Cancer Exercise study. Recruitment to the biomarker study will be performed in accordance with the described and approved manner in the biomarker study. Data on the biomarkers serum C-reactive protein (CRP), interleukin 6 (IL-6), YKL-40, GDF11 and GDF15 will be used in analyses in the TOLCA – Breast Cancer Exercise study to investigate whether the exercise-based intervention affects the inflammatory process, and to investigate the association between these biomarkers and clinical outcomes. Transmission of the biomarkers data to the TOLCA Breast Cancer Exercise study will be done in accordance to the regulations of the Danish Data Protection Agency and all necessary approvals will be obtained.

10. Hospital admissions: numbers, causes, and length of hospitalizations during the intervention and follow-up period. Contact to the Emergency Room with falls will be noted.

11. Mortality/survival: with a purpose to investigate whether the intervention may affect survival time/mortality, incidences of deaths (cancer-related and other cause) will be registered throughout the intervention period and during follow-up.

### 4.8 Inflammatory biomarkers (data collection and assessment)

At Herlev and Gentofte Hospital, translational research will be performed for all patients participating in the TOLCA – Breast Cancer Exercise study, provided that included patients give their separate informed consent to participate in these biomarker studies. Patients who refuse to participate in the biomarker studies will still be allowed to participate in the TOLCA – Breast Cancer Exercise study.

Patients will be informed and asked to participate in the biomarker study 'Prospektiv indsamling af blodprøver hos patienter med cancer mammae – giver biomarkører i blod ny information om diagnose, behandlingseffekt, bivirkning og prognose?" (PRIMA-b-protokollen) as described in the approved PRIMA-b protocol. Entering the PRIMA-b study, 30 ml blood will be collected at baseline (before the other baseline data is collected in TOLCA Breast Cancer Exercise Study), before the second cycle of chemotherapy (approximately midway intervention, 6 weeks), and at the time of CT scanning (approximately post intervention, 12 weeks) according to the PRIMA-b protocol (VEK ref.: KA-H-3-2014-120,; and Datatilsynet: HE-2014-083, I-Suite 03140). Blood samples will be stored as serum, plasma or buffy-coat for biomarker analyses in the approved PRIMA B biobank at Herlev Hospital until 2024. Transmission of the biomarkers data to the TOLCA Breast Cancer study, will be done in

accordance to the regulations of the Danish Data Protection Agency and all necessary approvals will be obtained.

Serum high sensitive CRP is measured by routine method at Department of Clinical Biochemistry at Herlev and Gentofte Hospital. Serum IL-6 is determined by ELISA (R&D) and YKL-40 is determined by ELISA (Quidel) at Department of Medicine, Herlev and Gentofte Hospital. 92 cancer- and-inflammatory protein profiles will be determined using the Olink array (www.Olink) at BioXpedia, Århus. Serum GDF11 and GDF15 are determined by ELISA at Department of Sports Science and Clinical Biomechanics, University of Southern Denmark. Data on the inflammatory biomarkers will be used in analyses in the present study to investigate whether the exercise-based intervention affects the inflammatory process, and to investigate the association between these biomarkers and clinical outcomes.

## 4.9 Time of data collection and tests

Data collection and tests will be performed at baseline, midway intervention (6 weeks), post-intervention (12 weeks), and follow-up (16 weeks). Schedule for data collection and tests are shown in Table 2.

**Table 2 Data collection and tests.**

| | Inclusion (baseline) | Midway (6 weeks) | Post-intervention (12 weeks) | Follow-up (16 weeks) |
|---|---|---|---|---|
| **Informed consent, TOLCA** | X | | | |
| **Informed consent (PRIMAB)** [1] | X | | | |
| **Clinical and medical data** | X | X | X | X |
| **Demographics** | X | | | |
| **Health status (ECOG, CCI, CARG toxicity risk score)** | X | | | |
| **Feasibility measures** | | | | |
| **Recruitment rates** | X | | | |
| **Retention** | X | X | X | X |
| **Adherence** | | X | X | |
| **Adverse events** | | X | X | |
| **Patients satisfaction** | | | X | |
| **PROMs** | | | | |
| **PRPS** | X | X | X | X |
| **MDASI (measured once weekly)** | X | X | X | X |
| **EORTC QLQ-C30 & BR23** | X | X | X | X |
| **HADS** | X | X | X | X |
| **Physical tests** | | | | |
| **30s-CST (primary outcome)** | X | X | X | X |
| **6MWT** | X | X | X | X |
| **Gait speed, 6 m and 10m** | X | X | X | X |
| **Handgrip strength** | X | X | X | X |
| **Stair climb test** | X | X | X | X |
| **Physical activity** | X | | X | |
| **Biomarkers related to inflammation** | X | X | X | |
| **Oncological treatment/toxicity** | X | X | X | X |
| **Body measures and composition** | | | | |
| **Weight, BMI** | X | X | X | X |
| **DXA scan** | X | | X | |
| **BI** | X | | X | |

[1]For patients with breast cancer who accept participation in the PRIMA B trial.

## 4.10Analyses and statistics

### 4.10.1 Sample size

No prior studies have investigated the minimal clinically important difference in the 30s-CST focusing on cancer patients. However, according to a previous study focusing on patients with osteoarthritis, the clinically important change in the 30s-CST was set at 2.6 repetitions (120). Based on results from prior studies focusing on patients with advanced cancer, a standard deviation (SD) of around 3 has been reported in the 30s-CST(121, 122). To be able to detect a difference of 2.6 repetitions in the between-group difference in the 30s-CST at the 12-week assessment, and to obtain a type I error rate of 5% and a power of 90%, a sample size of 29 patients per study arm will be needed. To account for an expected

dropout rate of ~40%, we decided to increase this number to a group size of 50. Thus, a total of 100 patients will be included in the study.

### 4.10.2Analysis plan

#### *4.10.2.1 Quantitative data*

Feasibility measures (acceptability, attrition, adherence, and adverse events) will be reported as numbers and percentages. Reasons for declining participation will be analyzed descriptively with numbers and percentages of patients declining for various reasons. Baseline characteristics will be calculated for all patients included (total) and separately for intervention group and control group. For all quantitative variables the median number and interquartile range (IQR) will be calculated, and for nominal variables the number and percentage distribution will be calculated. Results from physical tests, blood test, body measures, and questionnaires will be reported as means and standard deviations (SD) or as median and IQR, as appropriate. Change over time in ordinal categorical values will be evaluated by a trend test using logistic regression. In-group and between- group differences in continuous-level data, will be performed using a repeated measurement analysis. Survival analyses will be conducted with Kaplan-Meier method, competing risk analyses and Cox regression analyses. Using the Kaplan-Meier method, cancer-specific and overall survival time will be assessed for the intervention group and the control group, and comparison in survival between groups will be assessed using the log-rank test. To account for competing risks (deaths from other causes than cancer), the cumulative incidence of cancer-specific death will be assessed using competing risk analyses, and comparison between groups will be conducted using Grey's test. Cox proportional hazards regression will be used to estimate the hazards (risk) of death, and cause specific Cox proportional hazards regression will be used to assess the risk of cancer-related death. The significance level of all tests is set a $p < 0.05$, and analyses will be carried out in SAS or R by statisticians in collaboration with the primary investigator.

## 5 Ethical considerations

Study approval will be obtained by the Scientific Ethics Review Committee of the Capital Region of Denmark and the Danish Data Protection Agency. The study will also be registered at ClinicalTrials.gov. TOLCA – Breast Cancer Exercise will be carried out in accordance with the protocol, and according the Helsinki Declaration. All personal data will be treated with confidentiality and security in accordance with the Danish Personal Data Act.

All potential participants will be provided with full and adequate verbal and written information about the project and will have the right to ask questions about the study. Each patient will be informed about their personal rights when entering the study. It is emphasized that participation in the study is voluntary,

and that any included patients at any given time can cancel participation in the study. If the oncological treatment regime is changed or discontinued for included patients in the study, these patients will still be allowed to continue in the TOLCA – Breast Cancer Exercise study. Written informed consent forms will be obtained from all patients when entering the study. The primary investigator will also sign each informed consent form to confirm that all verbal and written information has been provided.

# 6 Potential risks and disadvantages

There are a few potential risks and disadvantages for patients in the intervention group, including exercise injuries and discomfort in performing the exercise program. However, risks and disadvantages are considered to be limited. An experienced physiotherapist will supervise all exercise sessions at the hospital setting. If a patient shows any signs of being physically unwell during an exercise session, the patient's blood pressure, heart rate, respiratory rate, and temperature will be measured, and appropriate actions will be taken. For safety reasons, patients will not be allowed to participate in the training sessions if there is fever (≥38.5ºC). If a patient reports any discomfort or incidence of injury during the intervention period, the safety and further program continuation for the patient will be discussed in the research group, and in consultation with the patient and the responsible physician. The investigators and the responsible oncologists have the rights to exclude a patient from the study at any given time, if it is considered unsafe for the patient to continue. Data on adverse events will be collected systematically every week, and patients will furthermore be informed to contact the primary investigator immediately if injuries or other adverse events related to the intervention program should occur.

## 6.1 Radiation exposure

Body composition will be assessed for all patients (intervention group and control group) by DXA scan and BI technique at baseline and after 12 weeks. BI causes no radioactive radiation and is a completely harmless method for assessment of body composition. DXA scans will be conducted with the Lunar iDXA from GE Healthcare (123). Depending on individual body size, patients will be exposed for a small radiation dose of approximately 3 μGY (= 0.003 mSv) in each of the two DXA scans (123). This dose of radiation is low and corresponds the radiation a person is exposed to by flying at 10 kilometers altitude (during the scan time = approximately 6 minutes). All patients will be informed, both verbally and in writing, about the DXA scans and about the expected radiation exposure before entering the study.

# 7 Publication of study results

Potentially positive, negative, or inconclusive results from the TOLCA – Breast Cancer Exercise study will be published in relevant international peer-reviewed journals. Co-authorship for the upcoming

publications will be offered to members of the project group or other collaborators based on contributions to the current work, and in accordance with the Vancouver recommendations.

## 8 Economy

The initiator of the TOLCA – Breast Cancer Exercise study is Dorte Nielsen, Professor, MD, PhD, DMSc, at Department of Oncology, Herlev and Gentofte Hospital

The TOLCA – Breast Cancer Exercise study is financially supported by grants from the VELUX Foundation (a total of 1,308.069 DKK). The support from The VELUX Foundation covers the salary for PhD student Ida Lundager during the 3-year period. The VELUX Foundation will be mentioned in all written and oral presentations, and in future publications. The VELUX Foundation (or other future funding organizations) will not have any role in the conduction of the study design or protocol, data collection, interpretation of data, or in the drafting or approval of coming publications. There is no commercial or politically binding relationship between any members of the TOLCA project group and the VELUX Foundation. Financially support from other funding organizations will be applied, to cover expenses related to the TOLCA – Breast Cancer Exercise study. The Scientific Ethics Review Committee of the Capital Region of Denmark and participants in the study will be informed about any further grants.

Patients included in TOLCA – Breast Cancer Exercise study will not receive any financial fees by participating in the trial.

## 9 Scientific statement

The TOLCA – Breast Cancer Exercise study is expected to involve low risk of adverse events and discomfort for patients involved. The intervention and all assessments will be led and conducted by experienced therapists and other health care practitioners with all relevant safety precautions installed. Patients involved in the research program will not experience any delays in their treatment due to participation in the program. Included patients can withdraw from the program at any time and without any specific reasons. It is the project group's assessment that it is necessary to carry out the current research project to gain important knowledge about the effect and feasibility of a exercise-based intervention as a rehabilitative approach to older patients with breast cancer during oncological treatment adjuvant or first line palliative systemic therapy. The project group estimates that the TOLCA – Breast Cancer Exercise intervention will maintain or increase physical function levels, reduce symptoms and side effect, increase tolerance to oncological treatment, and improve psychological well-being and QOL

in older patients with primary advanced breast cancer, and that the expected benefits of the intervention exceed the estimated limited risks for patients involved.

## 10 Clinical perspectives and implementation

With the aging population and expected increase of cancer incidence (especially among older people), new approaches of early rehabilitation are needed to maintain physical function levels and independence in older cancer patients. The TOLCA – Breast Cancer Exercise study has the potential to become a new model of early rehabilitation care for older patients with breast cancer. In the long term, it is our goal to investigate the program's effect among older patients with various malignancies in order to map out the effects, common features, and the differences across cancers, with an overall focus on the older cancer population. The TOLCA – Breast Cancer Exercise study supports the development of future health promotion guidelines for older cancer patients during anti-cancer treatment by reducing the complex symptom burden, supporting treatment tolerance, maintaining physical function and thereby enabling a better quality of life. The interventions pragmatic approach and integration in the hospital and home-setting will be implementable should the study prove effective and implementation is the goal.

# 11 References

# Appendix 1: Performance status

The Eastern Cooperative Oncology Group (ECOG) performance status (also known as the WHO or the Zubrod score). The ECOG performance score runs from 0-5, with 0 denoting good health with an independent and active lifestyle, and 5 death.

| **ECOG performance status*** | |
|---|---|
| Grade | ECOG |
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

* Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of The Eastern Cooperative Oncology Group. Am J ClinOncol 1982; 5: 649-655.

Kræftens Bekæmpelse (Danish version)*

| **Kræftens Bekæmpelses version af 'performance status'** | |
|---|---|
| Score | Status |
| 0 | Fuldt aktiv som før man blev syg. |
| 1 | Kan ikke udføre tungt fysisk arbejde, men alt andet. |
| 2 | Oppegående mere end halvdelen af dagen og selvhjulpen, men ude af stand til at udføre fysisk arbejde. |
| 3 | I seng eller siddende i stol mere end halvdelen af dagen, og brug for hjælp til at klare sig selv. |
| 4 | Bundet til seng eller stol og har brug for hjælp til alt. |

* Kræftens Bekæmpelse. Ordbog -performance status. From: https://www.cancer.dk/hjaelp-viden/fakta-om-kraeft/ordbog/performance-status/

## Appendix 2: Patient questionnaire (Danish)

### Deltageroplysninger

Kære deltager i TOLCA- Bryst Kræft Trænings studiet.

Du bedes venligst udfylde nedenstående spørgeskema og returnere det til den projektansvarlige fysioterapeut (Ida Lundager).

| |
|---|
| **Fødselsdato (DD.MM.ÅR):** _____<br>**Mand** □<br>**Kvinde** □<br>**Hvilket land er du født i?** _____ |
| **Hvad er din civilstatus?**<br>Gift / samboende □<br>Enlig/enke/enkemand □ |
| **Hvad er det højeste uddannelsesniveau du har gennemført?**<br>Mindre end 9. klasse □<br>9. eller 10. klasse (folkeskole) □<br>Gymnasial uddannelse □<br>Erhvervsuddannelse/faglig uddannelse □<br>Kort videregående uddannelse (under 3 år) □<br>Mellemlang videregående uddannelse (3-4 år)□<br>Lang videregående uddannelse (5 år og derover) □ |
| **Hvad er din beskæftigelsessituation?**<br>Pensionist/efterlønsmodtager □<br>Lønmodtager i arbejde eller selvstændig □<br>Sygedagpenge/revalidering □<br>Arbejdsløs □ |
| **Ryger du?**<br>Ja, jeg ryger dagligt □<br>Ja, men kun til festlige lejligheder □<br>Nej, jeg har aldrig røget □<br>Nej, men jeg har tidligere røget □<br><br>**<u>Hvis du er aktiv ryger, svar så venligst på følgende:</u>**<br>- Hvor mange cigaretter ryger du dagligt? _____<br>- Hvis du ryger andet end cigaretter, angiv hvilket her: _____, samt antal gram dagligt_____<br>- I hvor mange år har du røget? _____ |

**Hvor mange genstande drikker du typisk på en uge? _____ antal genstande.**

**Hvor ofte får du 6 genstande eller mere ved en enkelt lejlighed?**
Aldrig □
Sjældnere end én gang om måneden □
Månedligt □
Ugentligt □
Dagligt eller næsten dagligt □

**Hvilket aktivitetsniveau passede bedst på dig cirka 3 måneder inden du fik din kræftdiagnose? (sæt kun ét kryds)**
□ Stillesiddende *(mest stillesiddende aktiviteter såsom at læse eller se fjernsyn)*

□ Lettere fysisk aktiv *(spadserer, cykler eller har anden lettere motion i under 3 timer pr. uge)*

□ Moderat aktiv *(regelmæssig fysisk aktivitet mindst 3 timer om ugen – medregn også lettere havearbejde og søndagsture).*

□ Aktiv *(regelmæssig fysisk aktivitet og motion mindst 3 timer om ugen)*

□ Meget fysisk aktiv *(hård fysisk træning mere end 4 timer om ugen)*

**Hvilket aktivitetsniveau passer bedst på dig i din aktuelle situation? (sæt kun ét kryds)**
□ Stillesiddende *(mest stillesiddende aktiviteter såsom at læse eller se fjernsyn)*

□ Lettere fysisk aktiv *(spadserer, cykler eller har anden lettere motion under 3 timer pr. uge)*

□ Moderat aktiv *(regelmæssig fysisk aktivitet mindst 3 timer om ugen – medregn også lettere havearbejde og søndagsture).*

□ Aktiv *(regelmæssig fysisk aktivitet og motion mindst 3 timer om ugen)*

□ Meget fysisk aktiv *(hård fysisk træning mere end 4 timer om ugen)*

**Bruger du hjælpemidler for at komme omkring når du er derhjemme?**
Nej □
Ja, rollator □
Ja, stok □
Ja, gangbuk □
Ja, talerstol □
Andet: _____

**Bruger du hjælpemidler for at komme omkring når du er udendørs?**
Nej, jeg kommer omkring uden gangredskaber □
Ja, rollator □
Ja, stok □
Ja, gangbuk □
Ja, talerstol □
Andet: _____

**Hvordan kommer du omkring i det offentlige rum?**
Jeg har bil og kan selv køre □
Jeg har en pårørende/ven der uden besværlighed kan køre mig □
Jeg har en pårørende/ven der kan køre mig – dog ikke uden besvær og/eller planlægning □
Jeg er afhængig af offentlig transport (bus, tog, metro) □
Jeg har ikke bil eller kørelejlighed og er ikke i stand til at tage offentlig transport □

**Hvilket funktionsniveau passer bedst på dig i din nuværende situation (ECOG performance status)?:**

Fuldt aktiv. I stand til at udføre alle aktiviteter som før sygdommen uden begrænsninger □

Let nedsat ydeevne; kan ikke udføre tungt fysisk arbejde, men alt andet □

Oppegående mere end halvdelen af dagen og selvhjulpen, men ude af stand til at udføre fysisk arbejde □

I seng eller siddende i stol mere end halvdelen af dagen og begrænset selvhjulpen □

Bundet til seng eller stol og har brug for hjælp til alt □

## Mange tak for din deltagelse!

# Appendix 3: M.D. Anderson Symptom Inventory (Danish version)

**Dato:** _____ **Titel på undersøgelse:**_____

**Deltager initialer:** _____ **Protokol nummer:** _____

**Deltager nummer:** _____ **Undersøgelsesleder:**_____

## MD Anderson symptom spørgeskema (MDASI-Core)

**Del 1.** Hvor **svære** er dine symptomer?

Mennesker, der er behandlet for kræft, har ofte problemer forårsaget af deres sygdom eller deres behandling. Vi vil bede dig om at angive sværhedsgraden af de følgende symptomer inden for de **sidste 24 timer**. Vær venlig at besvare hvert af de nedenstående spørgsmål ved at markere dine svar fra 0 (symptomet har ikke været til stede) til 10 (symptomet har været det værst tænkelige).

| | Ikke til stede | | | | | | | | | | Værst tænkelige |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1. Dine **smerter** da de var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 2. Din **træthed** da den var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 3. Din **kvalme** da den var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 4. Din **forstyrrelse af søvnen** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 5. Din **følelse af at være psykisk belastet** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 6. Din **åndenød** da den var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 7. Dine **problemer med at huske** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 8. Dine problemer med **manglende appetit** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 9. Din **følelse af at være døsig (søvnig)** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 10. Din **mundtørhed** da den var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 11. Din **følelse af at være ked af det** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 12. Dine **opkastninger** da det var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 13. Din **føleforstyrrelse eller prikken/ snurren** i huden da den var værst | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Side 1 af 2**



MDASI-Core – Danish – November 2010

**Dato:** _____ **Titel på undersøgelse:**_____

**Deltager initialer:** _____ **Protokol nummer:** _____

**Deltager nummer:** _____ **Undersøgelsesleder:**_____

**Del 2.** Hvordan har symptomerne **begrænset** dit liv?
Symptomer kan ofte påvirke, hvordan vi har det, og hvordan vi fungerer i dagligdagen. Hvor meget har dine symptomer inden for **de sidste 24 timer** begrænset dig på følgende områder:

| | Har ikke begrænset mig | | | | | | | | | | Har begrænset mig i allerhøjeste grad |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 14. Dit **generelle aktivitetsniveau**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 15. Dit **humør**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 16. Dit **arbejde** (herunder husarbejde)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 17. Dit **forhold** til andre mennesker? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 18. Din **evne til at gå**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 19. Din **glæde ved livet**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Dato:** _____ **Titel på undersøgelse:**_____

**Deltager initialer:** _____ **Protokol nummer:** _____

**Deltager nummer:** _____ **Undersøgelsesleder:**_____

**Del 2.** Hvordan har symptomerne **begrænset** dit liv?
Symptomer kan ofte påvirke, hvordan vi har det, og hvordan vi fungerer i dagligdagen. Hvor meget har dine symptomer inden for **de sidste 24 timer** begrænset dig på følgende områder:

| | Har ikke begrænset mig | | | | | | | | | | Har begrænset mig i allerhøjeste grad |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 14. Dit **generelle aktivitetsniveau**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 15. Dit **humør**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 16. Dit **arbejde** (herunder husarbejde)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 17. Dit **forhold** til andre mennesker? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 18. Din **evne til at gå**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 19. Din **glæde ved livet**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

# Appendix 4: EORTC Quality of Life Questionnaire (Danish version)

## EORTC QLQ-C30 (version 3.0)

Vi er interesserede i at vide noget om Dem og Deres helbred. Vær venlig at besvare alle spørgsmålene selv ved at sætte en ring omkring det svar (tal), som passer bedst på Dem. Der er ingen "rigtige" eller "forkerte" svar. De oplysninger, som De giver os, vil forblive strengt fortrolige.

| | Slet ikke | Lidt | En del | Meget |
|---|---|---|---|---|
| 1. Har De nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller en kuffert? | 1 | 2 | 3 | 4 |
| 2. Har De nogen vanskeligheder ved at gå en lang tur? | 1 | 2 | 3 | 4 |
| 3. Har De nogen vanskeligheder ved at gå en kort tur udendørs? | 1 | 2 | 3 | 4 |
| 4. Er De nødt til at ligge i sengen eller at sidde i en stol om dagen? | 1 | 2 | 3 | 4 |
| 5. Har De brug for hjælp til at spise, tage tøj på, vaske Dem eller gå på toilettet? | 1 | 2 | 3 | 4 |

**I den forløbne uge:**

| | Slet ikke | Lidt | En del | Meget |
|---|---|---|---|---|
| 6. Var De begrænset i udførelsen af enten Deres arbejde eller andre daglige aktiviteter? | 1 | 2 | 3 | 4 |
| 7. Var De begrænset i at dyrke Deres hobbyer eller andre fritidsaktiviteter? | 1 | 2 | 3 | 4 |
| 8. Havde De åndenød? | 1 | 2 | 3 | 4 |
| 9. Har De haft smerter? | 1 | 2 | 3 | 4 |
| 10. Havde De brug for at hvile Dem? | 1 | 2 | 3 | 4 |
| 11. Har De haft besvær med at sove? | 1 | 2 | 3 | 4 |
| 12. Har De følt Dem svag? | 1 | 2 | 3 | 4 |
| 13. Har De savnet appetit? | 1 | 2 | 3 | 4 |
| 14. Har De haft kvalme? | 1 | 2 | 3 | 4 |
| 15. Har De kastet op? | 1 | 2 | 3 | 4 |

| **I den forløbne uge:** | **Slet ikke** | **Lidt** | **En del** | **Meget** |
|---|---|---|---|---|
| 16. Har De haft forstoppelse? | 1 | 2 | 3 | 4 |
| 17. Har De haft diarré (tynd mave)? | 1 | 2 | 3 | 4 |
| 18. Var De træt? | 1 | 2 | 3 | 4 |
| 19. Vanskeliggjorde smerter Deres daglige gøremål? | 1 | 2 | 3 | 4 |
| 20. Har De haft svært ved at koncentrere Dem om ting som f.eks. at læse avis eller se fjernsyn? | 1 | 2 | 3 | 4 |
| 21. Følte De Dem anspændt? | 1 | 2 | 3 | 4 |
| 22. Var De bekymret? | 1 | 2 | 3 | 4 |
| 23. Følte De Dem irritabel? | 1 | 2 | 3 | 4 |
| 24. Følte De Dem deprimeret? | 1 | 2 | 3 | 4 |
| 25. Har De haft svært ved at huske? | 1 | 2 | 3 | 4 |
| 26. Har Deres fysiske tilstand eller medicinske behandling vanskeliggjort Deres familieliv? | 1 | 2 | 3 | 4 |
| 27. Har Deres fysiske tilstand eller medicinske behandling vanskeliggjort Deres omgang med andre mennesker? | 1 | 2 | 3 | 4 |
| 28. Har Deres fysiske tilstand eller medicinske behandling medført økonomiske vanskeligheder for Dem? | 1 | 2 | 3 | 4 |

**Ved de næste 2 spørgsmål bedes De sætte en ring omkring det tal mellem 1 og 7, som passer bedst på Dem**

29. Hvordan vil De vurdere Deres samlede helbred i den forløbne uge?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Meget dårligt | | | | | | Særdeles godt |

30. Hvordan vil De vurdere Deres samlede livskvalitet i den forløbne uge?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Meget dårlig | | | | | | Særdeles god |

## EORTC QLQ - BR23 DANISH

Patienter fortæller undertiden, at de har følgende symptomer eller problemer. Anfør venligst, i hvilket omfang du har haft disse symptomer eller problemer inden for den forløbne uge.

| **I den forløbne uge:** | **Slet ikke** | **Lidt** | **En del** | **Meget** |
|---|---|---|---|---|
| 31. Var du tør i munden? | 1 | 2 | 3 | 4 |
| 32. Smagte mad og drikke anderledes end normalt? | 1 | 2 | 3 | 4 |
| 33. Havde du ondt i øjnene, var øjnene irriterede eller løb de i vand? | 1 | 2 | 3 | 4 |
| 34. Har du haft hårtab? | 1 | 2 | 3 | 4 |
| 35. Skal kun udfyldes, hvis du har haft hårtab: Var du ked af hårtabet? | 1 | 2 | 3 | 4 |
| 36. Følte du dig syg eller utilpas? | 1 | 2 | 3 | 4 |
| 37. Havde du hedeture? | 1 | 2 | 3 | 4 |
| 38. Havde du hovedpine? | 1 | 2 | 3 | 4 |
| 39. Har du følt dig mindre fysisk tiltrækkende på grund af din sygdom eller behandling? | 1 | 2 | 3 | 4 |
| 40. Har du følt dig mindre kvindelig på grund af din sygdom eller behandling? | 1 | 2 | 3 | 4 |
| 41. Havde du svært ved at se på dig selv nøgen? | 1 | 2 | 3 | 4 |
| 42. Har du været utilfreds med din krop? | 1 | 2 | 3 | 4 |
| 43. Var du bekymret for, hvordan dit helbred bliver i fremtiden? | 1 | 2 | 3 | 4 |

| **I de sidste fire uger:** | **Slet ikke** | **Lidt** | **En del** | **Meget** |
|---|---|---|---|---|
| 44. I hvilket omfang var du interesseret i sex? | 1 | 2 | 3 | 4 |
| 45. I hvilket omfang var du seksuelt aktiv? (med eller uden samleje) | 1 | 2 | 3 | 4 |
| 46. Besvar kun dette spørgsmål, hvis du har været seksuelt aktiv: I hvilket omfang nød du sex? | 1 | 2 | 3 | 4 |

Vær venlig at fortsætte på næste side

**DANISH**

| **I den forløbne uge:** | **Slet ikke** | **Lidt** | **En del** | **Meget** |
|---|---|---|---|---|
| 47. Havde du smerter i armen eller skulderen? | 1 | 2 | 3 | 4 |
| 48. Var armen eller hånden hævet? | 1 | 2 | 3 | 4 |
| 49. Var det svært at løfte armen eller bevæge den til siden? | 1 | 2 | 3 | 4 |
| 50. Har du haft smerter i "brystområdet"? | 1 | 2 | 3 | 4 |
| 51. Var "brystområdet" hævet? | 1 | 2 | 3 | 4 |
| 52. Var "brystområdet" ømfindtligt? | 1 | 2 | 3 | 4 |
| 53. Har du haft hudproblemer i "brystområdet" (f.eks. kløe, tørhed, afskalning)? | 1 | 2 | 3 | 4 |

# Appendix 5: The Hospital Anxiety and Depression Scale (Danish Version)

## Hospital Anxiety and Depression Scale (HAD)

*Dette spørgeskema er udformet med henblik på at hjælpe læger med at finde ud af, hvordan du har det.*

*Læs hvert spørgsmål og sæt kryds ved det svar, der bedst beskriver, hvordan du har haft det følelses-mæssigt inden for den sidste uge.*

**1. Jeg er anspændt eller stresset.**

- ☐ Det meste af tiden
- ☐ Meget af tiden
- ☐ Engang imellem
- ☐ Overhovedet ikke

**2. Jeg glæder mig stadig over de ting, jeg plejede at glæde mig over.**

- ☐ Helt bestemt
- ☐ Ikke helt så meget
- ☐ Kun lidt
- ☐ Næsten ikke

**3. Jeg får en slags skræmmende for-nemmelse, som om noget forfærdeligt skal til at ske.**

- ☐ Helt bestemt og temmelig slemt
- ☐ Ja, men ikke alt for slemt
- ☐ En smule, men det bekymrer mig ikke
- ☐ Overhovedet ikke

**4. Jeg kan le og se tingene fra den morsomme side.**

- ☐ Lige så meget som jeg altid har kunnet
- ☐ Ikke helt så meget nu
- ☐ Bestemt ikke så meget nu
- ☐ Overhovedet ikke

**5. Bekymrende tanker strejfer mig.**

- ☐ En meget stor del af tiden
- ☐ Meget af tiden
- ☐ Engang imellem, men ikke så tit
- ☐ Kun engang imellem

**6. Jeg er i godt humør.**

- ☐ Overhovedet ikke
- ☐ Ikke ofte
- ☐ Nogle gange
- ☐ Det meste af tiden

**7. Jeg kan sidde roligt og føle mig af-slappet.**

- ☐ Helt bestemt
- ☐ For det meste
- ☐ Ikke ofte
- ☐ Overhovedet ikke

**8. Jeg føler det som om, jeg virker sløv.**

- ☐ Næsten hele tiden
- ☐ Meget ofte
- ☐ Somme tider
- ☐ Overhovedet ikke

PB
v 03-1994

**9. Jeg får en slags bange fornemmelse, lige som "sommerfugle" i maven.**

- ❑ Overhovedet ikke
- ❑ Ikke ofte
- ❑ Ret ofte
- ❑ Meget ofte

**10. Jeg har mistet interessen for mit udseende.**

- ❑ Helt bestemt
- ❑ Jeg er ikke helt så omhyggelig, som jeg burde være
- ❑ Måske interesserer det mig knap så meget som før
- ❑ Jeg er lige så omhyggelig som før

**11. Jeg føler mig rastløs, som om jeg hele tiden skal være i gang.**

- ❑ I udtalt grad
- ❑ En hel del
- ❑ Ikke så ofte
- ❑ Overhovedet ikke

**12. Jeg ser med glæde frem til tingene.**

- ❑ Lige så meget, som jeg altid har gjort
- ❑ En del mindre, end jeg plejer
- ❑ Bestemt mindre, end jeg plejer
- ❑ Næsten ikke

**13. Jeg får pludselige fornemmelser af panik.**

- ❑ Absolut meget ofte
- ❑ Temmelig ofte
- ❑ Ikke ret tit
- ❑ Overhovedet ikke

**14. Jeg kan nyde en god bog, et radio- eller TV-program**

- ❑ Ofte
- ❑ Nogle gange
- ❑ Ikke ofte
- ❑ Meget sjældent

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