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Physical Exercise in Patients with Advanced Lung Cancer

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II. List of Abbreviations (in order of appearance)

CT: Computer tomography

PET: Positron emission tomography

NSCLC: Non-Small Cell Lung Cancer

SCLC: Small Cell Lung Cancer

RT: Radiotherapy, Radiation therapy

CHT: Chemotherapy

RCHT: Radio-chemotherapy

RCT: Randomized controlled trial

CMPC: Care Management Phone Call

EIP: Exercise Intervention Program

ESAS: Edmonton Symptom Assessment Scale

ECOG: Eastern Co-operative Oncology Group

NCT: National Center for Tumor Diseases (Heidelberg)

6MWT: 6-Minute walk test

MVIC: Maximum voluntary isometric contraction

MET: Metabolic equivalent of task

PA: Physical activity

BMI: Body mass index

ITT: intention-to-treat (analysis)

ANCOVA: analysis of covariance

ACSM: American College for Sports Medicine

TKI: Tyrosine kinase inhibitors

SD: standard deviation

EIPC: early integration of palliative care

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Preliminary remark

This dissertation is located in the interface area of oncology and sports science. To a large extent, this work is based on a randomized, controlled physical exercise intervention trial – the POSITIVE study Part III (from 2013 to 2017) with 232 participants. The study has been approved by the ethics committee of the Medical Faculty Heidelberg, Germany. The author of this work was a doctoral student from the German Cancer Research Center and the Heidelberg University Hospital, Germany. She was significantly responsible for the coordination of the POSITIVE study Part III, including recruitments, collection of all clinically relevant data, anthropometric assessments, data management, execution and evaluation of physical performance tests, introduction of patients to the home-based exercise manual, and coordination and supervision of exercise sessions at the clinic during in-patient stay, overall from January 2014 to - last patient out - expected in December 2017.

1. Introduction

Lung cancer accounts to the most commonly diagnosed cancer entities and represents the leading cause of cancer-related deaths worldwide. Patients with advanced lung cancer suffer of incurable disease with a limited prognosis and face a median survival of less than 12 months. In the course of disease and treatment, patients experience multidimensional impairments which may often result in physical fragility. Beneficial effects of physical exercise have been reported for early stage lung cancer patients. However, evidence demonstrating the efficacy of exercise interventions in patients with advanced disease remains unclear. The implementation of exercise interventions in patients with lung disease is often described as challenging due to physiological causes. As the lung is responsible for oxygen uptake, it is directly essential for physical capacity. Impairments of the lung itself display a performance-limiting factor. Thus, any reduction of oxygen absorption affects performance. This is an important fact to consider in studies addressing activities of daily living and physical exercise in patients with lung disease.

In lung cancer patients, physical exercise interventions have been mostly implemented in the pre- and post-operative setting. Improvement has been observed for physical performance and cardiorespiratory fitness. For inoperable lung cancer patients, only few studies investigated the effects of physical exercise. The evidence in lung cancer patients with advanced disease derives from few single arm intervention trials with a small number of participants - mostly feasibility and observational studies.

This work represents the impact of a 24-week physical exercise intervention in patients with advanced lung cancer. Moreover, the focus of this work builds up on results, evaluations, and analyses of a specifically implemented physical exercise intervention trial in patients with advanced lung cancer - the POSITIVE study (Part III).

In the following chapters, the background of lung cancer is presented and, therewith, the resulting relevant aspects for physical exercise therapy. Methods and design of the presented project are explained. The results and evaluations are presented and discussed afterwards. This work closes with a conclusion and summary.

1.1 Background of lung cancer

1.1.1 Epidemiology

Lung cancer represents one of the most aggressive human cancers with a 5-year survival rate of 10-15% [43]. A five-year-overall survival rate of 2% is currently achieved in patients with metastatic disease [35]. Worldwide, lung cancer was the most commonly diagnosed cancer and the leading cause of cancer deaths among males in 2012 [48, 103] and it is the main cause for cancer-related deaths in Germany [10]. Overall, the highest incidence rates are reported for Northern America and Europe [104]. In men, lung cancer incidence rates were highest in Europe, Eastern Asia, and Northern America. In women, lung cancer was the second leading cause of cancer related deaths in less developed countries and the leading cause of cancer deaths in more developed countries. The incidence rates were highest in Northern America, Northern and Western Europe, Australia/New Zealand, and Eastern Asia [103]. In Germany, approximately 53,000 new diagnosed lung cancer cases are reported each year. The average age at diagnosis is 68.3 years in women and 69.3 years in men. While incidence rates for women are increasing, incidence rates in men are decreasing. Approximately 44,800 lung cancer deaths have been reported each year also indicating the trend in increasing numbers in women and decreasing numbers in men [10, 14].

1.1.2 Risk factors and carcinogenesis

The pre-dominant cause for lung cancer is tobacco smoking including second-hand smoke. Other causes include exposure to radon, occupational and/or environmental exposure to polycyclic circumstances relevant to certain categories of work (asbestos, silica, e.g.), air pollution, specifically to particular matter and diesel engine exhaust, and indoor air pollution, including also second-hand tobacco smoke and emissions from household combustion of coal. Further risk factors describe alcohol use and cured meat consumption [10, 14, 38].

The genesis of malignant cancer cells is described as a multi-stage process which results in a complete malignant transformation. In lung cancer, two groups of cancer genes play an important role: the tumor suppressor genes and the cellular proto-oncogenes [60]. It is described that malignant cells proliferate in one (or both) lungs when previously normal cells change, increase, and multiply at an uncontrolled extent. Normal lung structure and function is disrupted by the resulting lesions. Once malignant cells spread to neighboring tissues and lymph nodes, prognosis for the patient is poor [38]. Preventive screening for early detection for lung cancer is under development and has not yet been established. In most cases, the disease is discovered late. Poor survival of lung cancer patients is due, at least in part, to 80% of patients having distant metastases [43]. Advanced diseases are not eligible for surgery and had also been resistant to traditional chemotherapy. However, recent advances have led to exciting progress in therapies that are dependent on histology and genetics [14].

1.1.3 Clinical diagnostics

For patients with signs and symptoms (see also 1.2 Symptoms and disease-related impairment) of lung cancer, a chest X-ray is often the first evaluation examination. A computer tomography (CT) of the chest provides information on size and location of the tumor. According to the CT scan, determination of surgically resection is discussed. Besides CT, a positron emission tomography (PET) is additionally used for evaluating the mediastinum for lymph node metastases. In the evaluation of therapy response, CT scans are performed regularly [21].

For the determination of lung cancer pathology, a biopsy is required. The cell type is necessary to guide treatment. In addition of the determination of the cell type, specific evaluation for molecular characteristics (EGFR-, ALK-mutations, e.g.) are evaluated [65].

Histologically, lung cancer is distinguished in Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) with a ratio of occurrence of 80% to 20%. The histological types of NSCLC include adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma is the most common type and moreover often diagnosed in women without smoking history. Further subtyping on the base of molecular mutations is under development [14, 38].

1.1.4 Tumor classification and histology

The criteria for the establishment of categories of the primary tumor (T1-T4) and status of lymph nodes (N1-N3) and metastases (M0, M1) are listed in the TNM-atlas of the "Union international contre le cancer". Besides the size of the tumor, infiltration of the pleura, distance of tumor expression to the hilar bronchus, and involvement of intrapulmonary lymph nodes are of interest. Thus, initial staging is performed according to the TNM-classification [72].

Lung cancer is classified in several stages (0, I, II, III, and IV), according to the size and location of the tumor, the number of invaded lymph nodes and tissue, and status of metastases [107]. In stage 0 to II, sometimes also in stage IIIA, a resection of the tumor is possible. In addition to surgery, radiation therapy (RT) and/or chemotherapy (CHT) are applied, in stages II and IIIA often as an adjuvant treatment [38]. If resection of the tumor is no option, patients are planned for palliative treatment including RT, CHT, a combination of RT and CHT (Radio-chemotherapy, RCHT), or a targeted therapy.

1.1.5 Treatment

According to histology and stage, options of treatment include resection, radiotherapy (RT), chemotherapy (CHT), radio-chemotherapy (CHT), and/or targeted therapy. The number of planned cycles of CHT as well as the dimension and scope of RT depends on the purpose of the therapy. Moreover, functional capacity of the patient (Karnofsky index, ECOG status) is crucial for therapy regimen.

1.1.5.1 Non-Small Cell Lung Cancer (NSCLC)

The consideration of treatment of NSCLC is decided in interdisciplinary exchange (tumor board). Treatment options include surgery, RT, and/or CHT. The overall goal of surgery is a post-operative absence of the tumor. With regard to the individual aim of the surgical intervention, it has to been distinguished between curative and palliative surgery. In early stage disease, a complete resection of lung and lymph nodes is often possible, often in combination with adjuvant RT. Further risk elimination is offered by adjuvant CHT within 60 days after surgery [27, 28, 57]. The surgical intervention is often expanded by RT including curative, pre-operative (neoadjuvant), post-operative (adjuvant), and palliative RT, and/or by CHT including simultaneously and sequentially applied RCHT [28]. In advanced disease, a complete resection is rarely an option. When a tumor resection is ineligible, RCHT is applied, depending on mobility and comorbidity status. In stage IV, the aim of treatment is to reduce symptoms while maintaining quality of life. Complementary and alternative options are targeted therapies with certain inhibitors (tyrosine kinase inhibitors, e.g.) [27, 28, 57].

1.1.5.2 Small Cell Lung Cancer (SCLC)

SCLC is distinguished in limited disease and extensive disease. A major prognostic factor is considered in the extent of the disease and functional capacity of the patient. CHT - including mono- and poly-chemotherapy - is the backbone of treatment in SCLC. In limited disease stage, a surgery may sometimes be possible in combination with adjuvant RT. Neo-adjuvant therapy is rarely common. In extensive disease stage, CHT is applied with cis- or carboplatin (depending on mobility and comorbidity status of the patient) in combination with etoposide [30]. The application of CHT of cisplatin and etoposide with contemporaneous RT is considered as the preferred therapy option [27, 28, 38, 57].

1.2 Symptoms and disease-related impairment

Many patients are former or current smokers and often show up with symptoms related to smoking, such as chronic cough, a cough that gets progressively worse, chest pain, hemoptysis, shortness of breath, or multiple, repeated bronchial infections. Patients often may ignore these initial symptoms until they get more severe. Once a patient notices symptoms such as neurologic changes, bone and/or muscle pain, and jaundice, the cancer may have spread to distant organs [38]. Increased symptom levels (e.g. fatigue, dyspnoea, pain, appetite loss) and reduced quality of life in lung cancer patients compared to other cancer diagnoses like head and neck, gynaecological, prostate, breast, gastrointestinal, or bladder tumors have been reported in a Danish survey including n=1360 patients [50]. Furthermore, it has been shown that patients with advanced lung cancer have specific problems including - besides coughing and shortness of breath - anorexia and insomnia that also need to be addressed [22, 38, 47, 62].

The severity of the disease is described by “icon symptoms” as dyspnoea, fatigue and pain. Prominent symptoms also include depressions. Additional burden arises from socioeconomic problems, dealing with the change or loss of role function, facing physical fragility, and in many cases end of life decisions [100]. Moreover, these patients face a very limited prognosis and have to deal with end-of-life decisions. Symptom load and existential distress is caused by anticancer treatment on the one hand and by the disease itself on the other hand. Psychological distress expressed by resignation, anxiety, and depression have often been described in these patients [9, 24, 46]. Within the last decade, an increasing focus on treatment-related side-effects regarding impairment in patients, in particular limitations and reduction of quality of life, pain, and cancer-related fatigue, has been reported [42, 99]. Patients with metastatic or advanced NSCLC often experience multidimensional impairments affecting quality of life during their course of disease. Impairments and limitations result from comorbidities and symptoms of the disease. Side-effects and complications are caused by the anticancer treatment [50].

With regard to physical capacity, prominent described symptoms are reduced physical performance [100] and function [50] resulting in physical fragility. In recent years, physical aspects have increasingly gained importance.

1.3 Physical activity and exercise in lung cancer patients

In exercise oncology, research has been published for physical activity and exercise. According to the World Health Organisation (WHO), physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. Regular moderate intensity physical activity – such as walking, cycling, or participating in sports – has significant benefits for health [110]. Whereas physical exercise is a planned, structured, and mostly repetitive intervention with a certain intention (conditioning any part of the body, improving in strength and/or endurance, e.g.) [19]. In the context of this dissertation, both terms are used according to their certain definition.

It has been reported that cancer patients are physically impaired both during and after [53] and also prior to anticancer treatment [70]. Physical exercise has been shown to alter symptoms in different tumor entities [89]. Based on evaluation on observational studies, an adequate level of physical activity has been recommended to reduce cancer-related symptoms and even cancer related death and all-cause mortality. Correspondingly, numerous studies have demonstrated that physical activity has a benefit on quality of life, physical capacity and fatigue in cancer patients, irrespective of the tumor type [59, 61, 69]. Specifically in lung cancer patients physical exercise studies showed an improvement in physical performance and cardiorespiratory fitness in the pre-and post-operative setting [5, 41, 52, 54, 77].

Physical exercise is a commonly used measure to support medical treatment approaches in cancer patients. Various studies report that the implementation of physical exercise programs in cancer survivors is feasible and safe during and after cancer treatment [89] and about 100 studies provide data of biopsychosocial benefits related to exercise interventions [4, 36, 66, 86, 91, 92, 96]. There is broad evidence that aerobic as well as resistance training or a combination of both are beneficial for these patients [96]. Based on these findings a growing number of experts suggest that exercise programs should be integrated into standard care of patients undergoing cancer treatment [67]. To date recommendations mainly address early stage cancer patients, focusing on acute cancer treatments either pre- and/or post-surgery or afterwards in the rehabilitation/recovery period [89]. A comprehensive review regarding the benefits of physical activity interventions in cancer patients with advanced disease has been done by Lowe et al. in 2011 [64]. Ten studies, including non-randomized trials, pilot trials, and feasibility studies, were included and analyzed relating to type of intervention, outcome parameter and assessment tools for symptoms, quality of life, physical performance and fatigue. The authors concluded that exercise as a supportive care intervention is promising. However, further studies are needed to substantiate preliminary findings and further advance this emerging area of research [102].

With regard on physical and functional aspects, anticancer treatment often induces muscle waste what is associated with reductions in quality of life. Loss of appetite, anorexia, insomnia, and vomiting are the main reasons for an insufficient nutrition uptake resulting also often in a loss of muscle mass. In lung cancer, muscle mass and associations to quality of life (QOL) have been evaluated. The results showed that maintaining muscle mass induces better QOL and physical functioning [15]. An increase in muscle mass – without showing sarcopenia at baseline – was a significant prognostic factor [95].

The relationship of physical performance and survival rates has been evaluated. In retrospective analyses, it has been shown that factors of physical performance (walking distance in 6MWT, e.g.) was a prognostic factor in lung cancer patients [53, 55] and metastatic breast cancer patients [51].

The importance of physical performance is considered with regard to treatment options. On the one hand, side-effects of both treatment and disease induce physical fragility and loss of physical performance. On the other hand, physical performance determines the therapy dose and extent, often even treatment regimen (radio-chemotherapy vs. chemotherapy alone, e.g.). Thus, physical performance of cancer patients undergoing treatment gains increasingly importance. Moreover, physical performance also determines resection options when surgery is considered.

For operable lung cancer patients, studies have been performed in the pre-operative and post-operative setting [5, 41, 52, 77]. Improvement was demonstrated in physical performance and cardiorespiratory fitness. For lung cancer patients with advanced disease ineligible for surgery only few studies investigated the impact of physical exercise on quality of life [1, 82, 98]. The evidence in lung cancer patients derives from few single arm intervention trials with a small number of participants - mostly feasibility and observational studies.

Temel et al. (2009) were the first to report beneficial effects of a structured exercise program in patients with advanced NSCLC. The eight-week program which had been conducted to patients shortly after diagnosis and was persecuted twice weekly led to a reduction in lung cancer symptoms and no deterioration in 6-minute walk distance and muscle strength. They reported that less than half of the patients were able to complete the intervention. However, those who completed experienced an improvement in their lung cancer symptoms [98].

Improvements in physiological indices and emotional health-related quality of life have been reported for patients with advanced lung cancer undergoing palliative treatment [82]. The same group demonstrated beneficial effects of a 6-week hospital-based, structured, and group-based exercise program, patients with advanced lung cancer improved their physical and functional capacity, anxiety level, and emotional well-being, however not in overall health-related quality-of-life [79].

Physical performance and psychosocial status in lung cancer patients have been evaluated in predominantly advanced disease stage (n=39; NSCLC stage IV: 73%; SCLC extensive disease: 64%; median age 62 years). Assessments for physical performance included muscle strength (maximum voluntary isometric contraction via handheld dynamometry) and endurance capacity (6-Minute walk distance). Psychosocial status was assessed by use of standardized questionnaires (Functional Assessment of Cancer Therapy – Lung, FACT-L). Performance status of the patients was compared to a healthy reference group. The results of this pilot trial indicated muscular weakness, lower endurance performance, and decreased quality of life in lung cancer patients [44]. This study (POSITIVE study, Part I) represents the first of three parts within the POSITIVE project.

The subsequently conducted feasibility study (POSITIVE study, Part II) evaluated the effects of a combined resistance and endurance exercise intervention program in patients with advanced NSCLC. Within the intervention period of eight weeks, patients (n=40) were instructed to exercise at least 5x/week (inpatient setting) and at 3x/week (outpatient setting, homebased). Physical performance status (maximum voluntary isometric contraction of various muscle groups and 6-Minute walk distance), quality of life (FACT-L), fatigue (MFI), and depression (PHQ-9) were assessed at baseline, after the exercise intervention, and at a follow-up time point eight weeks later. The primary endpoint of the study was adequate adherence (feasibility) defined as completing training sessions at least 2x/week in at least six of eight weeks. Completers of the intervention showed a significant improvement in 6-Minute walk distance and in knee-, elbow-, and hip muscle strength after the intervention period. Quality of life, fatigue, and depression scores remained stable or declined slightly. The authors concluded that exercise training is feasible in advanced and metastatic NSCLC patients during anticancer treatment. The improvement of endurance and strength capacity over time indicated the rehabilitative importance of the applied intervention [59].

The subsequent trial, the POSITIVE study (Part III), builds up on the pilot (Part I) and the feasibility study (Part II) and represents the base of the present work.

1.4 Intention of this dissertation

The studies mentioned above demonstrate that physical exercise beneficially affects not only psychosocial aspects in patients with cancer but also counteracts physical impairment in the course of disease and treatment related side effects. In lung cancer, supporting evidence exists for the pre- and post-operable setting while evidence of the effects of physical exercise in patients with advanced disease is lacking.

This shall be shown in my thesis with the results of a systematic literature review on physical exercise in patients with advanced cancer. Moreover, the intention was to close the gap of lacking evidence with data from a randomized controlled physical exercise intervention trial - the POSITIVE study (Part III) (ClinicalTrials.gov NCT02055508). The objectives of the POSITIVE study (Part III), and therewith, the intention of this dissertation, was to close the gap of lacking evidence on physical exercise in patients with advanced lung cancer. To reach this goal, this dissertation covered the implementation of the POSITIVE study (Part III).

In the recently introduced POSITIVE study (Part I) and POSITIVE study (Part II), safety and feasibility represented the primary objectives. The subsequently conducted RCT should provide further evidence with behalf of the effects of the exercise training separately. Between November 2013 to December 2016, patients were recruited. In June 2017, the last patient has completed the intervention program and follow-up assessments are expected to be completed in December 2017.

The high quality of the study design helped to achieve a better reliability and validity for my dissertation. In advance of the POSITIVE study (Part III), a literature review was carried out to provide an overview on physical exercise in patients with advanced cancer. The publications that have been and will be published in the course of this dissertation address questions about the effects of a physical exercise program in lung cancer patients undergoing palliative treatment.

An additional purpose of my thesis is to provide more knowledge for an optimal and efficient exercise therapy program as an integral part of cancer treatment for patients with non-operable lung cancer undergoing palliative treatment.

1.4.1 Aims and objectives of this thesis

The main objective of the studies presented in this thesis is to provide further insight into the impact of physical exercise in non-operable lung cancer patients during therapy on physical performance, to reveal potential benefits of a combined resistance and endurance exercise program during cancer treatment, and to evaluate how exercise prescriptions can be adapted and established for these patients. To reach this goal, the first publication provided a literature review of physical exercise in advanced cancer patients. The second publication described the study design of the POSITIVE study (Part III) to introduce assessments, objectives, and analyses. The third publication evaluated physical exercise behavior in the year before and shortly after lung cancer diagnosis and analyzed physical performance status of patients compared to healthy reference data. The fourth publication (in preparation) will evaluate the effects of the 24-week physical exercise program of the POSITIVE study (Part III). Moreover, patients' adherence and completion rates will be evaluated. The fifth publication (in preparation) will present results of the primary objectives of the POSITIVE study (Part III), which include analyses of the effects of a 12-week physical exercise on physical well-being, quality of life, and physical fatigue in patients with advanced lung cancer and is not part of this thesis. The objectives of this dissertation included several aspects that will be presented in detail in the following.

Notification: contents of the following sections are (partly) extracted from previous publications including Titz et al. 2016. Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment. Expert Rev Qual Life Cancer Care [102], Wiskemann/Hummler, Diepold et al., 2016. POSITIVE Study: Physical Exercise Program in Non-Operable Lung Cancer Patients Undergoing Palliative Treatment. BMC Cancer. [109], and Titz et al. 2017. Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer. (under review) [101].

1.4.1.1 Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment (1st publication)

It has been described that with diagnosis and during treatment period patients, relatives and also health care professionals are faced with various challenges since patients often experience multidimensional impairments affecting quality of life [50]. Impairments derive from symptoms of the disease and/or comorbidities as well as from treatment-related side effects and additional burden arises from the potential change or loss of role functions, facing physical fragility, and in many cases end of life decisions [100]. Physical exercise is a commonly used measure to support medical treatment approaches in cancer patients. Various studies report that the implementation of physical exercise programs in cancer survivors is feasible and safe during and after cancer treatment [89]. There is broad evidence that aerobic as well as resistance training or a combination of both are beneficial for these patients [96]. Based on these findings a growing number of experts suggest that exercise programs should be integrated into standard care of patients undergoing cancer treatment [67]. To date recommendations mainly address early stage cancer patients, focusing on acute cancer treatments either pre- and/or post-surgery or afterwards in the rehabilitation/recovery period [89]. The evidence on physical exercise in patients with advanced disease is unclear [102].

1.4.1.1.1 Objectives

The aim of this review was to analyze the current evidence of randomized controlled physical exercise intervention trials in patients with advanced cancer. The selected studies were discussed with regard to the content of the exercise interventions, primary and secondary outcomes as well as physical performance testing procedures [102].

1.4.1.2 POSITIVE study: Physical Exercise Program in Non-Operable Lung Cancer Patients Undergoing Palliative Treatment (2nd publication)

Numerous studies have shown that physical activity beneficially affects quality of life, physical capacity and fatigue in cancer patients, irrespective of the tumor type [59, 61, 69]. In lung cancer, exercise studies in the pre-and post-operative setting showed improvement in physical performance and cardiorespiratory fitness [5, 41, 52, 54, 77]. However, studies investigating the effects of physical exercise in non-operable patients with advanced lung cancer are rare. Particularly, the number of randomized controlled trials is limited and current knowledge derives from feasibility and observational studies [1, 18, 79, 81, 98]. Physical exercise provides beneficial effects in cancer patients as shown by numerous investigations [20, 58, 61]. Furthermore, there is strong evidence for physical exercise reducing cancer related fatigue [75] and there is some evidence from a limited number of studies that exercise has beneficial effects on quality of life in advanced lung cancer patients. Possible pathways how exercise may influence relevant lung cancer outcomes have not been studied yet. Therefore, the POSITIVE study (Part III) aims to investigate the benefits of a 24-week exercise intervention program in a randomized controlled setting. Beyond this, a translational program on immunological pathways will evaluate the potential relation between exercise-driven immunological changes and the influence on tumor specific T cell response. In contrast to other published studies, the POSITIVE study (Part III) is designed to isolate the actual impact of a 24 week exercise intervention on quality of life by the unique characteristic that social support is provided to each study participant by weekly Care-Management-Phone-Calls (CMPC) [109].

1.4.1.2.1 Objectives

The intention of the design paper of the POSITIVE study (Part III) was the introduction of the study design, eligibility criteria, assessments and analyses, and primary and secondary objectives.

The primary endpoint was the impact of a 24-week combined endurance and resistance training plus CMPCs (interventional group) compared to CMPCs alone (control group) on quality of life. Quality of life is measured by the FACT-L questionnaire, subcategory Physical Well-Being and General Fatigue measured by the Multidimensional Fatigue Inventory (MFI-20). Based on preliminary findings [44, 59], a beneficial effect on quality of life and fatigue scores for the interventional group compared to the control group after 12 weeks is expected. Furthermore, it is evaluated whether the intervention has a positive impact in terms of physical performance, depression, anxiety, demoralization and immunological parameters. In addition, sustainability and long-term effects of the intervention will be analyzed during the follow-up period [109].

1.4.1.3 Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer (3rd publication)

Despite previous physical exercise intervention studies, knowledge of exercise behavior in patients with advanced lung cancer remains limited. These patients show decreased physical and emotional function and QOL when compared with other cancer diagnoses [50]. Physical fragility and limitations of functional capacity have been observed in advanced lung cancer patients [44, 100]. Increased QOL was associated with higher step counts as well as reductions in dyspnea, pain and depression scores [8]. Investigations concerning physical performance and self-reported physical exercise behavior have not yet been reported in patients with advanced lung cancer.

Therefore, physical performance and exercise behavior in patients with advanced lung cancer shortly after diagnosis based on baseline assessments of the POSITIVE study (Part III) were evaluated [101].

The cross-sectional report including baseline data provided insight in exercise behavior of patients with advanced lung cancer. Physical activity, sports, and exercise in the year before and shortly after diagnosis (=at study enrolment) were evaluated and physical performance status of patients at study enrolment was compared with reference data.

1.4.1.3.1 Objectives

The objectives were to compare physical performance in these patients with reference data of healthy individuals and to evaluate the level of physical performance with regard to their previous (during childhood/adolescence; in the year before diagnosis) exercise and walking behavior and shortly after diagnosis [101].

1.4.1.4 Effects of a 24-week Physical Exercise Program in Patients with Advanced Lung Cancer (in preparation)

The aim of the intervention analysis was the evaluation of the 24-week exercise program of the POSITIVE study (Part III) with regard to physical performance parameters and analysis of patients' adherence and completion rates. The primary goal was to evaluate the impact on endurance capacity and muscle strength performance. Change and progression of endurance and resistance performance have been evaluated and discussed. Furthermore, adherence to the exercise program and completion rates have been evaluated and discussed. Subgroup and explorative analysis provided insight in potential prognostic factors determining performance, adherence, and completion rates. The secondary aim was to address which patients have benefitted most of the physical exercise intervention program.

1.4.1.4.1 Objectives

The analyses included different time periods of the intervention program which were considered and evaluated separately. The total intervention period of 24 weeks was evaluated (Part 1). Additionally, the first (Part 2A) and second (Part 2B) 12-week period of the physical exercise intervention program were evaluated. The subgroup and explorative analyses included primarily adherence characteristics (good vs. limited/inadequate) of the patients of the exercise arm, including evaluations on supervised and non-supervised/home-based exercise sessions. Clinical relevant characteristics with potential impact on physical performance were considered including lung cancer histology, treatment regimen at study enrolment, and patients’ exercise history. This is presented and discussed in the following work.

2. Methods and Design

The following chapter is structured with regard to the methods and design of the within this thesis presented publications. These contain the literature review (2.1 Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment), the design paper of the POSITIVE study (Part III) (2.2 POSITIVE study: Physical Exercise Program in Non-operable Lung Cancer Patients Undergoing Palliative Treatment), the cross-sectional baseline data analysis of the POSITIVE study (Part III) (2.3 Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer), and the intervention analysis of the POSITIVE study (Part III) (2.4 Effects of a 24-week Exercise Program in Patients with Advanced Lung Cancer).

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2.1 Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment (Systematic literature review)

2.1.1 Search strategy and selection criteria

The analysis was based on a systematic literature search in the electronic online databases PubMed (MEDLINE), CINAHL, and the Cochrane Library. The databases were searched for randomized controlled exercise intervention trials in advanced cancer patients undergoing palliative treatment including the key words *palliative care*, *advanced cancer*, and *physical exercise*. Only studies with no specific exercise treatment (“care as usual” or “treatment as usual”) applied in the control group were included. ‘Physical exercise’ in the intervention groups consisted of regular planned endurance or resistance exercise training or a combination of both. ‘Advanced cancer’ was defined as advanced disease in cancer patients with loco-regional or distant metastases (stage IV disease) not eligible for curative treatment including curative surgery. In the context of the review, ‘palliative treatment’ was defined as palliative oncologic treatment for advanced/metastatic disease with an estimated life expectancy of three months up to two years [37, 74] and a 5-year survival estimate of <50% [17].

2.1.2 Data extraction and validity assessment

The preselected literature of the databases was read for titles regarding the defined inclusion criteria to make a first selection. This selection was read for abstracts whereby articles with matching titles found by hand search in the reference lists (snowball method) were also included. All selected abstracts were checked for relevance with regard to the purpose of this review. All articles not fulfilling the predefined inclusion criteria of the literature search were excluded, resulting in a final selection. Study contents were assessed in an overview table presenting entities, number of included patients, inclusion and exclusion criteria, questionnaires, primary and secondary endpoints, type of applied exercise, details of exercise intervention, duration of intervention, test procedures, and study results [102].

2.1.3 Rating of study quality

The study quality was assessed by using a checklist for randomized controlled trials provided by Schulz et al. [90]. The selected studies were rated based on the following criteria: (1) evidence of randomization, (2) statistical similarity of control and intervention group at baseline, (3) specification of eligibility criteria, (4) blinding of outcome assessors, (5) report of compliance, (6) supervision in exercise intervention program, (7) report of drop-outs, (8) presenting data for both primary and secondary outcomes, (9) intention to treat-analysis, (10) report of (severe) adverse events. Each criterion is worth 1.0 numerical point. Trials rated with seven points or higher are defined as high quality studies [102].

2.1.4 Statistical analyses

The original literature only aggregated data of baseline and re-test (T1) assessment. In case of missing data, the responsible author was contacted. For descriptive presentation of change from baseline to re-test (T1), percentage differences based on the means of baseline and T1-assessments were computed. To enable comparisons across the different measure assessments, effect sizes (Hedge’s g) for the given outcome parameters were modified on recommendations by Morris and DeShon [71].

2.2 POSITIVE Study: Physical Exercise Program in Non-operable Lung Cancer Patients Undergoing Palliative Treatment (Study design)

2.2.1 Study design

The POSITIVE study (Part III) was a randomized controlled intervention trial. All eligible patients who gave written informed consent were randomized (1:1) either to the control group or to the intervention group. The intervention was provided for 24 weeks starting immediately after baseline assessment. Outcome measures were assessed at baseline (T0), after 12 weeks (T1), after 24 weeks (T2) and thereafter at 9 months (T3) and 12 months (T4), so that the maximum study duration per patient was one year (see Figure 1). The intervention group involved “Exercise Intervention Program (EIP) and Care Management Phone Calls (CMPC)” while the control arm performed “Care Management Phone Calls (CMPC)” only. The protocol of the POSITIVE study (Part III) has been reviewed and approved by the ethics committee of the Medical Faculty of Heidelberg (S-326/2013). The POSITIVE study (Part III) was registered at ClinicalTrials.gov (registration number NCT02055508).

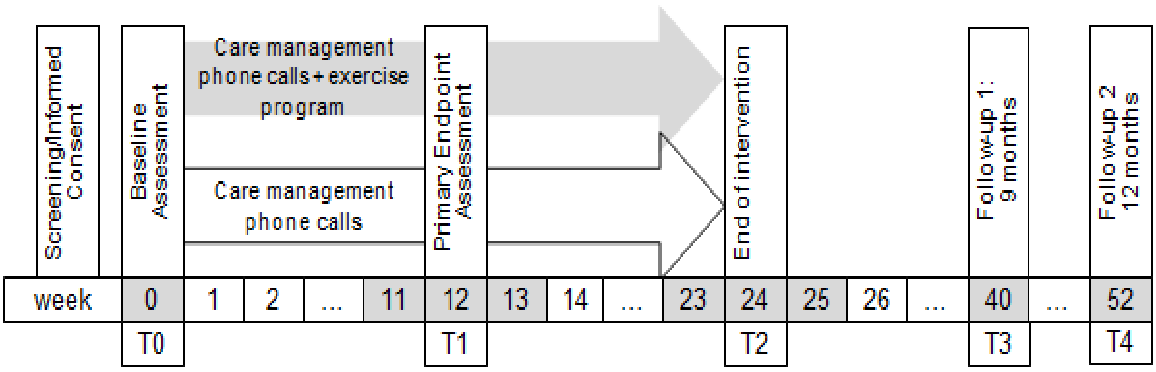


Figure 1: Design of the POSITIVE study (Part III) presenting the time points of endpoint and follow-up assessments (T0 to T4). This figure has been adapted from the original figure of Wiskemann/Hummler, Diepold et al. (2016).

2.2.2 Patients and setting

Patients were screened by the study nurse for eligibility at the Clinic for Thoracic Diseases Heidelberg, Germany. Patients were informed when all inclusion criteria were present and exclusion criteria were absent. Inclusion criteria included histologically confirmed NSCLC stage IIIA, IIIB or IV or SCLC limited or extensive disease, non-eligible for surgery, date of first diagnose did not exceed three months (unless the patients were receiving first line EGFR+ or ALK+ tyrosine kinase inhibitors), planned or already receiving systematic treatment, age ≥18 years, BMI ≥18 kg/m^2, and mobility index ECOG ≤2. Main exclusion criteria were instable bone metastases, immobility, reduced condition, and symptomatic brain metastases treated with ≥8mg/day of Dexamethason [109].

2.2.3 Study interventions

The intervention for all study patients of both study arms included weekly phone calls for symptom management and monitoring (care management phone calls; CMPCs). Patients in the exercise arm were additionally instructed to a home-based exercise program and were conveyed to a local (near patients' home) training facility. The intervention period lasted for 24 weeks after baseline assessment.

For patients with advanced lung cancer the adequate management of disease- and treatment-related side effects determine quality of life, psychosocial burden and the extent of fatigue. Therefore weekly phone calls were provided to all patients. The CMPCs were based on the Edmonton Symptom Assessment Scale (ESAS), a 9-item patient-rated symptom visual analogue scale developed for patients receiving palliative care. The modified version comprised of one additional question to assess the patient´s quality of life. Patients rated their symptoms on an 11-point scale from 0 to 10 and at pre-specified cut off values (e.g. uncontrolled pain or breathlessness) the attending physician is contacted by the study nurse to manage symptoms and side-effects [109].

2.2.3.1 Exercise intervention program (EIP)

The exercise intervention included supervised and non-supervised resistance and endurance exercise. During the first 12 weeks of the intervention program, supervised training sessions were conducted twice weekly with an additional self-administered home based training once a week. With the beginning of week 13 supervised training in cooperating training facilities was reduced to 1x/week and two home based training sessions per week were recommended. Training frequency was scheduled for three times a week. For endurance exercise, the training duration started at least 15 minutes minimum and ideally increase over time to 45 minutes depending on the patients' individual capacity. Endurance exercise was carried out by a cycle ergometer, treadmill, or outdoor walking. The intensity for endurance training was defined between 12 and 14 on the Borg Scale [13]. Training duration and intensity for resistance training sessions were adapted using the Borg Scale (14-16) and a well-established self-rating procedure from a lung cancer feasibility and allogeneic transplant study, also conducted of the Heidelberg group [108]. At the beginning of each training session patients are asked to self-assess pain, fatigue, emotional status, and distress. This self-assessment was designed to help the patient choose the appropriate exercise volume category. There were three different categories, representing the traffic light colors red, yellow and green, for tailoring the exercise intervention. Depending on the color, patients set their individual training volume higher or lower. After each training session patients were asked to document their training in an exercise log.

Inpatient exercise periods were conducted (supervised by the attending physiotherapist/sports scientist) at the exercise facilities of the clinic. Patients in the exercise intervention group were given a manual for individualized home based exercising. The program combined resistance (using body weights and rubber bands) and endurance (walking) instructions for brisk exercises. To allow for a supervised training near the patients´ home, patients performed exercise sessions in specific training facilities cooperating with the National Center for Tumor Diseases (NCT) Heidelberg. The supervised training sessions in the local training facilities comprised of resistance exercise on machines and endurance training on an ergometer/treadmill. Responsible exercise specialists in cooperating facilities were appropriately trained in the outpatient setting.

On the basis of the CMPCs the study nurse regularly reviewed exercise adherence and identifies barriers and problems with regard to exercise. Exercise sessions were stopped if pain, dizziness, or other contraindications (e.g. infections with body temperature ≥38°C, impaired hematopoietic capacity or 24 hours after receiving chemotherapeutical treatment with possible nephro- and/or cardiotoxicity) occurred.

2.2.4 Physical function tests

Data were collected at five time points (T0 – T4) every 12 weeks starting with baseline (T0). Accompanying the intervention period, testing procedures were carried out after 12 weeks and after weeks 24. After the intervention period, follow-up testing procedures were executed 9 months and 12 months after baseline. Physical performance testing procedures included endurance and resistance testing procedures. Endurance testing included the walk distance of the 6-Minute walk test. Resistance testing was performed by maximum voluntary isometric contraction via handheld dynamometry of certain various muscles bilaterally.

2.2.4.1 Endurance capacity

The 6-Minute walk test (6MWT) [31] is a feasible and safe test to determine patients physical capacity and is well established in cancer patients [111]. The test was conducted on a ward floor at the clinic with 30 meters of distance. Patients were instructed to walk in six minutes as many meters as possible. Oxygen saturation and pulse rate were monitored before, during and after testing. After the test, patients were asked to rate their individual perceived exertion using the Borg Scale [13].

2.2.4.2 Muscle strength

Maximum voluntary isometric contraction (MVIC) was measured according to defined and standardized test positions [11] via handheld dynamometry. The reliability of this test has been shown before in healthy individuals and patients. MVIC was assessed in knee extension, knee flexion (both in seated position with 90° angle of knee flexion), elbow flexion, elbow extension, hip flexion, and hip abduction (all in recumbent position) for the dominant and non-dominant limb. Three attempts were performed in each muscle group and corresponding the best value (maximum value) was used for further calculations. Muscle strength values were recorded in Newton. Body weight adjusted muscle strength values were calculated in Newton per kilogram. Analyses include results of the dominant limb only. The dominant limb was defined at baseline.

2.3 Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer (Cross-sectional baseline data analysis)

2.3.1 Patient characteristics

Medical characteristics were obtained from medical charts including histological diagnosis, stage of disease, and type of chemotherapy and/or radiotherapy. Patient demographics were self-reported and included marital status, educational background, employment status, and smoking history [101].

2.3.2 Physical performance

Physical performance assessments included the 6-Minute walk test (6MWT) and isometric strength testing (maximum voluntary isometric contraction, MVIC) of certain muscle groups of the upper and lower limbs via hand-held dynamometry (CITEC©, Netherlands). Only data of the dominant limbs are reported. Detailed information have already been presented in chapter “2.2.4 Physical function tests”.

2.3.3 Exercise and walking behavior

Exercise behavior was assessed with well-established self-reported patient questionnaires [78, 87] regarding sports/exercise at baseline, i.e. shortly after diagnosis, as well as retrospectively in the year before diagnosis and during childhood and adolescence (age <21 years). Information on walking behavior for walks of at least 20 minutes was collected additionally.

For exercise and walking in the year before diagnosis and shortly after diagnosis, frequency (twice or more per week vs. once per week or less), duration (hours per week), and exercise type were assessed. For sports/exercise, intensity (light, moderate, intensive, or vigorous) was assessed additionally. The corresponding MET values were assigned using the tables of the Compendium of Physical Activities [2, 3]. MET*hours per week were calculated (categorized in >0-9 MET*hours/week, >9-21 MET*hours/week, and >21 MET*hours/week) of the provided information on frequency, intensity and duration. The amount of minutes of physical exercise per week was calculated for moderate, intensive and vigorous activities to determine the percentage of patients meeting the current exercise recommendations of 150 minutes of moderate to vigorous physical activity (PA) per week [85, 88]. Walking was considered as PA with no distinction being made between vigorous or moderate intensity. Walking and physical exercise were analyzed and considered separately [101].

2.3.4 Comparison of patient and reference data

For comparison analyses, the predicted distance of the 6MWT was calculated for each patient via the validated formula of Enright et al. [32] according to sex, age, height, and weight. Reference data for MVIC was obtained from Bohannon et al. [11]. Reference data for muscle strength values of knee flexion have not been published and were not included in this analysis.

2.3.5 Statistical analyses

Patient demographics and medical characteristics were reported by descriptive analyses. Comparisons between observed and reference and standard data of the 6MWT and MVIC were done by paired Student's t-tests. Multiple regression analyses were performed to calculate determinants of physical performance in this patient population. Relative muscle strength values of elbow flexors and knee extensors and the distance of the 6MWT (in meter) of the baseline physical performance assessment were defined as independent variables. Demographic data (sex, age, body mass index (=BMI), smoking status), lung cancer histology, time between first diagnosis and study enrolment, status of metastases, as well as initial therapy regimen and information on previous and current (shortly after diagnosis) physical exercise behavior were considered as dependent variables. P-values below .05 were considered significant. All statistical calculations were performed with using SAS Enterprise Guide (version 6.1, SAS statistics) [101].

2.4 Effects of a 24-week Exercise Program in Patients with Advanced Lung Cancer (Intervention analysis including physical performance parameter)

2.4.1 Intervention results

Secondary endpoints of the POSITIVE study (Part III) were analyzed including physical performance (see “2.2.4 Physical function tests” for assessment of physical performance) and patients’ adherence and completion rates to the intervention program. Progression and change of physical performance parameter from T0 to T2 (24 weeks), from T0 (baseline) to T1 (12 weeks), and from T1 to T2 (12 weeks) were evaluated. The intervention period of 24-weeks was divided in two periods of 12 weeks each.

2.4.2 Patient adherence and completion rates

Training adherence and completion rates were calculated according to the possible amount of exercise sessions within the intervention period. Patients in the exercise intervention program were asked to exercise (at least) 3 times per week. This required 36 training sessions within the first 12 weeks (week 0 – week 11) and another 36 training sessions within the second 12 weeks (week 12 – week 24). Data on adherence and completion rate were calculated based on weekly records when conducting the patients. Separately, the exercise logs were evaluated regarding type and intensity of exercise and duration. Frequency of exercise was covered in the weekly phone calls.

The exercise intervention program included home-based and supervised exercise sessions 3x/week for 24 (2x12 weeks) weeks. Patient adherence was calculated by the amount of percent of completed sessions. Patients showed good adherence when exercising ≥3/week, and limited adherence when exercising 1-2x/week. Inadequate adherence was reported for patients who did not exercise and/or were not able to exercise at all. Accordingly, the required weekly amount of exercise sessions was calculated and overall adherence was rated good, when >75% of the required exercise sessions were carried out, limited adherence when 30-70% of the required exercise sessions were carried out and inadequate adherence when less than 30% of the required exercise sessions were carried out. The results and interpretation have to consider the reasons for poor adherence rates: loss of motivation or disease progression. Patients of the exercise arm were asked in the weekly phone calls (CMPC) about their effort in exercising. Additionally, the patients were asked to track their exercise sessions in an exercise log.

The exercise log was implemented in the exercise manual and consisted of 24 sheets - one sheet per week - and assessed information on exercise uptake according to the FITT criteria. The sheet showed a schedule from Monday to Sunday with the option for the patient mark with a cross what type of exercise (endurance, resistance, both), length of exercise sessions (<10 minutes, 10-20 minutes, 20-30 minutes, >30 minutes), exercise alone (yes/no), and training facility (yes/no). Additionally, patients rated the intensity of their exercise session according to the Borg scale (9-20). Patients were asked to exercise between 12 and 14 for endurance exercise and between 14 and 16 for resistance exercise if there were no limitations or contraindications present. The patients were also asked to indicate if the exercise session was not carried out because it was not scheduled on that day or because of side-effects, lack of motivation or temporal aspects, e.g.

2.4.3 Statistical analyses

Clinical and patient demographics were calculated by descriptive analyses. Standard methods were used for data analysis. Data were analyzed on the intent-to-treat-basis (ITT). Analysis of covariance (ANCOVA) was used with pre- to post-intervention change as dependent variable, the intervention group (CMPC+EIP) as independent variable, and the baseline measure as covariate. All ANCOVAs were adjusted on sex and age. Randomization was stratified on histology (NSCLC/SCLC), treatment (thoracic-radiotherapy/no radiotherapy), brain metastases (yes/no), and sex (male/female). Besides ANCOVA calculations, individual percentage change from T0 to T1, from T1 to T2, and from T0 to T2 was calculated separately to better identify increase and decline in performance within different subgroups.

In subgroup analyses, patient of the EIP-arm with good adherence (>75% of required exercise sessions) and patients with poor/inadequate adherence (<30% of required exercise sessions) were considered in directly comparison to the CMPC-arm.

Treatment-related analyses described the progression of performance of 6MWT and MVIC of elbow flexion and knee extension between the corresponding assessment points with regard to the applied treatment regimen.

In explorative analyses, regression analyses were calculated to identify possible determinants for improvement in physical performance in patients with advanced lung cancer. Performance of 6MWT (meter), knee extension (Newton/kilogram), and elbow flexion (Newton/kilogram) at T1 and T2 were considered as dependent variables. Sex (male/female), age (≤62 years, >62 years), BMI (<20 kg/m^2, 20-25 kg/m^2, ≥25 kg/m^2), sports/exercise behavior before lung cancer diagnosis, days since study enrolment (<48 days, ≥48days), advanced/metastatic disease (yes/no), therapy (thoracic-radiotherapy alone, sequential chemo-radiotherapy, simultaneous chemo-radiotherapy, tyrosine kinase inhibitors, consolidating radiotherapy in SCLC patients, chemotherapy alone), adherence to the exercise intervention program (EIP-arm only; good, limited, inadequate) were considered as dependent variables. P-values below .05 were considered significant. All statistical calculations were performed with using SAS Enterprise Guide (version 6.1, SAS statistics).

3. Results

In the following chapter the results of the publications presented within this thesis are demonstrated. This contains the results of the literature review (3.1 Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment), the cross-sectional baseline data analysis of the POSITIVE study (Part III) (3.2 Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer), and the intervention analysis of the POSITIVE study (Part III) (3.3 Effects of a 24-week Exercise Program in Patients with Advanced Lung Cancer).

Notification: contents of the following sections are (partly) extracted from previous publications including Titz et al. 2016. Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment. Expert Rev Qual Life Cancer Care [102], Wiskemann/Hummler, Diepold et al., 2016. POSITIVE Study: Physical Exercise Program in Non-Operable Lung Cancer Patients Undergoing Palliative Treatment. BMC Cancer. [109], and Titz et al. 2017. Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer. (under review) [101].

3.1 Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment

The literature search resulted in 960 studies of which six trials met the eligible criteria and were selected for the review. Altogether, the selected trials enrolled 590 patients with three studies including various tumor entities [17, 74, 83], two studies including breast cancer [37, 63], and one study including prostate cancer patients [33]. The analyzed studies included 243 men and 347 women. The most common cancer types were breast (n=205), gastrointestinal (n=112), lung (n=73), and prostate cancer (n=71). All patients showed advanced disease. The average age of patients across the reported studies was 59.3 years.

For physical performance assessment, the Tinetti gait and balance test and 30-meter walk test [17], one repetition maximum testing (chest press, seated row, leg extension, leg press), timed chair rise to standing (5 times), 6-meter usual and fast walk, and a 400-meter walk [33], the chair-stand test [83], Bruce Ramp treadmill test [63], and sit-to-stand, grip strength, maximal step length, and shuttle walk test [74] were used for physical performance testing procedures (see Table 1).

The primary endpoints of the selected studies included physical well-being and fatigue [17], body and regional lean mass [33], fatigue and quality of life [37], physical fatigue [74], and chair-stand test [83]. Secondary endpoints included muscle strength and function, cardiorespiratory capacity, blood biomarkers and quality of life [33], physical performance [74], and pain score [83], and physical functioning [63] (see Table 1).

The exercise types included combined progressive resistance and aerobic exercise [33], structured physical therapy [17], resistance training [83], supervised circuit training [74], moderate-intensity aerobic exercise program [63], and home videotape, seated exercise program [37]. The duration of the intervention programs lasted between eight and 14 weeks [33, 63, 74, 83]. In two studies, the duration was not defined on a certain amount of weeks but on the amount of sessions (eight sessions) [17] or cycles of chemotherapy (four cycles) [37].

For physical performance, significant results were shown for the shuttle walk test after an eight-session truncal and upper-limb strengthening program [74] and for the timed chair-stand test after a 2-week inpatient plus a 12-week home-based isometric resistance training program [83]. Significant changes in muscle strength for chest press, seated row, leg press, and leg extension after a 12-week machinebased resistance training were observed [33]. With regard to the 400-m walk, chair rise to standing and stair climbs assessment, the effect sizes are negative since a reduction in time (all in seconds) corresponds to a better performance. For parameters regarding the numbers of repetitions, centimeter or meter, the effect sizes are positive. The relative improvement (% change) indicates the extension of change between baseline and retest assessment. In the remaining studies, physical performance was not tested/not assessed [37] or studies provided only baseline results for physical performance [17], or just reported change without providing pre- and post-testing values [63].

For quality of life, the Spitzer Uniscale, the Linear Analog Self Assessment of physical well-being [17], the Short Form-36 (SF-36) [33], and the Functional Assessment of Chronic Illness Therapy-Fatigue Version IV (FACIT-F) [37] were used. Studies found improved physical well-being scores [17] and also greater changes in general health (p=.022), vitality (p=.019), and the physical health composite scores (p=.020) in the exercise group [33]. In a mixed modeling approach, a decline in QOL scores for the entire patient cohort was observed with the application of a third cycle of chemotherapy [37]. However, the decline in the exercise group was significantly slower (p=.02) compared to the control arm. For physical functioning and overall QOL (EORTC-QLQ-C30), no significant increases were reported for the intervention group [63].

Further analyzed outcomes included fatigue and pain. Three studies included fatigue scores as a primary endpoint [17, 37, 74]. Overall, no significant effects were reported. A trend was observed in favor of the exercising groups. Beneficial effects for fatigue were also described in the 12-week resistance training trial in prostate cancer patients, where fatigue scores had been significantly reduced in the exercise group [33]. However, these findings were inconsistent to Oldervoll et al. and Cheville et al. [17, 74]. For pain, Rief et al. demonstrated reduced pain perception in advanced cancer patients exercising during and after palliative radiotherapy for vertebral bone metastasis in comparison to non-exercising controls [83].

The reported adherence rate (training frequency) was between 69% and 94% and there were no differences observed between supervised (69-78%) and non-supervised (75%) exercise interventions. One study reported higher study attrition in the exercise group than in the control group (14 participants vs. 8 participants, p=.15) [63]. No adverse events either during testing procedures or exercise sessions were reported [33, 63, 74].

Table 1: Results of the literature review including entities, number and gender of enrolled patients, primary and secondary endpoints, exercise intervention contents and test procedures, as well as a summary of the results of the presented studies themselves. This table has been adapted from the original tables of Titz et al., 2016.

Study	Entity	N (m/f)	Primary endpoints	Secondary endpoints	Exercise intervention	Test procedures	Results
Cheville et al., 2010 [17]	mixed[A]	66:37	Physical well-being, fatigue	-	Truncal and upper-limb strengthening activities alternated between standing and seated exercise; educational components.	Tinetti gait and balance test, 30-meter walk test	Intervention group improved mean physical well-being scores
Galvão et al., 2010 [33]	prostate	57:0	Body and regional lean mass	Muscle strength and function, cardiorespiratory capacity, blood biomarkers, quality of life.	Resistance exercise: Chest press, seated row, shoulder press, triceps extension, leg press, leg extension, leg curl, abdominal crunches. 12- to 6-RM for 2-4 sets; aerobic exercise: 15-20 min of cycling/walking/jogging, 65%-80% of HR_{max} (Borg Scale 6-20). Small groups of 1-5 participants.	DXA (whole body and regional lean mass, fat mass, percent fat) 1-RM (chest press, seated row, leg extension, leg press); chair rise to standing (5 times); 6-m usual and fast walk, cardiovascular capacity 400-m walk	Patients of the exercise group showed an increase in lean mass (total body, P=.047; upper limb, P>.001; lower limb, P=.019) and better muscle strength (P<.01); 6-m walk time (P=.024) and 6-m backward walk time (P=.039). Patients of the exercise group showed improved QOL including general health (P=.022) and reduced fatigue (P=.021).
Headley et al., 2004 [37]	breast	0:38	Exercise, fatigue, Quality of life	-	Homebased via video "Armchair Fitness: Gentle-Exercise", 3 times a week (at least a one-day break between sessions), 5 minute warm-up, 20 minutes of moderate-intensity repetitive motion exercises, 5 minute cooldown.		FACIT-F-scores declined but at a slower rate for the experimental group (p=0.02). Fatigue scores indicated less increase and physical well-being subscale scores showed less decline for the experimental group (P=0.008 and P=0.02).
Oldervoll et al., 2011 [74]	mixed[B]	87:144	Physical fatigue	Physical performance	Circuit Training consisting of lower and upper limb muscle strength, standing balance, and aerobic endurance	Sit-to-stand, grip strength, maximal step length, shuttle walk test.	Intervention group improved in shuttle walk test (P=.008) and grip strength test (P=.01)
Rief et al., 2014 [83]	mixed[C]	33:27	Chair-stand test	Pain score	Three different exercises to ensure an even isometric training of the muscles along the entire vertebral column.	Chair-stand test	In the intervention group, fatigue and psychological stress decreased (p<.001), patients improved in the chair-stand tests (p<.0001), intervention group improved in pain scores (p<.001)
Ligibel et al., 2016 [63]	breast	0:101	Physical functioning	Physical performance, Quality of life, Fatigue	Weekly in-person meetings within the first month and monthly thereafter, weekly telephone contacts. Goal: 150 minutes of moderate-intensity exercise /week. Participants were provided with a heart rate monitor, pedometer, and an exercise journal. Participants were provided with a 16-week membership to a local gym.	Bruce Ramp treadmill test	The intervention group experienced a non-significant increase with regard to minutes of weekly exercise (p=0.17), physical functioning (p=0.23), and Bruce Ramp treadmill test (p=0.35). Study attrition was higher in the exercise group than in the control group.

[A] Gastrointestinal (n=39), Head and neck (n=18), Lung (n=15), Brain (n=12), Sarcoma (n=3), endometrial (n=2), breast (n=4), mesothelioma (n=1), lymphoma (n=2), cervical (n=1), melanoma (n=1), vaginal/vulvar (n=3), Merkel cell (n=1), metastatic carcinoma of unknown primary (n=1); [B] Gastrointestinal (n=73), Breast (n=51), Lung (n=38), Urological (n=30), Gynecological (n=12), Haematological (n=7), Other (n=20); [C] Lung (n=20), Breast (n=11), Prostate (n=14), Melanoma (n=2), Renal (n=3), Other (n=10).

3.2 Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer

Within the POSITIVE study (Part III), 2557 patients were screened for eligibility between November 2013 and December 2016 (see Figure 2). Due to at least one present exclusion criterion 1954 patients (76.4%) were excluded. In total, 301 patients (11.8%) declined participation and 70 patients (2.7%) were not enrolled due to organizational flow (n=63) or death of the patient prior to the first contact with the study personnel (n=7). 232 patients (9.1%) were enrolled in the study (132 men, 98 women, mean age 62.2±8.8, range 26-79 years). 151 patients (66.5%) showed metastatic disease at study enrolment. Approximately 88% of the patients were current (43.2%) or ex-smokers (44.5%). Twenty-eight patients (12.3%) were never smokers [101].

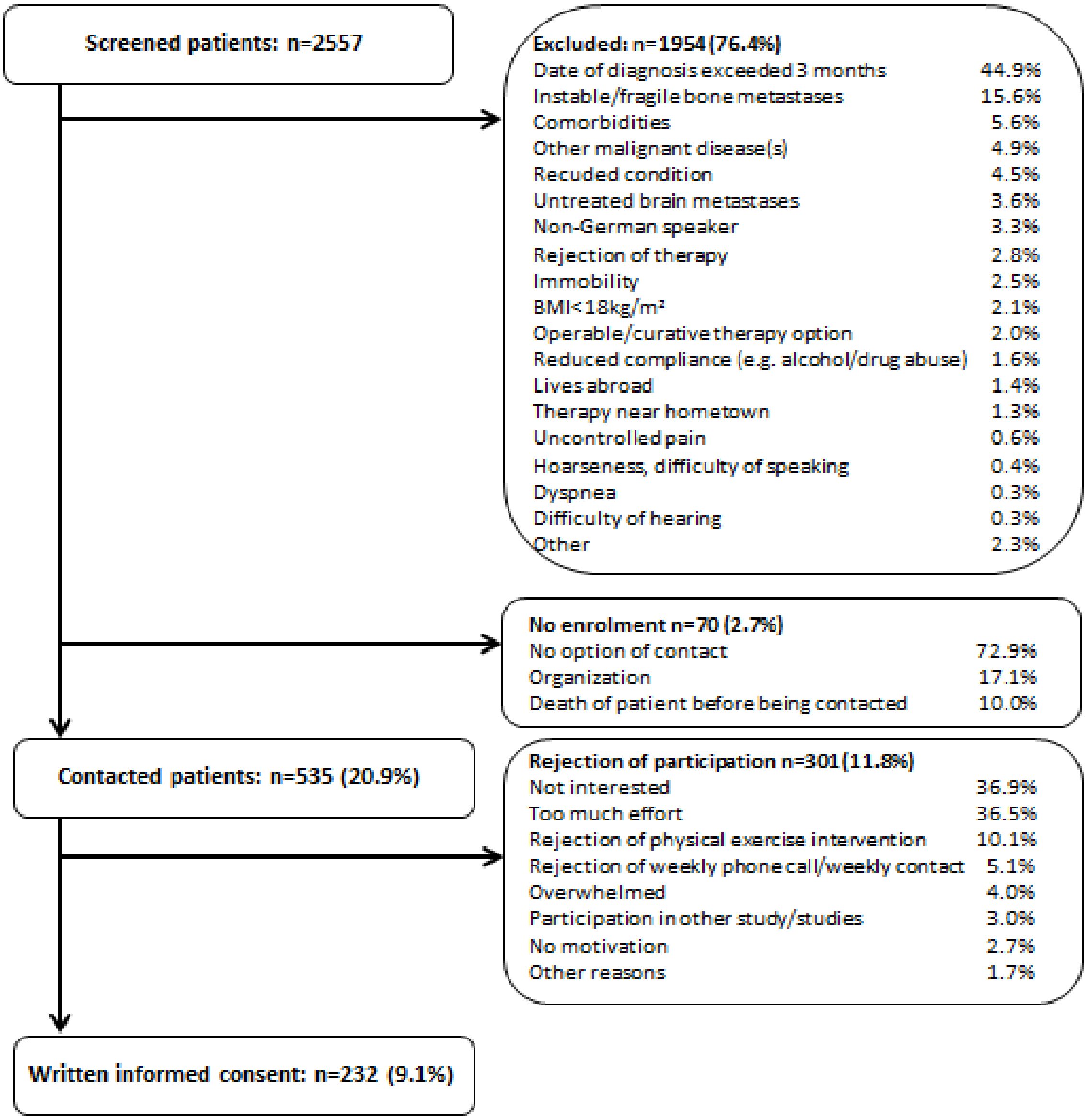


Figure 2: Recruitment flow-chart of the POSITIVE study (Part III) with the total number of overall screened lung cancer patients and excluded patients, patients being not enrolled, patients being contacted, patients who rejected a participation in the study, and patients who gave written informed consent.

3.2.1 Exercise and walking behavior

The baseline patient questionnaire assessing sports/exercise and walking behavior was completed by 213 patients. In childhood and adolescence (age ≤21 years) 139 (61.2%) patients participated in any sports beyond physical education at school with 53 patients reporting competitive sports. The average duration of participation was 4.0±0.45 years. In the year before diagnosis, ninety-seven (42.7%) patients reported regular participation in sports/exercise and 79 patients (34.8%) exercised more than twice a week. Fifty-three patients (23.3%) showed >21 MET*hours per week. Patients performed endurance training (18.5%), resistance training (12.8%), or other sports/exercise (11.5%). 116 patients (51.5%) did not participate in regular sports/exercise. The recommended 150 minutes of moderate PA per week according to the ACSM guidelines were met by 64 patients (28.2%). Shortly after diagnosis - at study enrolment - 46 patients (20.3%) reported participation in sports/exercise. 167 patients (73.6%) reported no regular participation in physical exercise. Of those who reported PA, 34 patients (15.0%) met the ACSM guidelines. With regards to the FITT criteria, a decrease of at least 50% in frequency (-57%, 79 vs. 34), duration (-50%, 64 vs. 32) and intensity (-54%, 90 vs. 41) was observed from in the year before to shortly after diagnosis [101].

3.2.2 Physical performance

3.2.2.1 Muscle strength

MVIC was assessed in 209 patients. Muscle strength values of the lung cancer population and their corresponding reference values [11] are presented in Table 2 for men and women. In men, significant differences were for hip abduction (p<.01) and knee extension (p<.01). In women, significant differences were observed in elbow flexion (p<.01) in favor of the patients. Strength values in knee extension and hip abduction were significantly lower ($p<.01$) compared to the reference data [101].

3.2.2.2 Endurance capacity

Baseline assessment for 6MWT was completed by 211 patients. Both men and women showed significantly lower performance ($p<.01$) compared to the calculated normative data [101]. The results are presented in Table 2.

Table 2: Deviations of strength performance of elbow flexion, elbow extension, hip flexion hip abduction, and knee extension and endurance capacity (6-minute walk distance in meter) from reference and standard data at baseline in male and female patients. This table has been adapted from the original table of Titz et al., 2017.

Men					
	Strength performance (N/kg)				
	n	**mean**	**SD**	**Ref[A]**	***p-value***
Elbow flexion	117	3.12	0.67	3.23	
Elbow extension	116	2.17	0.53	2.17	
Hip flexion	110	2.27	0.59	2.18	
Hip abduction	120	2.33	0.48	3.36	**
Knee extension	121	4.59	1.05	5.06	**
	Endurance performance (m)				
	n	**mean**	**SD**	**Ref[B]**	***p-value***
Walk distance	120	478.3	93.5	580.9	**

Women					
	Strength performance (N/kg)				
	n	**mean**	**SD**	**Ref[A]**	***p-value***
Elbow flexion	81	2.50	0.55	2.25	**
Elbow extension	82	1.65	0.41	1.58	
Hip flexion	83	1.87	0.62	1.74	
Hip abduction	84	2.10	0.50	2.90	**
Knee extension	88	4.12	1.07	4.57	**
	Endurance performance (m)				
	n	**mean**	**SD**	**Ref[B]**	***p-value***
Walk distance	91	441.5	104.2	506.8	**

Abbreviations: SD=standard deviation; N/Kg= Newton/kilogram; m=meter
[A]mean of reference data of Bohannon et al. 1997 in N/kg; [B]mean of calculated standard data according to the formula of Enright et al. 2003 in m; *p<.05; **p<.01.

3.2.3 Determinants of physical performance

Male sex was significantly associated with higher physical performance in walk distance (p<.05), elbow flexion (p<.0001), and knee extension (p<.01). Lower age was significantly associated with higher physical performance in walk distance ($p<.0001$), elbow flexion ($p<.05$), and knee extension ($p<.01$). For patients with BMI ≥25 kg/m², significantly lower performance in elbow flexion ($p<.01$) and knee extension ($p<.01$) compared to patients with lower BMI were observed. In elbow flexion, patients with median date of first diagnosis <48 days performed significantly better ($p<.01$). Metastatic patients showed significantly higher performance in the 6MWT ($p<.05$). With regard to exercise behavior, significant associations were observed between sports/exercise during childhood/adolescence and knee extension ($p<.05$). Patients who participated in walking in the year before diagnosis performed significantly better during the 6MWT ($p<.01$) at baseline [101]. The results for walk distance and knee extension are presented in Table 3.

Table 3: Results of multiple regression analysis of strength performance (knee extension) and endurance capacity (6-minute walk distance) in correlation to sex, age, body mass index, smoking status, lung cancer histology, upfront radio-chemotherapy, days between enrolment and date of first diagnosis, metastatic status, sports/exercise history (adapted from the original table of Titz et al., 2017).

Variables		**Walk distance (m)** R^2: .23		**Knee extension (N/kg)** R^2: .21	
		Beta[A]	**p-value**	**Beta[A]**	**p-value**
Sex	female	-35.46	*	-0.48	**
	male	*reference*			
Age	<62 years	54.51	***	0.46	**
	≥62 years	*reference*			
Body mass index	<20 kg/m^2	-10.23		0.70	**
	20-25 kg/m^2	0.03		0.64	***
	≥25 kg/m^2	*reference*			
Smoking	yes	-10.75		-0.01	
	no	*reference*			
Lung cancer histology	NSCLC	11.75		-0.15	
	SCLC	*reference*			
Upfront radio-chemotherapy	yes	32.35		-0.09	
	no	*reference*			
Days between enrolment and date of first diagnosis (median)	≥48 days[B]	-0.62		-0.19	
	<48 days	*reference*			
Metastasis	yes	31.91	*	0.05	
	no	*reference*			
Sports/exercise in youth/adolescence[C]	yes	26.12		0.34	*
	no	*reference*			
Sports/exercise in the year before diagnosis[C]	yes	27.33		0.18	
	no	*reference*			
Walking in the year before diagnosis[C]	yes	57.36	**	0.31	
	no	*reference*			

[A]Regression coefficient from multiple regression model, all variables were included simultaneously in the model; [B]48 days=median of time between date of first diagnosis and study enrolment; [C]based on the self-reported patient-questionnaire; *p<.05; **p<.01; ***p<.0001.

3.3 Effects of a 24-week Physical Exercise Intervention in Patients with Advanced Lung Cancer

Between November 2013 and December 2016, 232 patients were enrolled in the POSITIVE study (Part III) and four patients had to be excluded from analysis due to eligibility for surgery after two cycles of chemotherapy. The evaluation of the intervention included 223 patients (128 men, 95 women, mean age 62.2±8.9, range 26-79 years). 112 patients were allocated to the EIP+CMPC-arm (=EIP), 111 patients to the CMPC-arm. More than half of the patients (57.0%) presented ECOG 0 at study enrolment. Thirty patients (13.5%) were never smokers, 130 patients (58.3%) were former smokers and 62 patients (28.3%) were current smokers. The level of education was rather low in 134 patients (64.7%). More than two thirds of the patients (66.8%) presented metastatic disease at the time of study enrolment and 78.4% were diagnosed with NSCLC, 21.6% with SCLC. Thirty-five patients (15.7%) showed brain metastasis at study enrolment. More than two thirds of the patients (71.3%) received chemotherapy alone. Twenty patients (9.0%) were undergoing sequential chemo-radiotherapy and 23 patients (10.3%) simultaneous chemo-radiotherapy. Ten patients (4.5%) received radiotherapy alone and another ten patients (4.5%) were treated with tyrosine kinase inhibitors (TKI). One patient (0.5%) received immunotherapy at study enrolment. With regard to physical exercise behavior in this patient population, 109 patients (53.4%) reported sports/exercise before diagnosis while 95 patients (46.6%) patients reported no participation in any sports/exercise. The baseline patient characteristics showed no significant differences between the EIP- and CMPC-arm. Patient characteristics are shown in Table 4.

Table 4: Patient characteristics at study enrolment/baseline of the POSITIVE study (Part III) presented in total (n=223) and separated by study arm (EIP, n=112; CMPC, n=111) including sex, age, body mass index, weight and height, weight loss since initial diagnosis, performance status (ECOG), smoking status, education status, lung cancer histology and stage, metastatic status, therapy regimen, sports/exercise history.

		TOTAL		EIP		CMPC	
Total, n (%)		223	(100)	112	(100)	111	(100)
Sex, n (%)	Male	128	(57.4)	63	(56.2)	65	(58.6)
	Female	95	(42.6)	49	(43.8)	46	(41.4)
Age, mean (SD)		62.2	(8.9)	62.6	(9.1)	61.8	(8.9)
BMI[A] (kg/m^2), mean (SD)		25.3	(4.5)	25.1	(4.6)	25.3	(4.4)
Weight (kg), mean (SD)		75.6	(15.8)	74.4	(15.9)	76.9	(15.6)
Height (cm), mean (SD)		172.7	(0.1)	171.6	(8.7)	173.9	(9.4)
Weight loss since diagnosis (kg), mean (SD)		2.5	(3.7)	2.2	(3.8)	2.8	(3.7)
ECOG[B], n (%)	0	127	(57.0)	65	(58.0)	62	(55.9)
	1	91	(40.8)	46	(41.1)	45	(40.5)
	2	5	(2.2)	1	(0.9)	4	(3.6)
Smoking status, n (%)	Never smoker	30	(13.5)	12	(10.7)	18	(16.2)
	Current smoker	63	(28.3)	35	(31.3)	28	(25.2)
	Former smoker	130	(58.3)	65	(58.0)	65	(58.6)
Education status, n (%)	Low	59	(28.5)	31	(29.3)	28	(27.7)
	Basic	75	(36.2)	42	(39.6)	33	(32.7)
	Advanced	39	(18.8)	17	(16.0)	22	(21.8)
	Academic	33	(15.9)	16	(15.1)	17	(16.8)
	None	1	(0.5)			1	(1.0)
	Missing	*16*		*6*		*10*	
Lung cancer histology and stage, n (%)	NSCLC[C] IIIA	9	(4.0)	5	(4.5)	4	(3.6)
	NSCLC IIIB	48	(21.5)	19	(17.0)	29	(26.1)
	NSCLC IV	118	(52.9)	63	(56.3)	55	(49.6)
	SCLC[D] LD	17	(7.6)	10	(8.9)	7	(14.4)
	SCLC ED	31	(13.9)	15	(13.4)	16	(6.3)
Metastasis, n (%)	None	74	(33.2)	34	(30.4)	40	(36.0)
	Brain	35	(15.7)	20	(17.9)	15	(13.5)
	Other	114	(51.1)	58	(51.8)	56	(50.5)
Therapy, n (%)	Chemotherapy alone	159	(71.3)	79	(70.5)	80	(72.1)
	Radio-chemotherapy (sequ[E])	20	(9.0)	11	(9.8)	9	(8.1)
	Radio-chemotherapy (sim[F])	23	(10.3)	12	(10.7)	11	(9.9)
	Radiotherapy alone	10	(4.5)	5	(4.5)	5	(4.5)
	Tyrosine kinase inhibitors	10	(4.5)	4	(3.6)	6	(5.4)
	Immunotherapy	1	(0.5)	1	(0.9)		
Sports/exercise before diagnosis, n (%)	Yes	109	(53.4)	59	(56.7)	50	(50.0)
	No	95	(46.6)	45	(43.3)	50	(50.0)
	Missing	*19*		*8*		*11*	

[A]BMI: Body mass index; [B]ECOG: Eastern Co-Operative Oncology Group, standardized mobility index; [C]Non-Small Cell Lung Cancer; [D]Small Cell Lung Cancer; [E]sequentially performed radio-chemotherapy; [F]simultaneously performed radio-chemotherapy.

There were six non-starters in the CMPC-arm and one non-starter in the EIP-arm. Within the first 12 weeks of the intervention - from T0 to T1 - there were five drop-outs in the CMPC-arm (withdrawal of informed consent n=3; unable to perform intervention n=2) and six drop-outs in the EIP-arm (withdrawal of informed consent n=4; unable to perform intervention n=2). In the CMPC-arm, three patients died before T1 and three patients were lost-to-follow-up. In the EIP-arm, five patients died before T1 and two patients were lost-to-follow-up. 149 patients (66.8%) have completed T0 and T1 assessment and change and progression of physical performance was analyzed.

Within the second 12 weeks of the intervention - from T1 to T2 - there were two drop-outs in the CMPC-arm (unable to perform intervention n=2) and four drop-outs in the EIP-arm (withdrawal of informed consent n=4). In the CMPC-arm, eight patients died from T1 to T2 and six patients were lost-to-follow-up. In the EIP arm, three patients died from T1 to T2 and six patients were lost-to-follow-up. 89 patients (39.9%) have completed T1 and T2 assessment and change and progression of physical performance was analyzed.

Overall, including the entire intervention period of 24 weeks from T0 to T2, there were seven drop-outs in the CMPC-arm and eleven patients died and another seven patients were lost to follow up. In the EIP-arm, there were ten drop outs in total, eight patients died and eleven patients were lost to follow up. Ninety-five patients (42.6%) have completed T0 and T2 assessment and change and progression of physical performance was analyzed (see Figure 3).

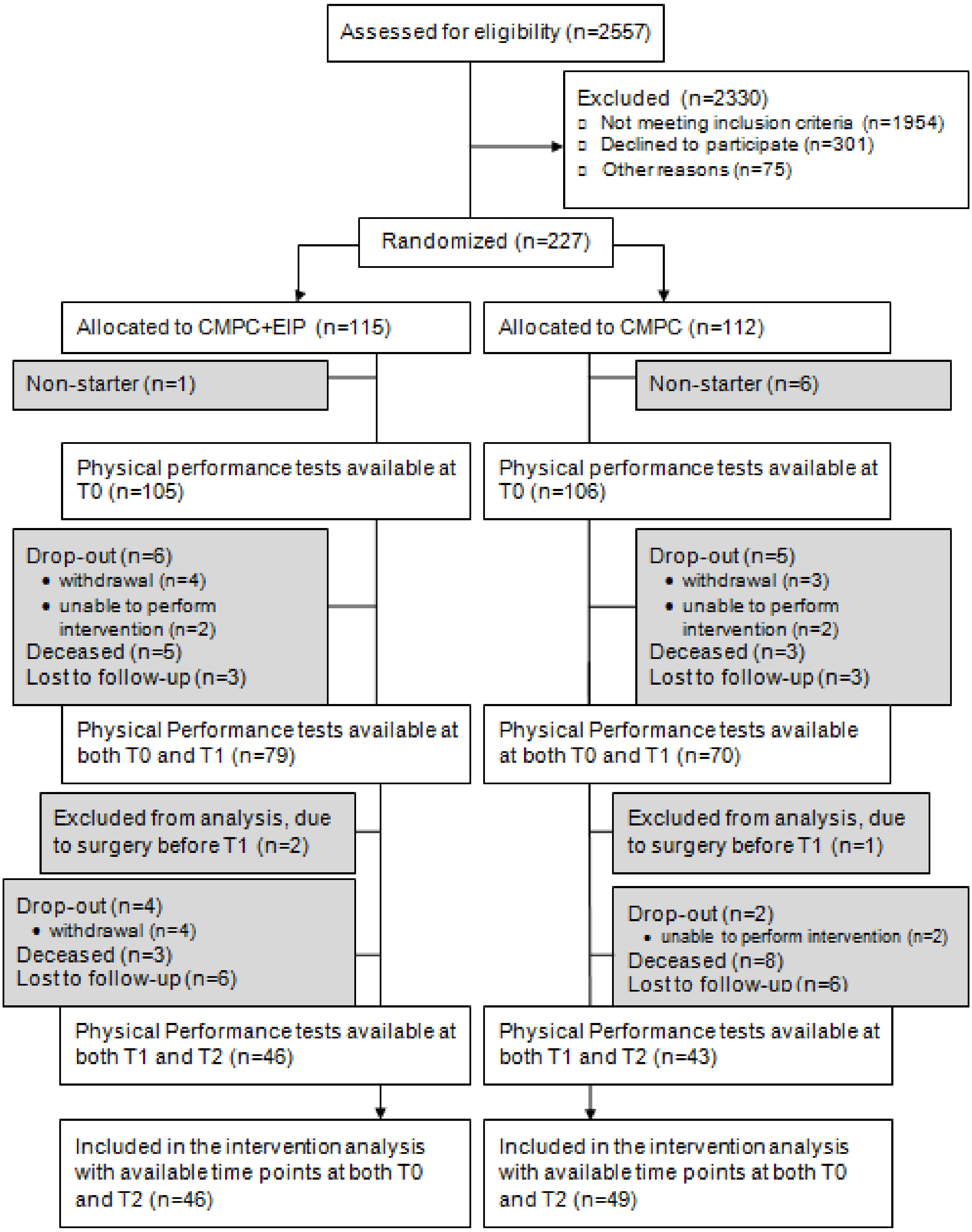


Figure 3: CONSORT diagram of assessed physical performance parameter of the POSITIVE study (Part III) from T0 to T2.

The presented results of the POSITIVE study (Part III) covered the entire intervention period and include assessment of physical performance (6MWT and

MVCI) at baseline (T0), 12 weeks after baseline (T1) and 24 weeks after baseline (T2). To generate analyses separately not only for the entire intervention period but also for the first and second 12 weeks of the intervention, the presentation of the results was split up as follows:

- Change and progression of endurance and strength capacity throughout the entire intervention period (T0 to T2) are presented in **Part 1** (3.3.1 Part 1: Intervention results from T0 to T2 (24 weeks)) including analyses of patients' adherence to the exercise program and explorative analyses.
- Change and progression of physical performance parameter are separately presented in **Part 2** for the period from T0 to T1 (Part 2A) (3.3.2 Part 2A: Intervention results from T0 to T1) and from T1 to T2 (Part 2B) (3.3.3 Part 2B: Intervention results from T1 to T2) including also analyses of patients' adherence to the exercise program and explorative analyses.

3.3.1 Part 1: Intervention results from T0 to T2 (24 weeks)

3.3.1.1 Patient adherence (T0-T2)

The analyses of adherence to the intervention program from T0 (week 0) to T2 (week 24) were based on 112 patients of the EIP-arm. One patient withdrew from participation before baseline assessment and eight patients did not start the exercise intervention due to being overwhelmed and/or exhausted (n=4) and treatment-related side-effects (n=4). From T0 to T2, seven patients (6.3%) dropped out, eleven patients died (9.8%), and seven patients (6.3%) were lost-to-follow up.

3.3.1.1.1 Adherence according to weekly patient-reported information via CMPC

Adherence to exercise program was evaluated for 108 patients (96.4%). Patients reported a mean of 41.0±23.9 of 72 required exercise sessions, 6.7±6.7 in training facilities. Thirty patients (26.8%) reported ≥75% of required exercise sessions and exercised regularly supervised in a training facility (see Table 5).

3.3.1.1.2 Adherence according to exercise log

Exercise logs of 72 patients (64.3%) were analysed. In total, 4437 exercise sessions were reported from T0 to T2, of which at least 776 exercise sessions were performed in a training facility and 2249 exercise sessions were performed home-based. On average, patients exercised at level 13 (range 5-19) on the Borg Scale. Patients performed 1028 exercise sessions <20 minutes, 2407 sessions >20 minutes. Patients rather exercised alone compared to group-based exercise or with a partner (1874 vs. 632). The required number of exercise sessions within the 24 weeks of the intervention program was 72. Patients showed 60.2±38.9

exercise sessions, 10.8±11.2 in training facilities. From T0 to T2, 24 patients (21.4%) showed ≥75% of required exercise sessions and showed regular attendance in supervised exercise sessions (see Table 5).

Table 5: Patient-reported adherence by exercise log and weekly phone calls from T0 to T2 for totally analyzed numbers and separated for patients showing good adherence.

T0 T2*	**Reported by exercise log**	**Reported by weekly calls**
Totally analyzed, n% Exercise sessions, mean±SD (range) Exercise sessions in training center, mean±SD (range)	72, 64.3% 60.2±38.9 (0-158) 10.8±11.2 (0-42)	108, 96.4% 41.0±23.9 (0-96) 6.7±6.7 (0-21)
Patients showing good adherence**, n % Exercise sessions, mean±SD (range) Exercise sessions in training center, mean±SD (range)	24, 21.4% 95.1±30.9 (55-158) 19.5±10.1 (8-42)	30, 26.8% 68.5±12.6 (54-96) 15.1±3.5 (8-12)

*the evaluation is based on the total number of 112 enrolled EIP-patients, irrespective of drop-outs, deceased patients, and patients who were lost to follow up;
**at least 54/72 (≥75% of required exercise sessions within 24 weeks) and at least 8/24 supervised exercise sessions in a local training facility.

3.3.1.4 Endurance performance (6MWT)

6MWT was completed by 95 patients and was prematurely terminated in four patients due to safety issues (dizziness, n=1; dyspnoea n=1) or other reasons (patient did not want to come to Heidelberg for performance assessment n=1; muscular pain in lower legs before 6MWT assessment, n=1). In 60 patients, the 6MWT was not assessed according to safety issues (n=17), concerns of the patient (n=32), and other reasons (n=11).

The range of percentage change in performance of the 6MWT was overall from -39% to 142%. In total, 33.3% of patients declined in performance with a decline of ≥10% in 10.4% of patients. Improvement in performance from T0 to T2 was observed in 63.5% of patients with an increase of ≥10% in 33.3% of patients. As shown in Figure 4, more patients of the CMPC-arm performed both T0 and T2 assessment of 6MWT overall improvement was higher in the EIP-arm. However, the highest increase of performance was observed in the CMPC-arm. In overall performance progression, both EIP- and CMPC-arm improved in 6MWT.

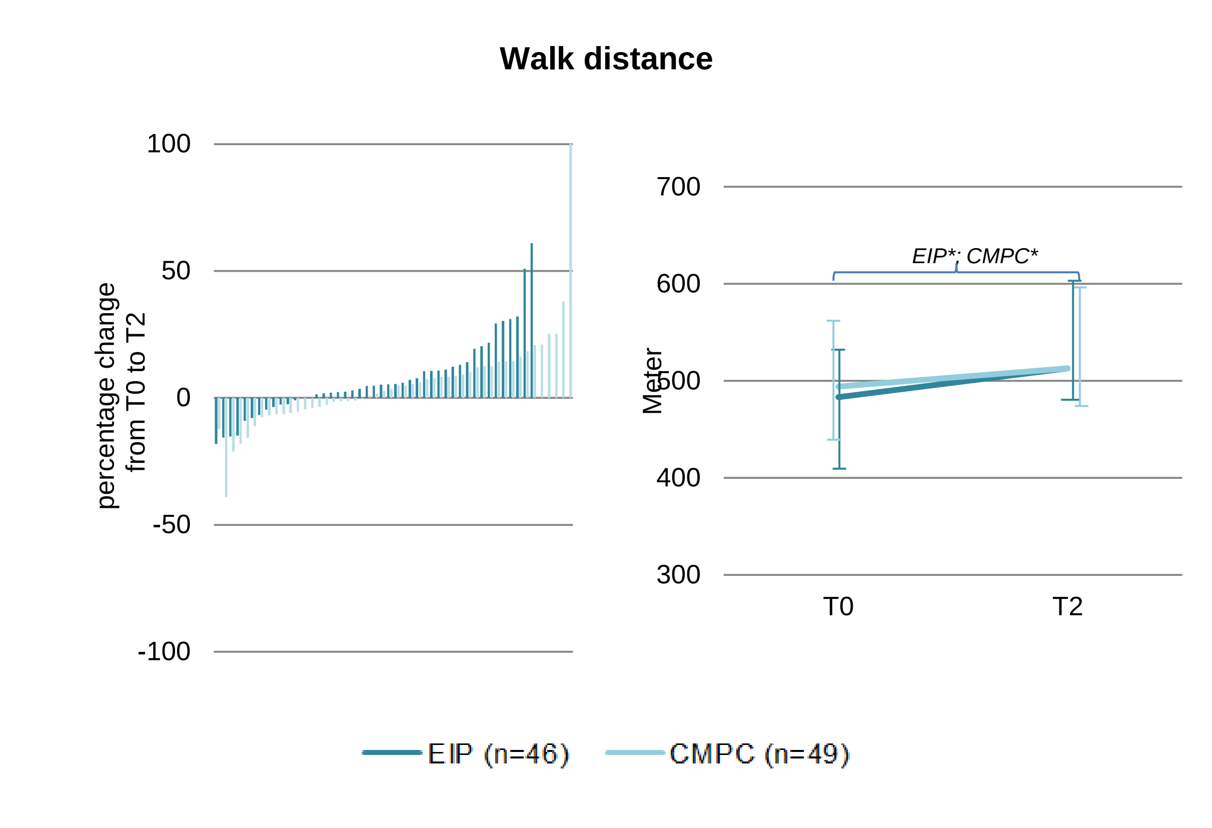


Figure 4: Percentage change (left) and overall performance progression (right) from T0 to T2 in walk distance of 6MWT for the EIP- and CMPC-arm.

3.3.1.4.1 Intention-to-treat-analysis

Data for measures at both time points were available for, in total 95 patients with 46 patients of the EIP-arm and 49 patients of the CMPC-arm. Significant inner group improvement was observed in both the EIP-arm (483.2±100.2m vs. 512.8±93.6m; adjusted mean change 30.1 95%CI 12.3, 47.8) and in the CMPC-arm (493.7±946.1m vs. 512.5±98.9m; adjusted mean change 17.6 95%CI 0.3, 34.8). No significant between group differences were observed. The results are shown in Table 6.

3.3.1.4.2 Subgroup analysis

With regard to patients' adherence of ≥75% and attendance in supervised exercise sessions (n=29), no significant between group or inner group differences were observed. The results are shown in Table 7.

3.3.1.5 *Strength performance (MVIC)*

Strength performance was assessed in 100 patients and was prematurely terminated in eleven patients due to safety issues (patient was not able to get in recumbent position for testing procedures, n=1), concerns of the patient (joint and/or muscle pain, n=3), and other reasons (joint and/or muscle pain, n=6; organisational flow, n=1). In 55 patients the MVIC was not assessed due to safety issues (newly diagnosed unstable bone metastases, n=5; acute bone fractures, n=3; pain, n=3; reduced condition/immobility, n=3; disease progression with unclear status on bone metastases, n=1; cardiovascular complications, n=1), concerns of the patient (n=27), and other reasons (n=12).

The range of percentage change in performance of knee extension was from -34% to 87% and of elbow flexion from -52% to 61%. In total, 43.6% of patients declined in performance in knee extension with a decline of ≥10% in 22.8% of patients. Improvement in performance of knee extension from T0 to T2 was observed in 56.4% of patients with an increase of ≥10% in 32.7% of patients. For elbow flexion, a decline in performance was observed in 43.2% of patients with a decline of ≥10% in 22.1% of patients. Improvement was observed in 52.6% of patients, 31.6% of patients showed an increase in performance of ≥10%. As shown in Figure 5, decline was lower and increase in performance was higher in the EIP-arm. In overall performance progression, both EIP- and CMPC-arm improved in performance. In elbow flexion (Figure 6), patients of the CMPC-arm showed lower decline and higher increase in performance from T0 to T2. The performance of elbow flexion from T0 to T2 is identical in both study arms.

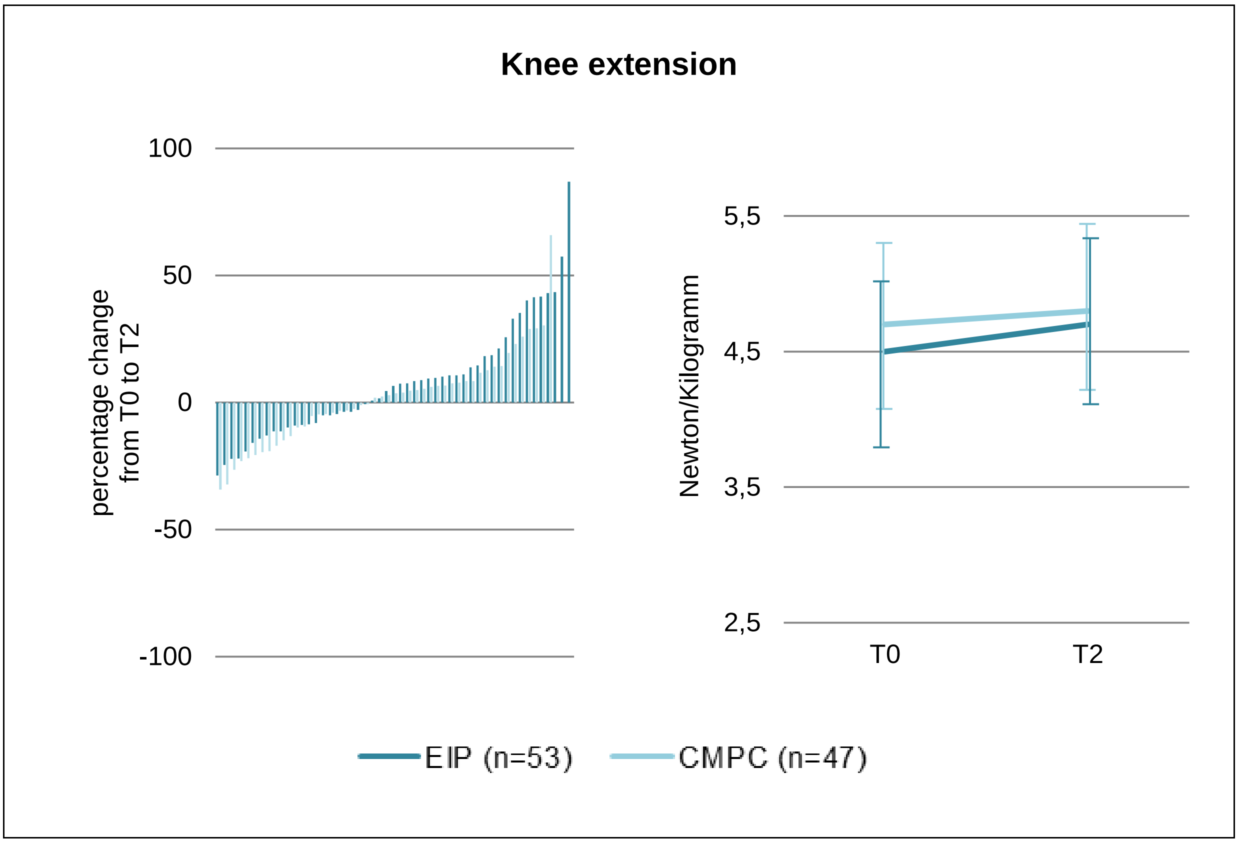


Figure 5: Percentage change (left) and overall performance progression (right) from T0 to T2 in knee extension (MVIC) for the EIP- and CMPC-arm.

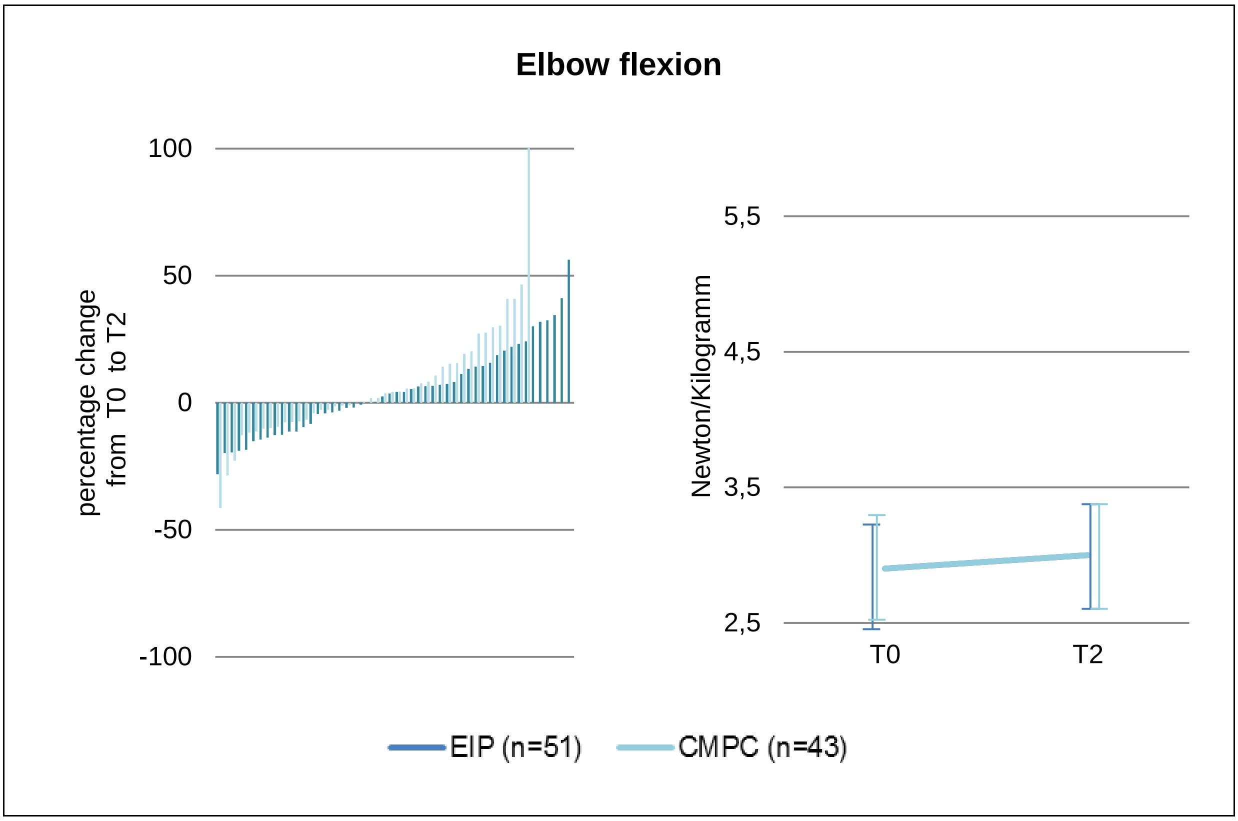


Figure 6: Percentage change (left) and overall performance progression (right) from T0 to T2 in elbow flexion (MVIC) for the EIP- and CMPC-arm.

3.3.1.5.1 Intention-to-treat-analysis

No significant between group differences were observed. Significant inner group improvement was observed in patients of the EIP-arm hip flexion. In the CMPC-arm, significant inner group improvement was observed in hip abduction. The results are shown in Table 6.

3.3.1.5.2 Subgroup analysis

With regard to patients with adherence of ≥75% and attendance in supervised exercise sessions, significant between group differences were observed for hip flexion (p=.03). Significant inner group differences were observed in the EIP-arm in knee flexion and hip flexion. A significant inner group difference was also observed in the CMPC-arm in hip abduction. With regard to patients with very limited and inadequate adherence no significant between group differences were observed from T0 to T2 (data not shown). The results are shown in Table 7.

Table 6: ANCOVA results of intention-to-treat analysis including physical performance parameter of MVIC from T0 to T2, adjusted on sex and age.

Outcome	Group	n*	T0 Mean (SD)	T2 Mean (SD)	Adjusted mean change (95CI) from T0 to T2	Adjusted difference (95CI) between groups	p(diff)
BMI[A]	EIP	66	24.9 (4.1)	24.9 (4.4)	-0.0 (-0.5, 0.4)	-0.3 (-0.9, 0.3)	0.33
	CMPC	65	25.8 (4.6)	26.1 (5.1)	0.3 (-0.2, 0.7)		
Weight[B]	EIP	67	73.9 (13.5)	73.8 (14.7)	0.0 (-1.2, 1.3)	-0.3 (-2.0, 1.5)	0.76
	CMPC	65	77.6 (16.9)	78.1 (18.1)	0.3 (-0.9, 1.6)		
Walk distance[C]	EIP	46	483.2 (100.2)	512.8 (93.6)	30.1 (12.3, 47.8)	12.5 (-12.4, 37.4)	0.32
	CMPC	49	493.7 (96.1)	512.5 (98.9)	17.6 (0.3, 34.8)		
Knee flexion[D]	EIP	53	2.9 (0.8)	3.0 (0.8)	0.1 (-0.0, 0.3)	0.1 (-0.1, 0.3)	0.34
	CMPC	47	2.8 (0.7)	2.9 (0.7)	0.0 (-0.1, 0.2)		
Knee extension[D]	EIP	53	4.5 (1.1)	4.7 (1.1)	0.2 (-0.0, 0.4)	0.2 (-0.1, 0.5)	0.18
	CMPC	47	4.7 (1.0)	4.7 (1.1)	-0.0 (-0.2, 0.2)		
Elbow flexion[D]	EIP	51	2.9 (0.6)	3.0 (0.7)	0.1 (-0.0, 0.2)	0.0 (-0.2, 0.2)	0.88
	CMPC	43	2.9 (0.7)	3.0 (0.8)	0.1 (-0.1, 0.2)		
Elbow extension[D]	EIP	51	2.0 (0.5)	2.0 (0.5)	0.0 (-0.1, 0.1)	-0.0 (-0.2, 0.1)	0.90
	CMPC	42	2.0 (0.5)	2.1 (0.6)	0.0 (-0.1, 0.1)		
Hip abduction[D]	EIP	49	2.3 (0.4)	2.4 (0.5)	0.1 (-0.0, 0.2)	-0.0 (-0.2, 0.1)	0.69
	CMPC	47	2.2 (0.6)	2.4 (0.6)	0.1 (0.0, 0.3)		
Hip flexion[D]	EIP	45	2.2 (0.5)	2.4 (0.6)	0.2 (0.1, 0.4)	0.2 (-0.0, 0.4)	0.12
	CMPC	44	2.2 (0.7)	2.3 (0.7)	0.1 (-0.1, 0.2)		

*number of patients with measures at both time points; presented data include dominant limbs only, [A]in kg/m^2; [B]in kg; [C]in m; [D]in N/kg.

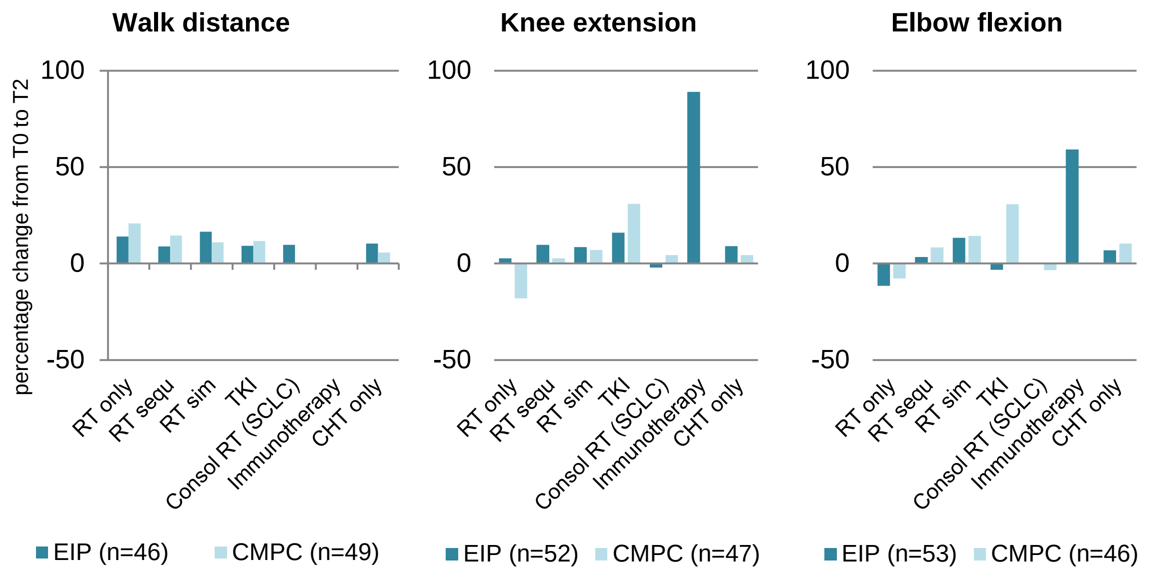
Table 7: ANCOVA results of subgroup analysis including physical performance parameter of MVIC from T0 to T2 in EIP-patients with ≥75% adherence and supervised exercise sessions, adjusted on sex and age.

Outcome	Group	n*	T0 Mean (SD)	T2 Mean (SD)	Adjusted mean change (95CI) from T0 to T2	Adjusted difference (95CI) between groups	p(diff)
Walk distance[C]	EIP+	29	497.1 (84.4)	511.8 (85.7)	17.4 (-6.1, 41.0)	0.8 (-29.2, 30.8)	0.96
	CMPC	49	493.7 (96.1)	512.5 (98.9)	16.6 (-1.5, 34.8)		
Knee flexion[D]	EIP+	31	2.9 (0.8)	3.1 (0.9)	0.2 (0.0, 0.4)	0.2 (-0.0, 0.5)	0.08
	CMPC	47	2.8 (0.7)	2.9 (0.7)	0.0 (-0.2, 0.2)		
Knee extension[D]	EIP+	31	4.5 (1.2)	4.8 (1.0)	0.2 (-0.0, 0.5)	0.3 (-0.1, 0.6)	0.15
	CMPC	47	4.7 (1.0)	4.7 (1.1)	-0.0 (-0.2, 0.2)		
Elbow flexion[D]	EIP+	30	2.9 (0.6)	3.1 (0.7)	0.2 (-0.0, 0.3)	0.1 (-0.2, 0.3)	0.49
	CMPC	43	2.9 (0.7)	3.0 (0.8)	0.1 (-0.1, 0.2)		
Elbow extension[D]	EIP+	30	2.0 (0.5)	2.1 (0.5)	0.1 (-0.1, 0.2)	0.0 (-0.1, 0.2)	0.63
	CMPC	42	2.0 (0.5)	2.1 (0.6)	0.0 (-0.1, 0.1)		
Hip abduction[D]	EIP+	29	2.3 (0.4)	2.4 (0.5)	0.1 (-0.0, 0.3)	-0.0 (-0.2, 0.2)	0.79
	CMPC	47	2.2 (0.6)	2.4 (0.6)	0.1 (0.0, 0.2)		
Hip flexion[D]	EIP+	26	2.2 (0.5)	2.4 (0.7)	0.3 (0.1, 0.5)	0.2 (0.0, 0.5)	0.03
	CMPC	44	2.2 (0.7)	2.3 (0.7)	0.1 (-0.1, 0.2)		

*number of patients with measures at both time points; EIP+: Patients of the EIP-arm with ≥75% adherence and regular exercise sessions in training facility; [C]in m; [D]in N/kg.

3.3.1.6 Treatment-related analysis

In walk distance, increase was observed across almost all therapy regimens. In patients with radiotherapy only, sequentially radiotherapy, and TKIs the CMPC-arm improved more compared to the EIP-arm. Patients with SCLC and consolidating radiotherapy improved in the EIP-arm while there was a percentage decrease in the CMPC-arm. In patients with chemotherapy only, the EIP-arm improved better compared to the CMPC-arm. In muscle strength of knee extension, patients of the EIP-arm with radiotherapy only, sequential or simultaneous radiotherapy, and chemotherapy only increased better than patients of the CMPC-arm. A very strong improve was observed for patients under immunotherapy. In patients with TKIs, the CMPC-arm improved better than the EIP-arm. In muscle strength of elbow flexion, the CMPC-arm increased higher across all therapy regimens except immunotherapy. Although patients with radiotherapy only of both study arms show percentage decrease, the decrease in the CMPC-arm was lower compared to the EIP-arm. Highest improve was observed for patients of the EIP-arm undergoing immunotherapy. See Figure 7.



		RT only	RT sequ	RT sim	TKI	Consol RT (SCLC)	Immuno-therapy	CHT only
Walk distance	EIP, n	2	9	5	3	4		23
	CMPC, n	2	5	6	4	8		24
Knee extension	EIP, n	3	11	5	3	4	1	25
	CMPC, n	2	5	5	4	7		24
Elbow flexion	EIP, n	3	11	5	3	5	1	25
	CMPC, n	2	4	5	4	7		24

Figure 7: Performance progression of endurance capacity (walk distance) and strength performance (knee extension, MVIC; elbow flexion, MVIC) with regard to treatment regimen RT (radiotherapy) only, RT sequ (sequentially), RT sim (simultaneously), TKI (tyrosine kinase inhibitors), consolidating radiotherapy in SCLC (Small Cell Lung Cancer), immunotherapy, and CHT (chemotherapy) only from T0 to T2 and corresponding number of patients of EIP- and CMPC-arm.

3.3.1.7 Regression analysis

The regression analysis included T2 performance of 6MWT (walk distance) and MVIC (knee extension, elbow flexion). In demographic variables, significant correlations were observed in 6MWT for patients ≤62 years ($p<.05$) and for knee extension in patients with a BMI of 20-25 kg/m^2 ($p<.05$). In elbow flexion performance was significantly correlated with male sex ($p<.01$), age ≤62 years (p<.01), and BMI 20-25 kg/m^2 (p<.01). Disease-related variables indicated no correlation with performance of 6MWT and elbow flexion. In knee extension, patients with radiotherapy alone performed significantly worse compared to patients with chemotherapy alone (p<.05). No correlations were observed in patients who had been physically active before diagnosis. Adherence to the EIP program did not correlate with physical performance parameter. The regression analysis is presented in Table 8.

3.3.1.8 Additional parameter

The ITT-analysis also included body weight (in kg) and BMI (in kg/m^2) from T0 to T2. There were no significant inner group or between group differences observed. In the EIP- and CMPC-arm, BMI remained stable. Body weight remained stable in the EIP-arm (73.9±13.5 vs. 73.8±14.7) and slightly increased in the CMPC-arm (77.6±16.9 vs. 78.1±18.1). The results are shown in Table 6.

Table 8: Results of multiple regression analysis of strength performance (knee extension, elbow flexion) and endurance capacity (6-Minute walk distance) in correlation to sex, age, body mass index, smoking status, lung cancer histology, upfront radio-chemotherapy, days between enrolment and date of first diagnosis, metastatic status, sports/exercise history at T2.

		Meter		**Knee extension**		**Elbow flexion**	
		R^2=.47		R^2=.44		R^2=.59	
		Beta[A]	*p*	Beta[A]	*p*	Beta[A]	*p*
Sex	male	33.58		0.40		0.71	**
	female	reference		reference		reference	
Age	≤62 yrs.	70.94	*	0.50		0.60	**
	>62 yrs.	reference		reference		reference	
BMI	<20 kg/m^2	16.89		0.51		0.13	
	20-25 kg/m^2	41.83		1.00	*	0.60	**
	≥25 kg/m^2	reference		reference		reference	
Sports/exercise before diagnosis	Yes	-24.34		0.16		-0.13	
	No	reference		reference		reference	
Days since study enrolment	≥48 days	25.00		-0.18		-0.11	
	<48 days	reference		reference		reference	
Advanced disease	Yes	19.25		-0.46		-0.16	
	No	reference		reference		reference	
Therapy	RT alone	-80.23		-1.77	*	-0.91	
	RCHT, sequentially	32.94		-0.76		-0.26	
	RCHT, simultaneously	68.47		-0.23		-0.11	
	TKI	112.92	()	0.73		-0.46	
	Consolidating RT[C]	9.35		-0.59		-0.48	
	CHT alone	reference		reference		reference	
Adherence[B] (EIP-arm only)	Good	-8.58		0.07		0.02	
	Limited	1.35		-0.64		-0.31	
	Inadequate	reference		reference		reference	

[A] Regression coefficient from multiple regression model, all variables were included simultaneously in the model; () trend (p<0.07); * p<.05; **p<.01; ***<.0001; [B]Good (>75% of required exercise sessions and regular supervised exercise sessions); Limited (30-75% of required exercise sessions); Inadequate (<30% of required exercise sessions); [C]in SCLC patients; RT: radiotherapy; sequ: sequentially, sim: simultaneously, TKI: tyrosine kinase inhibitors, CHT: chemotherapy.

3.3.2 Part 2A: Intervention results from T0 to T1

3.3.2.1 Patient adherence (T0-T1)

The exercise intervention was performed by 103 patients (92.0%) of the EIP-arm from baseline (T0) to week 12 (T1). One patient withdrew from participation before baseline assessment and eight patients did not start the exercise intervention due to being overwhelmed and/or exhausted (n=4) and treatment-related side-effects (n=4). One patient started the exercise intervention in week 10 due to treatment-related side-effects. With regard to the performed exercise sessions, fifty-six patients (53.8%) showed good adherence, 26 patients (25.0%) showed limited and twenty-two patients (21.2%) showed inadequate adherence. Sixty-two patients (59.6%) exercised regularly supervised in training facilities near their home-town (n=61) and one patients exercise supervised with a personal coach (n=1). Thirty-nine patients (34.8%) exercised home-based only. Eight patients (7.1%) were not able to get to the training facility and for three patients (2.7%) there was no training facility in their hometown available. Weekly exercise sessions within the previous week were reported by the patients within the weekly phone calls. Additionally, patients reported their exercise sessions weekly in standardized exercise logs.

3.3.2.1.1 Adherence according to weekly patient-reported information via CMPC

The exercise intervention could not be started by 10 patients (8.9%) due to treatment-related side-effects. Within the first 12 weeks, 14 patients prematurely terminated the exercise intervention due to treatment-related side-effects (n=6), lost-to-follow-up (n=3), or death (n=5). The minimum number of required exercise sessions within the first 12 weeks of the intervention program was 36. Patients showed 21.3±11.3 exercise sessions, 3.1±3.2 in training facilities. Twenty-six patients (23.2%) showed ≥75% of required exercise sessions and exercised regularly supervised (see Table 9).

3.3.2.1.2 Intervention uptake and completion rates according to exercise log

Within the first 12 weeks of the intervention, patients performed 2464 exercise sessions with an average Borg level of 13 (range 5-19). At least 395 exercise sessions were performed in a training facility. Patients showed 34.1±20.1 exercise sessions, 5.4±5.4 in training facilities. Twenty-seven patients (24.1%) showed ≥75% of required exercise sessions and exercised regularly supervised in training facilities (see Table 9).

With regard to the number of weekly exercise sessions of the patients of the EIP-arm, patients exercised most from week 2 to week 5. Afterwards, we observed a decline in the number of exercise sessions until week 12. The allocation of the type of exercise showed that patients preferred rather resistance and combined training sessions instead of endurance training sessions. From week 8 to week 11, the allocation is even in resistance, endurance and combined training sessions (see Figure 8).

Table 9: Patient-reported adherence by exercise log and weekly phone calls from T0 to T1 for totally analyzed numbers and separated for patients showing good adherence.

T0 T1*	**Reported by exercise log**	**Reported by weekly calls**
Totally analyzed, n% Exercise sessions, mean±SD (range) Exercise sessions in training center, mean±SD (range)	73, 65.2% 34.1±20.1 (0-72) 5.4±5.4 (0-21)	108, 96.4% 21.3±11.3 (0-49) 3.1±3.2 (0-10)
Patients showing good adherence**, n % Exercise sessions, mean±SD (range) Exercise sessions in training center, mean±SD (range)	27, 24.1% 47.4±14.6 (27-72) 10±4.0 (4-21)	26, 23.2% 33.7±5.8 (27-47) 6.9±2.0 (4-10)

*the evaluation is based on the total number of 112 enrolled EIP-patients, irrespective of drop-outs, deceased patients, and patients who were lost to follow up;
**at least 27/36 (≥75% of required exercise sessions within 12 weeks) and at least 4/12 supervised exercise sessions in a local training facility.

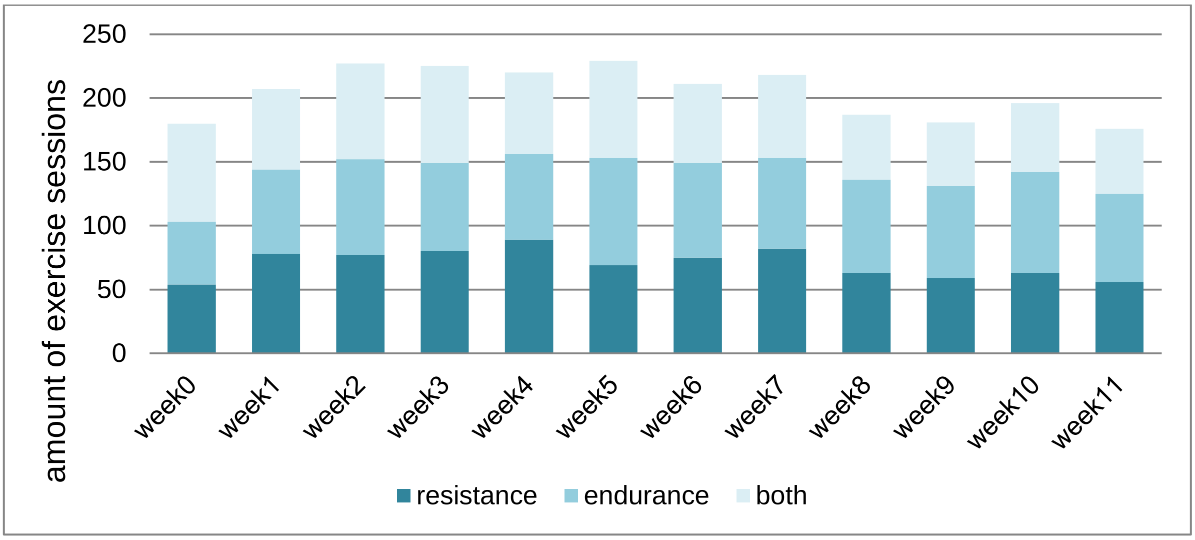


Figure 8: Exercise sessions performed by EIP-arm patients from T0 to T1 regarding weekly uptake of resistance, endurance and combined resistance and endurance exercise sessions.

3.3.2.2 Endurance performance (6MWT)

6MWT was completed by 149 patients both at T0 and T1. The test was prematurely terminated in two patients (muscular pain in lower limbs, n=2). In 37 patients 6MWT was not assessed due to safety issues (immobility, n=3; reduced condition, n=3; newly diagnosed unstable bone metastases, n=2; cardiac complications, n=1; surgery, n=1), concerns of the patient (n=17), and other reasons (n=10).

The range of percentage change in performance of the 6MWT was from -53% to 168%. In total, 40.3% of patients declined in performance with a decline of ≥10% in 9.4% of patients. Improvement in performance was observed in 57.7% of patients with an increase of ≥10% in 24.8% of patients. As shown in Figure 9, more patients of the EIP-arm performed T0 and T1 assessment for 6MWT. Overall, patients of both study arms improved performance.

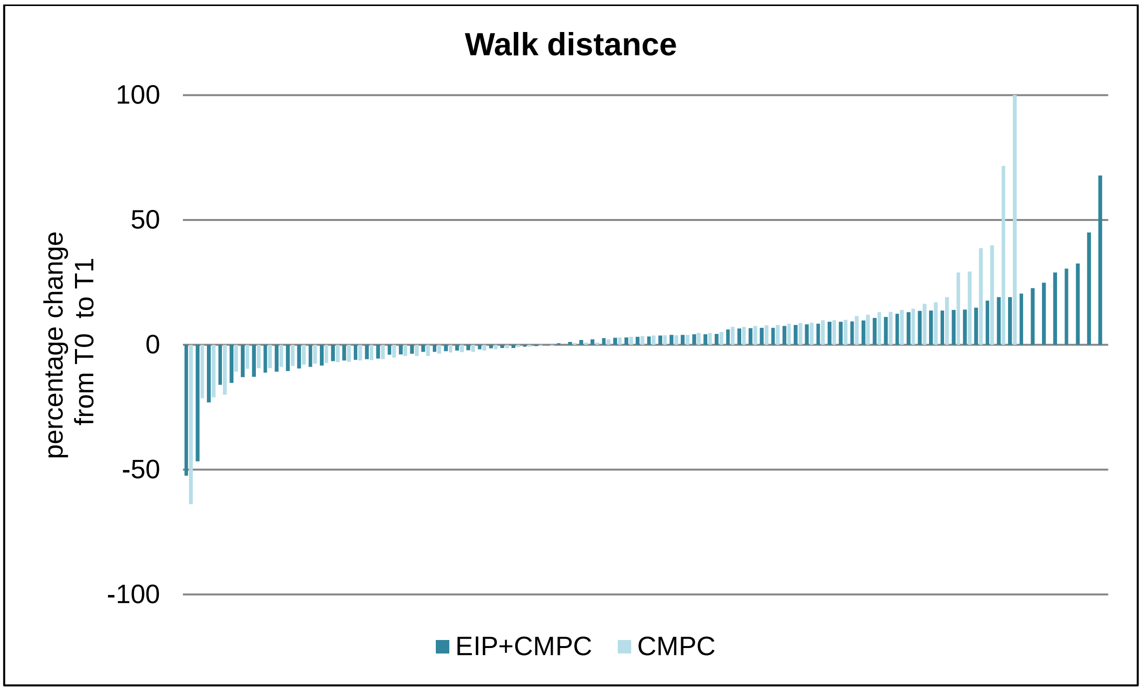


Figure 9: Percentage change from T0 T1 in walk distance of 6MWT in EIP- and CMPC-arm.

3.3.2.2.1 Intention-to-treat-analysis

Data for measures at both time points were available for 79 patients of the EIP-arm and 70 patients of the CMPC-arm. Significant improvement was observed in both the EIP-arm (464.9±94.0m vs. 478.9±98.1m; adjusted mean change 14.4 95%CI 2.5, 26.2) and in the CMPC-arm (496.0±88.9m vs. 510.3±82.5m; adjusted mean change 18.2 95%CI 5.6, 30.8). No significant between group differences were observed. The results are shown in Table 10.

3.3.2.2.2 Subgroup analysis

With regard to patients' adherence of ≥75% and attendance in supervised exercise sessions (n=43), no significant between group differences were observed. Significant improvement was observed in the CMPC-arm (496.0±88.9m vs. 510.3±82.5m; adjusted mean change 16.0 95%CI 4.0, 28.0) and in the EIP-arm (484.7±81.0m vs. 502.2±79.6m; adjusted mean change 18.3 95%CI 3.1, 33.6). No significant between group differences were observed. The results are shown in Table 11.

3.3.2.3 Strength performance (MVIC)

The MVIC was assessed in 146 patients and was prematurely terminated in seven patients due to concerns of the patient (patient was not able to get in recumbent position for testing procedures, n=1; other: n=1), complications with handheld-device (n=1), organisational flow (n=3), and other (n=1). In forty-five patients, the MVIC was not assessed in order to safety issues (pain, n=3; reduced condition, n=3; unstable bone metastases, n=2; surgery, n=1; cardiac complications, n=1; other, n=2), concerns of the patient (n=18), and other reasons (n=13).

The range of percentage change in performance of knee extension was from -50% to 85% and of elbow flexion from -38% to 84%. In total, 54.1% of patients declined in performance in knee extension with a decline of ≥10% in 26.7% of patients. Improvement in performance of knee extension from T0 to T1 was observed in 43.8% of patients with an increase of ≥10% in 32.2% of patients. For elbow flexion, a decline in performance was observed in 44.4% of patients with a decline of ≥10% in 20.0% of patients. Improvement was observed in 54.1% of patients, 25.9% of patients showed an increase in performance of ≥10%. As shown in Figure 10, percentage deviation of knee extension in performance was lower in decline and higher in increase in the EIP-arm. In elbow flexion (Figure 11), performance improved higher in the CMPC-arm.

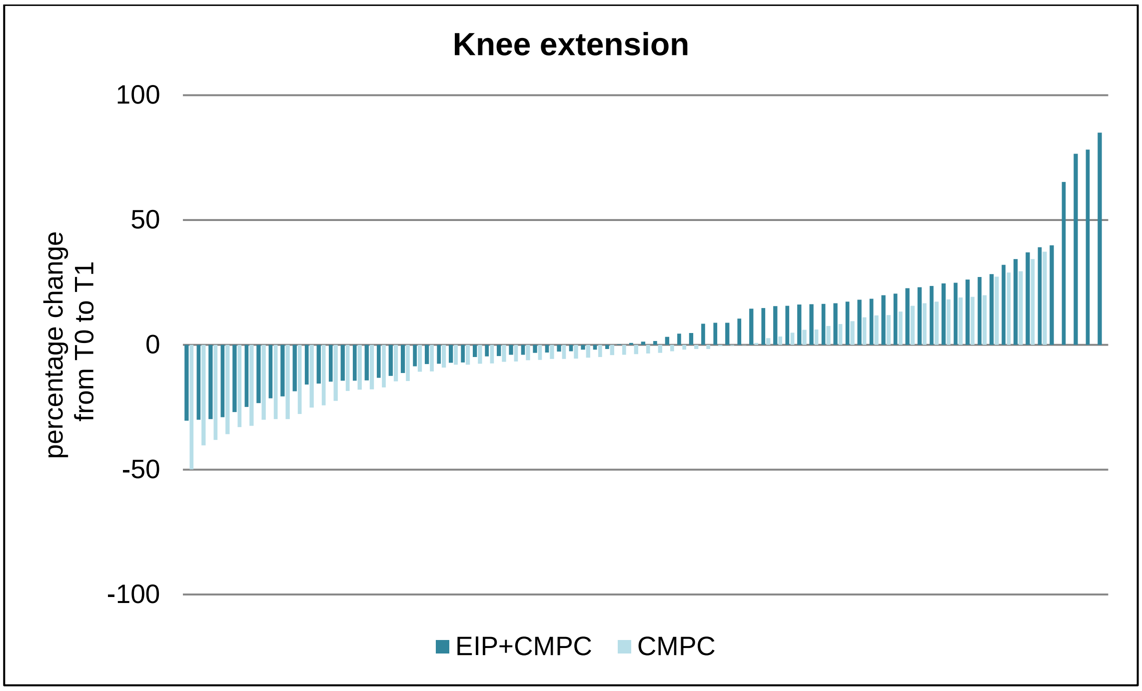


Figure 10: Percentage change from T0 T1 in knee extension of MVIC in EIP- and CMPC-arm.

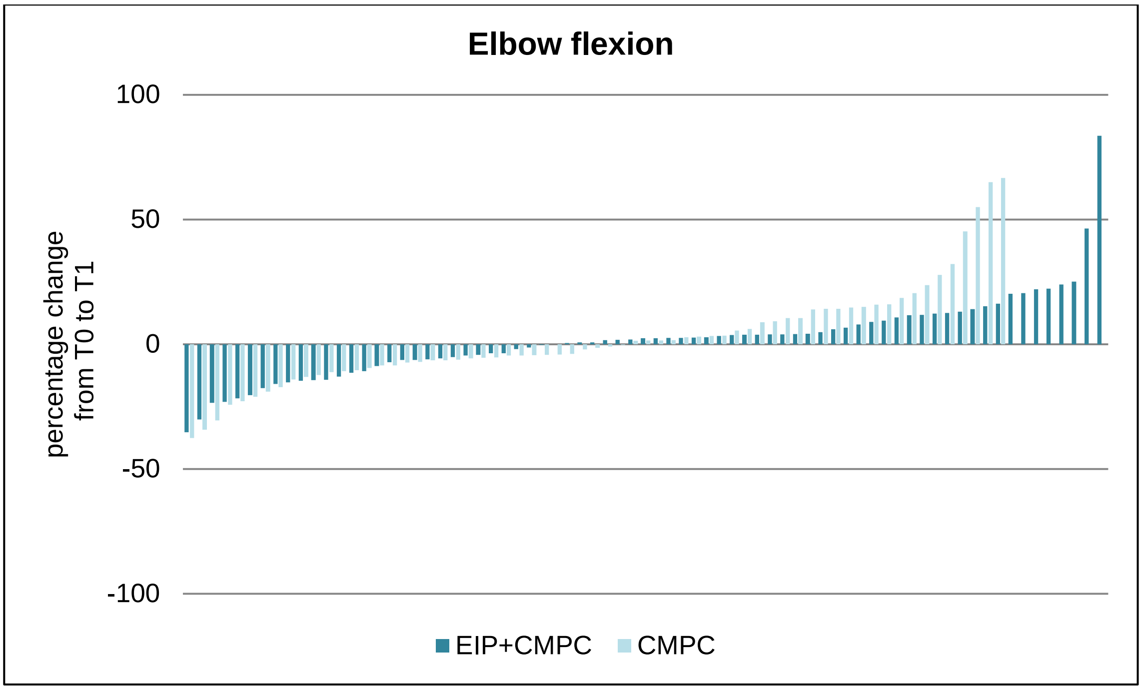


Figure 11: Percentage change from T0 T1 in elbow flexion of MVIC in EIP- and CMPC-arm.

3.3.2.3.1 Intention-to-treat-analysis

Significant between group differences were observed in knee extension (p=.02). Inner group significant improvement was observed in patients of the EIP-arm in hip flexion. The results are shown in Table 10. Overall, the results show strength values of knee flexion, knee extension, elbow extension, and hip flexion in the EIP-arm improving whereas in the CMPC-arm strength values remained or declined.

3.3.2.3.2 Subgroup analysis

With regard to patients with adherence of ≥75% and attendance in supervised exercise sessions, significant between group differences were observed for knee flexion (p<.01), knee extension (p<.01), and hip flexion (p<.01). Further, significant improvement was observed in knee flexion, knee extension, elbow flexion, hip abduction, and hip flexion in patients with good adherence and supervised exercise. With regard to patients (n=4) showing very limited and inadequate adherence to the exercise program (<30% of required exercise sessions and no supervised exercise sessions) due to treatment-related side-effects and reduced/bad condition, the results show significant between group differences in elbow flexion ($p=.02$), elbow extension ($p<.01$), and hip flexion ($p=.03$) of the EIP-arm compared to consistent performance in the CMPC-arm. Significant inner group decline was observed in the EIP-arm in knee extension, elbow flexion, elbow extension, and hip flexion. The results are shown in Table 11.

Table 10: ANCOVA results of intention-to-treat analysis including physical performance parameter of MVIC from T0 to T1, adjusted on sex and age.

Outcome	Group	n*	T0 Mean (SD)	T1 Mean (SD)	Adjusted mean change (95CI) from T0 to T1	Adjusted difference (95CI) between groups	p(diff)
BMI[A]	EIP	91	25.0 (4.4)	25.1 (4.6)	0.1 (-0.2, 0.4)	0.0 (-0.4, 0.5)	0.84
	CMPC	82	25.3 (4.6)	25.4 (4.9)	0.0 (-0.3, 0.4)		
Weight[B]	EIP	91	74.3 (15.3)	74.4 (15.9)	0.2 (-0.7, 1.0)	0.3 (-0.9, 1.5)	0.65
	CMPC	83	76.7 (16.6)	76.7 (17.3)	-0.1 (-1.0, 0.8)		
Walk distance[C]	EIP	79	464.9 (94.0)	478.9 (98.1)	14.4 (2.5, 26.2)	-3.9 (-21.2, 13.5)	0.66
	CMPC	70	496.0 (88.9)	510.3 (82.5)	18.2 (5.6, 30.8)		
Knee flexion[D]	EIP	77	2.9 (0.7)	3.0 (0.7)	0.1 (-0.0, 0.2)	0.1 (-0.0, 0.3)	0.18
	CMPC	69	2.9 (0.7)	2.9 (0.7)	-0.1 (-0.2, 0.1)		
Knee extension[D]	EIP	77	4.4 (1.1)	4.6 (1.1)	0.1 (-0.0, 0.3)	0.3 (0.1, 0.6)	0.02
	CMPC	69	4.6 (1.0)	4.4 (1.1)	-0.2 (-0.4, 0.0)		
Elbow flexion[D]	EIP	73	3.0 (0.7)	3.0 (0.6)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.2)	0.73
	CMPC	62	2.9 (0.7)	2.9 (0.7)	-0.0 (-0.1, 0.1)		
Elbow extension[D]	EIP	71	2.0 (0.5)	2.1 (0.5)	-0.0 (-0.1, 0.1)	-0.1 (-0.2, 0.1)	0.32
	CMPC	62	2.0 (0.6)	2.0 (0.6)	0.1 (-0.0, 0.1)		
Hip abduction[D]	EIP	74	2.3 (0.4)	2.3 (0.5)	0.1 (-0.0, 0.2)	0.0 (-0.1, 0.2)	0.56
	CMPC	68	2.2 (0.6)	2.3 (0.5)	0.0 (-0.1, 0.1)		
Hip flexion[D]	EIP	69	2.1 (0.6)	2.2 (0.7)	0.1 (0.0, 0.2)	0.1 (-0.0, 0.3)	0.09
	CMPC	65	2.2 (0.7)	2.2 (0.7)	-0.0 (-0.1, 0.1)		

*number of patients with measures at both time points; presented data include dominant limbs only, [A]in kg/m^2; [B]in kg; [C]in m; [D]in N/kg.

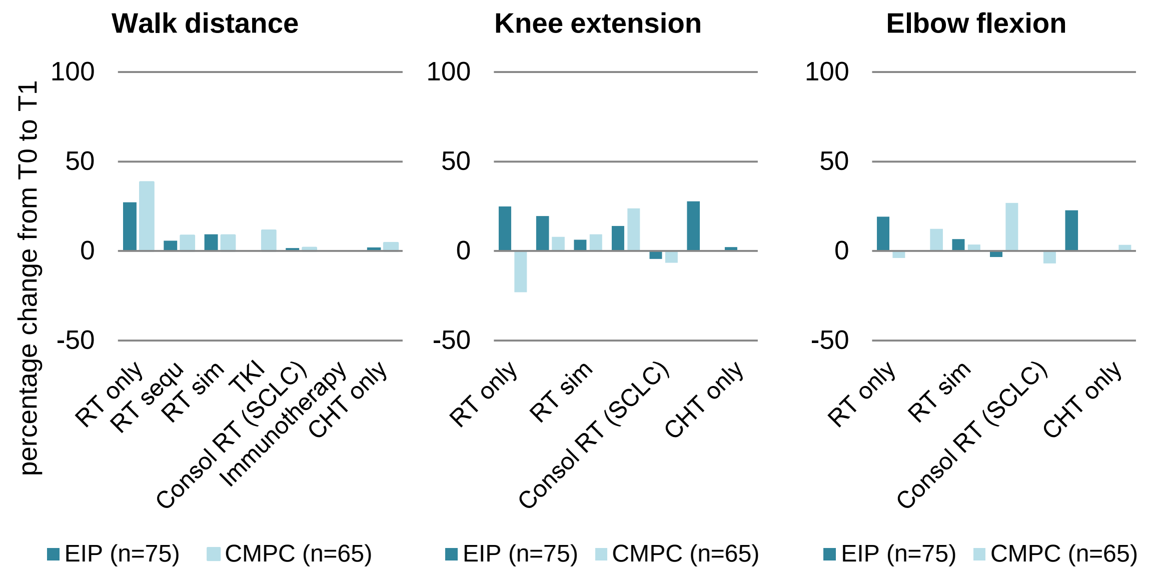
Table 11: ANCOVA results of subgroup analysis including physical performance parameter of MVIC from T0 to T1 in EIP-patients with ≥75% adherence and supervised exercise sessions, adjusted on sex and age.

Outcome	Group	n*	T0 Mean (SD)	T1 Mean (SD)	Adjusted mean change(95CI) from T0 to T1	Adjusted difference (95CI) between groups	p(diff)
Walk distance[C]	EIP+	43	484.7 (81.0)	502.2 (79.6)	18.3 (3.1, 33.6)	2.3 (-17.1, 21.8)	0.81
	CMPC	70	496.0 (88.9)	510.3 (82.5)	16.0 (4.0, 28.0)		
Knee flexion[D]	EIP+	44	2.8 (0.7)	3.1 (0.7)	0.2 (0.1, 0.4)	0.3 (0.1, 0.4)	<.01
	CMPC	69	2.9 (0.7)	2.9 (0.7)	-0.1 (-0.2, 0.0)		
Knee extension[D]	EIP+	44	4.4 (1.2)	4.8 (1.2)	0.4 (0.1, 0.6)	0.5 (0.2, 0.9)	<.01
	CMPC	69	4.6 (1.0)	4.4 (1.1)	-0.2 (-0.4, 0.0)		
Elbow flexion[D]	EIP+	43	2.9 (0.6)	3.0 (0.6)	0.1 (0.0, 0.3)	0.1 (-0.0, 0.3)	0.09
	CMPC	62	2.9 (0.7)	2.9 (0.7)	-0.0 (-0.1, 0.1)		
Elbow extension[D]	EIP+	43	2.0 (0.5)	2.1 (0.5)	0.1 (-0.0, 0.2)	0.0 (-0.1, 0.2)	0.59
	CMPC	62	2.0 (0.6)	2.0 (0.6)	0.1 (-0.0, 0.2)		
Hip abduction[D]	EIP+	43	2.3 (0.4)	2.4 (0.5)	0.1 (0.0, 0.3)	0.1 (-0.0, 0.3)	0.16
	CMPC	68	2.2 (0.6)	2.3 (0.5)	0.0 (-0.1, 0.1)		
Hip flexion[D]	EIP+	40	2.1 (0.5)	2.3 (0.6)	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	<.01
	CMPC	65	2.2 (0.7)	2.2 (0.7)	-0.0 (-0.1, 0.1)		

*number of patients with measures at both time points; EIP+: patients with ≥75% adherence and regular exercise sessions in training facility; [C]in m; [D]in N/kg

3.3.2.4 Treatment-related analysis

In walk distance an increase in performance was observed in patients receiving radiotherapy only. However, the increase in the CMPC-arm was higher compared to the increase in the EIP-arm. A slight increase in both study arms was observed for patients undergoing sequentially and simultaneously radiotherapy and treatment with tyrosine kinase inhibitors. For muscle strength in knee extensors an increase in the EIP-arm was observed while there was a decrease in the CMPC-arm in patients with radiotherapy only. Overall, there was higher increase in the EIP-arm in patients with sequentially and simultaneously radiotherapy. In patients under TKI therapy, the increase was higher in the CMPC-arm. For patients with SCLC receiving consolidating radiotherapy, there was a decrease observed in both study arms in knee extension. Similar results were observed for muscle strength in elbow flexion. For patients receiving chemotherapy only, which was the largest group in treatment, lowest percentage change was observed for both walk distance and strength capacity (see Figure 12).



		RT only	RT sequ	RT sim	TKI	Consol RT (SCLC)	Immuno-therapy	CHT only
Walk distance	EIP, n	3	10	9	4	10		44
	CMPC, n	3	8	7	4	9		41
Knee extension	EIP, n	3	11	8	4	9	1	41
	CMPC, n	3	8	7	4	9		38
Elbow flexion	EIP, n	3	11	8	4	8	1	40
	CMPC, n	2	6	7	4	9		37

Figure 12: Performance progression of endurance capacity (walk distance) and strength performance (knee extension, MVIC; elbow flexion, MVIC) with regard to treatment regimen RT (radiotherapy) only, RT sequ (sequentially), RT sim (simultaneously), TKI (tyrosine kinase inhibitors), consolidating radiotherapy in SCLC (Small Cell Lung Cancer), immunotherapy, and CHT (chemotherapy) only from T0 to T1 and corresponding number of patients of EIP- and CMPC-arm.

3.3.2.5 Regression analysis

The regression analysis included T1 performance of 6MWT and MVIC (knee extension, elbow flexion). In demographic variables, significant correlations were observed in 6MWT for patients ≤62 years ($p<.0001$). Men performed significantly better than women in knee extension ($p<.05$) and elbow flexion ($p<.0001$).

Diagnose-related variables indicated no correlation with performance of 6MWT and knee extension. In elbow flexion, patients with diagnosis ≥48 days performed significantly worse compared to patients with diagnosis <48 days ($p<.05$) and patients with metastatic disease at study enrolment performed significantly worse in elbow flexion compared to patients with non-metastatic disease ($p<.05$). Patients with limited adherence to the EIP program performed significantly worse in knee extension compared to patients with inadequate adherence ($p<.05$). No correlations were observed in patients who had been physically active before diagnosis. The complete regression analysis is presented in Table 12.

3.3.2.6 Additional parameter

The ITT-analysis also included body weight (in kg) and BMI (in kg/m^2) from T0 to T1. There were no significant inner group or between group differences observed. BMI and body weight remained stable in both study arms. The results are shown in Table 10.

Table 12: Results of multiple regression analysis of strength performance (knee extension, elbow flexion) and endurance capacity (6-minute walk distance) in correlation to sex, age, body mass index, smoking status, lung cancer histology, upfront radio-chemotherapy, days between enrolment and date of first diagnosis, metastatic status, sports/exercise history at T1.

		Meter		**Knee extension**		**Elbow flexion**	
		R^2=.40		R^2=.40		R^2=.45	
		Beta[A]	*p*	Beta[A]	*p*	Beta[A]	*p*
Sex	male	25.05		0.50	*	0.62	***
	female	reference		reference		reference	
Age	≤62 yrs.	88.44	***	0.30		0.05	
	>62 yrs.	reference		reference		reference	
BMI	<20 kg/m^2	-7.60		0.50		-0.07	
	20-25 kg/m^2	28.36		0.57		0.36	()
	≥25 kg/m^2	reference		reference		reference	
Sports/exercise before diagnosis	Yes	-39.55		-0.23		0.10	
	No	reference		reference		reference	
Days since study enrolment	≥48 days	-3.72		-0.34		-0.32	*
	<48 days	reference		Reference		reference	
Advanced disease	Yes	16.93		-0.44		-0.43	*
	No	reference		reference		reference	
Therapy	RT alone	-41.57		-0.68		-0.08	
	RCHT, sequentially	38.13		0.90		-0.26	
	RCHT, simultaneously	59.20		0.30		0.04	
	TKI	60.27		1.00	()	0.14	
	Consolidating RT	-0.50		-0.76		0.45	
	CHT alone	reference		reference		reference	
Adherence[B] (EIP-arm only)	Good	33.88		-0.06		0.03	
	Limited	0.29		-0.98	*	-0.52	()
	Inadequate	reference		reference		reference	

[A] Regression coefficient from multiple regression model, all variables were included simultaneously in the model; () trend (p<0.07); * p<.05; **p<.01; ***<.0001; [B]Good (>75% of required exercise sessions and regular supervised exercise sessions); Limited (30-75% of required exercise sessions); Inadequate (<30% of required exercise sessions).

3.3.3 Part 2B: Intervention results from T1 to T2

3.3.3.1 Patient adherence (T1-T2)

From T1 to T2, four patients (3.6%) withdrew from participation after T1 assessment and thirteen patients (11.6%) were not able to continue the exercise intervention due to and treatment-related side-effects and/or disease progression. One patient was lost to follow up after T1. Fifty-two patients (46.4%) exercised regularly supervised in training facilities near their home-tow. Forty-two patients (37.5%) exercised home-based only. Weekly exercise sessions within the last week were reported by the patients within the weekly phone calls. Additionally, patients reported their exercise sessions weekly in standardized exercise logs.

3.3.3.1.1 Intervention uptake and completion rates according to weekly patient-reported information via CMPC (weekly phone calls)

Adherence was evaluated for 98 patients (85.2%) of the EIP-arm. The minimum number of required exercise sessions within the second 12 weeks of the intervention program was 36. Patients showed 19.7±14.6 exercise sessions, 3.6±4.2 in training facilities. Thirty-three patients (29.5%) showed ≥75% of required exercise sessions and showed regular attendance in supervised exercise sessions (see Table 13).

3.3.3.1.2 Intervention uptake and completion rates according to exercise log

From T1 to T2, patients performed 1618 exercise sessions at an average Borg level of 13 (range 8-19). Patients performed 319 exercise sessions in training facilities.

Patients showed 25.3±20.1 exercise sessions, 5.0±6.0 in training facilities. Twenty-one patients (18.8%) showed ≥75% of required exercise sessions and exercised regularly supervised (see Table 13). With regard to the number of weekly exercise sessions of the patients of the EIP-arm, patients exercised overall less compared to the first 12 weeks of the intervention. With regard to the second 12 weeks though, exercise sessions rates were highest between weeks 12 and 16. Afterwards, there was a decline in the number of exercise sessions until week 24. The allocation of the type of exercise showed that patients preferred rather endurance and combined training sessions instead of resistance training sessions (see Figure 13).

Table 13: Patient-reported adherence by exercise log and weekly phone calls from T1 to T2 for totally analyzed numbers and separated for patients showing good adherence.

T1 T2*	**Reported by exercise log**	**Reported by weekly calls**
Totally analyzed, n% Exercise sessions, mean±SD (range) Exercise sessions in training center, mean±SD (range)	64, 57.1% 25.3±20.1 (0-76) 5.0±6.0 (0-24)	108, 96.4% 19.7±14.6 (0-49) 3.6±4.2 (0-13)
Patients showing good adherence**, n % Exercise sessions, mean±SD (range) Exercise sessions in training center, mean±SD (range)	21, 18.8% 48.0±14.8 (28-76) 11.8±6.2 (5-24)	33, 29.5% 36.8±7.0 (27-49) 8.5±2.7 (4-13)

*the evaluation is based on the total number of 112 enrolled EIP-patients, irrespective of drop-outs, deceased patients, and patients who were lost to follow up;
**at least 27/36 (≥75% of required exercise sessions within 12 weeks) and at least 4/12 supervised exercise sessions in a local training facility.

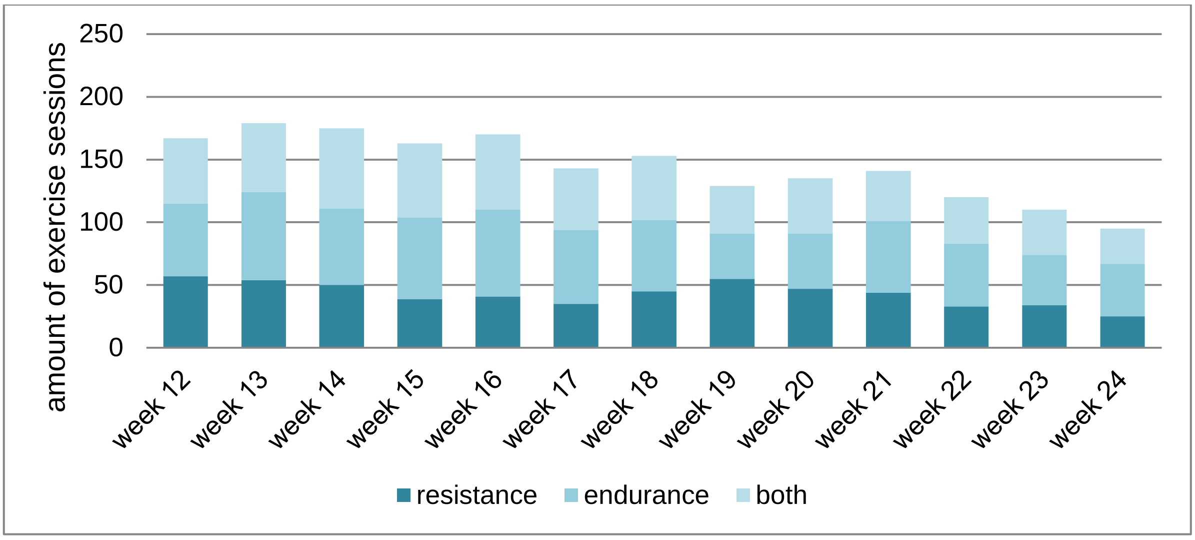


Figure 13: Exercise sessions performed by EIP-arm patients from T1 to T2 regarding weekly uptake of resistance, endurance and combined resistance and endurance exercise sessions.

3.3.3.2 Endurance performance (6MWT)

6MWT was completed by 89 patients at both T1 and T2.

3.3.3.2.1 Intention-to-treat-analysis

Data for measures at both time points were available for 46 patients of the EIP-arm and 43 patients of the CMPC-arm. No significant between group or inner group differences were observed. The results show a slight increase in the EIP-arm (505.2±87.3 vs. 512.8±93.6m) and a slight decrease in the CMPC-arm (527.7±85.1 vs. 521.3±99.4m). The results are shown in Table 14.

The range of percentage change in performance of the 6MWT was from -42% to 23%. In total, 41.1% of patients declined in performance with a decline of ≥10% in 14.4% of patients. Improvement in performance from T1 to T2 was observed in 50.0% of patients with an increase of ≥10% in 18.9% of patients.

3.3.3.2.2 Subgroup analysis

With regard to patients' adherence of ≥75% and attendance in supervised exercise sessions (n=29), no significant between group or inner group differences were observed. The results are shown in Table 15.

3.3.3.3 Strength performance (MVIC)

The MVIC was assessed by 94 patients at both T1 and T2. The range of percentage change in performance of knee extension was from -36% to 60% and of elbow flexion from -52% to 61%. In total, 50.0% of patients declined in performance in knee extension with a decline of ≥10% in 23.2% of patients. Improvement in performance of knee extension from T1 to T2 was observed in 50.5% of patients with an increase of ≥10% in 45.3% of patients. For elbow flexion, a decline in performance was observed in 44.6% of patients with a decline of ≥10% in 16.3% of patients. Improvement was observed in 50.0% of patients, 28.3% of patients showed an increase in performance of ≥10%.

3.3.3.3.1 Intention-to-treat-analysis

Significant between group differences from T1 to T2 were not observed. Significant inner group improvement was observed in patients of the CMPC-arm in hip abduction. The results are shown in Table 14.

3.3.3.3.2 Subgroup analysis

With regard to patients with adherence of ≥75% and attendance in supervised exercise sessions, no significant between or inner group differences were observed. For patients with very limited and inadequate adherence (<30%), no significant between group differences were observed. The results are shown in Table 15.

Table 14: ANCOVA results of intention-to-treat analysis including physical performance parameter of MVIC from T1 to T2, adjusted on sex and age.

Outcome	Group	n*	T1 Mean (SD)	T2 Mean (SD)	Adjusted mean change(95CI) from T1 to T2	Adjusted difference (95CI) between groups	p(diff)
BMI[A]	EIP	64	25.0 (4.4)	24.9 (4.4)	-0.1 (-0.4, 0.2)	-0.3 (-0.8, 0.1)	0.18
	CMPC	59	26.1 (5.1)	26.3 (5.2)	0.2 (-0.1, 0.5)		
Weight[B]	EIP	65	74.3 (15.0)	74.0 (14.9)	-0.3 (-1.2, 0.6)	-0.7 (-2.0, 0.6)	0.26
	CMPC	60	77.9 (18.3)	78.4 (18.7)	0.4 (-0.5, 1.3)		
Walk distance[C]	EIP	46	505.2 (87.3)	512.8 (93.6)	7.2 (-6.6, 21.1)	16.1 (-4.0, 36.1)	0.11
	CMPC	43	527.7 (85.1)	521.3 (99.4)	-8.9 (-23.2, 5.5)		
Knee flexion[D]	EIP	52	3.1 (0.7)	3.0 (0.8)	-0.0 (-0.2, 0.1)	-0.0 (-0.2, 0.2)	0.94
	CMPC	42	2.9 (0.7)	3.0 (0.7)	-0.0 (-0.2, 0.1)		
Knee extension[D]	EIP	52	4.7 (1.1)	4.7 (1.1)	0.0 (-0.2, 0.2)	-0.1 (-0.4, 0.2)	0.66
	CMPC	42	4.5 (1.2)	4.7 (1.1)	0.1 (-0.1, 0.3)		
Elbow flexion[D]	EIP	51	3.0 (0.6)	3.1 (0.7)	0.0 (-0.1, 0.1)	-0.1 (-0.3, 0.1)	0.29
	CMPC	40	3.0 (0.7)	3.1 (0.8)	0.1 (-0.0, 0.3)		
Elbow extension[D]	EIP	51	2.1 (0.4)	2.0 (0.5)	-0.0 (-0.1, 0.1)	0.0 (-0.1, 0.2)	0.61
	CMPC	39	2.1 (0.6)	2.1 (0.6)	-0.1 (-0.2, 0.0)		
Hip abduction[D]	EIP	50	2.4 (0.5)	2.4 (0.5)	-0.0 (-0.1, 0.1)	-0.1 (-0.3, 0.0)	0.13
	CMPC	42	2.3 (0.6)	2.5 (0.6)	0.1 (0.0, 0.2)		
Hip flexion[D]	EIP	47	2.4 (0.7)	2.4 (0.7)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.3)	0.32
	CMPC	41	2.3 (0.7)	2.3 (0.7)	-0.0 (-0.1, 0.1)		

*number of patients with measures at both time points; presented data include dominant limbs only, [A]in kg/m^2; [B]in kg; [C]in m; [D]in N/kg.

Table 15: ANCOVA results of subgroup analysis including physical performance parameter of MVIC from T1 to T2 in EIP-patients with ≥75% adherence and supervised exercise sessions, adjusted on sex and age.

Outcome	Group	n*	T1 Mean (SD)	T2 Mean (SD)	Adjusted mean change(95CI) from T1 to T2	Adjusted difference (95CI) between groups	p(diff)
Walk distance[C]	EIP+	29	510.9 (79.5)	511.8 (85.7)	0.8 (-17.2, 18.9)	10.0 (-13.5, 33.6)	0.40
	CMPC	43	527.7 (85.1)	521.3 (99.4)	-9.2 (-24.1, 5.6)		
Knee flexion[D]	EIP+	31	3.1 (0.7)	3.1 (0.9)	0.0 (-0.2, 0.2)	0.1 (-0.2, 0.3)	0.55
	CMPC	42	2.9 (0.7)	3.0 (0.7)	-0.0 (-0.2, 0.1)		
Knee extension[D]	EIP+	31	4.8 (1.2)	4.8 (1.0)	0.0 (-0.2, 0.2)	-0.1 (-0.4, 0.2)	0.66
	CMPC	42	4.5 (1.2)	4.7 (1.1)	0.1 (-0.1, 0.3)		
Elbow flexion[D]	EIP+	30	3.1 (0.6)	3.1 (0.7)	0.0 (-0.2, 0.2)	-0.1 (-0.3, 0.1)	0.31
	CMPC	40	3.0 (0.7)	3.1 (0.8)	0.1 (-0.0, 0.3)		
Elbow extension[D]	EIP+	30	2.1 (0.4)	2.1 (0.5)	-0.0 (-0.2, 0.1)	0.0 (-0.1, 0.2)	0.60
	CMPC	39	2.1 (0.6)	2.1 (0.6)	-0.1 (-0.2, 0.0)		
Hip abduction[D]	EIP+	29	2.4 (0.5)	2.4 (0.5)	0.0 (-0.1, 0.2)	-0.1 (-0.3, 0.1)	0.37
	CMPC	42	2.3 (0.6)	2.5 (0.6)	0.1 (-0.0, 0.2)		
Hip flexion[D]	EIP+	27	2.5 (0.8)	2.5 (0.8)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.3)	0.37
	CMPC	41	2.3 (0.7)	2.3 (0.7)	-0.0 (-0.2, 0.1)		

*number of patients with measures at both time points; EIP-good: ≥75% adherence and regular exercise sessions in training facility; [C]in m; [D]in N/kg.

4. Discussion

The intention of this work was to provide a holistic presentation of the analyses elaborated in the course of this dissertation. This included previously published results of a literature review on physical exercise in patients with advanced cancer [102], the design paper of the POSITIVE study (Part III) [109], a cross-sectional report of baseline data of the POSITIVE study (Part III) including exercise behavior and physical performance in patients with advanced lung cancer [101], and the intervention analyses of the 24-week physical exercise program of the POSITIVE study (Part III) (in preparation).

4.1 Main findings

Previously, the field of physical exercise in patients with advanced cancer and in particularly lung cancer was found to be extremely understudied. Now, an increasing number of exercise intervention trials in the lung cancer continuum exists including RCTs in the non-operable setting. However, consistent evidence is still lacking. The results differ from what has been observed and demonstrated for example in breast cancer, so far. Yet, studies in the lung cancer continuum that provide consistent evidence are still pending.

From the current literature including patients with advanced cancer no specific guidelines or recommendations have been established. The implemented physical exercise interventions varied in each trial: the programs included resistance training, supervised circuit training, home videotape seated exercise program, and structured physical therapy. However, it has been shown that patients benefit from exercise programs physically and mentally. Although there was large inconsistency regarding contents, durations, types, and intensities in the exercise intervention programs, the beneficial impact for patients has been demonstrated.

In the cross-sectional analyses of baseline data, the observed findings showed clear differences in physical exercise and walking behavior shortly after diagnosis compared to the year before diagnosis. A strong decline in sports/exercise participation and low physical exercise levels shortly after first diagnosis were observed. The recommended amount of 150 minutes per week was only met by less than a third of participants in the year before diagnosis and by only 15% shortly after diagnosis. Further, significantly lower 6MWT performance and MVIC in lower extremities in male and female patients were observed.

In the intervention analyses of the 24-week exercise intervention no effects on physical performance were observed in intention-to-treat analyses. In the first 12 weeks of the intervention, effects were demonstrated in knee extension in the exercise group. No effects were observed from week 12 to week 24. In subgroup analyses, with regard to patients showing good adherence, significant effects were observed in hip flexion from week 0 to week 24. Significant effects on physical performance were observed after the first 12 weeks of the exercise intervention in knee flexion and extension, and hip flexion. No effects were observed from week 12 to week 24. Good adherence - including ≥75% of required exercise sessions and regular attendance in supervised exercise sessions - was shown in nearly 30% (self-reported) and in 21.4% (according to the exercise log) from week 0 to week 24. Only few patients showed inadequate adherence. The amount of physical exercise sessions declined with week 10 overall.

4.2 Physical Exercise in Patients with Advanced Cancer Undergoing Palliative Treatment

The literature review provided overview of physical exercise programs in patients with advanced cancer. Six trials were selected including 590 patients. There was a weak trend that resistance exercises were more applied compared to endurance exercises. For endpoint assessments, parameters were mainly recorded for physical performance, fatigue, quality of life, and pain. The results of the addressed studies were consistently in favor of the exercise groups.

Previous physical exercise intervention trials have focused on cancer survivors who completed their treatment [20, 54, 56, 61, 76, 88] aiming on regaining physical functioning, increasing quality of life and reducing fatigue. This has been shown numerously in patients undergoing curative therapy and/or surgery. For advanced cancer patients undergoing palliative treatment, outcomes may be similar but exercise interventions have to deal with a much higher variability regarding patients ‘exercisability’. The analyzed RCTs showed a wide range of entities including many patients with gastrointestinal, lung, urological, and gynecological cancer representing a different approach, in comparison to studies done in the curative setting where mostly defined entity groups were examined [34, 96]. One reason for that might be that advanced cancer patients per se are very heterogeneous within one entity e.g. depending on the site of metastasis, date of first diagnose, type and progress of therapy, age, number of comorbidities and history of physical activity. Thus, feasibility, safety and adherence may vary regarding the intervention content. The reported adherence rates were ≥69% and no adverse events were observed. The interventions varied in content, intensity, type and frequency. All applied intervention programs focus on resistance/strengthening exercise either supervised or home-based. Aerobic and/or endurance exercise training was included only in two studies [33, 74]. The included RCTs reported various improvements in favor of the exercising groups. Patients increased their physical performance [17, 33, 74, 83], decreased fatigue levels [33], increased physical well-being [17, 37] and improved quality of life [33]. Altogether, the intervention programs were confirmed as safe and feasible for advanced cancer patients undergoing palliative treatment. Reasons for the prevalence on resistance exercise training can be seen in decreased musculoskeletal constitution and the risk of sarcopenia and cachexia in these patients [6, 94]. With regard to muscle dysfunction in cancer patients across all stages and diagnoses, resistance exercise has been found to be a promising intervention with the capacity to maintain and/or improve muscle mass, strength and metabolism during and after cancer treatment [20].

The results of the literature review have been confirmed and extended by the findings of two previously published literature reviews [29, 40]. Exercise has been indicated as a promising intervention to prevent or delay decline in aerobic fitness, strength, and physical function and exercise may improve QOL. However, an overall interpretation of outcomes was difficult as the benefits of exercise for patients with advanced cancer vary widely in study design, quality, implied exercise intervention, supervision, duration/length, and target population. Nevertheless, exercise appeared to be consistently beneficial [29]. On the base of 25 studies including 1088 patients with advanced cancer - the implementation of exercise interventions appeared to be safe and feasible [40]. The results showed benefits for fatigue, quality of life, and physical performance in particular. Effects of physical exercise intervention studies were in favor of the experimental groups.

Furthermore, patients take advantage of physical exercise interventions and benefit physically and psychologically.

What this study adds

- Physical exercise interventions in patients with advanced cancer show large variations in frequency, time (duration), and type.
- Patients with advanced cancer benefit both physically and mentally from exercise programs, including physical performance, pain, fatigue, and quality of life.
- Exercise programs in patients with advanced cancer help to maintain independence, mobility, physical functioning, and activities of daily living.

4.3 Physical Exercise Behavior and Performance Status in Patients with Advanced Lung Cancer

The cross-sectional report of baseline data of the POSITIVE study (Part III) [109] compared physical performance parameter of strength and endurance capacity with reference data of healthy individuals [11] and calculated normative data [32]. Clear differences in exercise and walking behavior from shortly after to the year before diagnosis were demonstrated. Patients showed a strong decline in sports/exercise participation and low physical exercise levels shortly after first diagnosis. The recommended amount of 150 minutes per week was only met by less than a third of participants in the year before diagnosis and by only 15% shortly after diagnosis. Significantly lower 6MWT scores in male and female patients were observed. Significantly lower values were observed for MVIC in lower extremities. Poor muscle strength performance has been previously described in patients with lung cancer [44]. In women, predominantly higher strength values in upper limbs compared to reference data were observed what might be explained by an increase in PA and exercise of nearly 20% in women in Germany within the last two decades [84]. The large percentage deviations of muscle strength in men and women in lower extremities suggest the potential of improvement with a physical exercise intervention program in order to counteract further loss of physical performance. Pilot studies have demonstrated promising results of an increase in muscle strength in patients with advanced lung cancer [59, 82]. For endurance capacity, walk distance of 6MWT was positively correlated with sports/exercise during youth/adolescence as well as with sports/exercise and walking behavior in the year before diagnosis, suggesting a potential increase in endurance capacity by an exercise intervention program. At baseline, patients showed a significantly lower walk distance of 6MWT (467±100m vs. 561m) compared to calculated normative data [32]. These patients, however, performed better compared to other data (467±100m vs. 243m) reported for advanced lung cancer patients [25]. The self-reported patient questionnaire indicated low levels of sports/exercise participation and walking in this population. Shortly after diagnosis, only 30% showed adequate walking behavior. Regarding the recommendations of the ACSM guidelines, compared to patients with advanced prostate cancer [112], patients showed lower PA (29% vs. 15%). These results demonstrated that patients practiced less sports/exercise shortly after diagnosis compared to the year before diagnosis.

The limitations included that the cross-sectional design (i.e. using baseline assessment from a RCT) do not offer causal interferences. Assessment of physical performance was repeated at several time points within the POSITIVE study (Part III). Longitudinal evaluations including the primary endpoint analyses are pending. The recruitment rate of 9.1% indicated the challenge in implementing a physical exercise intervention trial in this patient setting. It must be assumed that patients who have been previously physically active were more likely to participate in this study. Moreover, 76.4% were not eligible for participation resulting in a selected patient population. Comparisons between participants and non-participants regarding physical exercise behavior could be of interest in future investigations. Physical exercise behavior of non-participants was not assessed. A methodological issue was that validity and reliability of the reference data of Bohannon et al. (1997) is questionable. Additionally worth to mention is the fact that PA levels have changed in the past and therefore performance reference data may no longer reflect current performance levels. However, no other data which can be applied for comparisons exist so far.

What this study adds

- Insights of physical exercise behavior in patients pre and post of being diagnosed with advanced lung cancer.
- Patients with advanced lung cancer show reductions of physical activity and exercise shortly after diagnosis compared to year before diagnosis.
- Patients show lower performance in 6-Minute walk distance and strength performance in lower extremities compared to healthy reference and normative data.
- Sex, age, BMI <25kg/m^2, sports/exercise in the youth/adolescence, and walking in the year before diagnosis were found to be prospective determinants in physical performance.

4.4 Effects of a 24-week Physical Exercise Program in Patients with Advanced Lung Cancer

The individually tailored, combined resistance and endurance exercise program applied in the POSITIVE study (Part III) was based on the previously conducted feasibility study of an 8-week exercise intervention trial in patients with advanced NSCLC [59]. Endurance and resistance training are considered to be the most frequently performed training with lung cancer patients [1, 26, 39, 45, 49, 59, 81, 93, 98]. The analysis of the 24-week exercise program of the POSITIVE study (Part III) covered evaluations from week 0 (T0) to week 24 (T2). Further analyses included week 0 (T0) to week 12 (T1) and from week 13 (T1) to week 24 (T2). The main findings showed no significant between group differences of endurance capacity in the intention-to-treat (ITT) analyses. Within the subgroup analysis of patients with good adherence and regular attendance in supervised training sessions, no difference in performance and/or capacity was observed. For MVIC, from T0 to T2 no significant between group differences were observed in the ITT analyses. The subgroup analysis identified significant between group differences in hip flexion in favor of patients with good adherence.

Within the first 12 weeks (T0 to T1) of the intervention program, mean endurance capacity improved significantly in both study arms. An explanation for this observation could be the influence of >2nd cycle of chemotherapy application and temporarily regression in physical functioning and immobility. For MVIC, significant between group differences were observed in the ITT analyses for knee extension. Subgroup analyses showed significant between group differences for knee flexion, knee extension, and hip flexion in favor of patients with good adherence.

The second 12 weeks of the intervention showed improvement in 6MWT in the EIP-arm and decrease in the CMPC-arm in the ITT analyses. For MVIC, no significant between or inner group differences were found in both the ITT and subgroup analyses.

Patients with advanced lung cancer experienced physical, functional and emotional benefits after a 6-week intervention of supervised and unsupervised, home-based exercise [1]. Similar results have been reported in a single-arm intervention trial [81]. These observations cannot be confirmed by the reported results. However, these findings were confirmed by results of a RCT in patients with advanced lung cancer [25]. No significant between group differences were observed in fatigue, quality of life, symptoms, physical or functional status, or survival. Adherence to the intervention was good and also proved once more that patients with advanced lung cancer are able to participate in a structured physical activity program. The intervention group did not increase their physical activity enough compared to the control group and the intervention program may not have been intensive enough to produce a difference in physical activity between groups [25].

It must be considered that in patients with advanced cancer, additional support and care may play a more important role than originally assumed. The within the POSITIVE study (Part III) integrated CMPCs for both control and exercise arm provided patients a continuous, psychosocial contact for the period of 24 weeks. The importance of additional care applied with early integration of palliative care (EIPC) in patients with advanced lung cancer has been demonstrated in a randomized controlled trial [97]. Patients with advanced lung and GI cancer (n=350) of the intervention group reported greater improvement in QOL from baseline to week 24. Patients did not improve significantly between baseline and week 12. Further, they reported that the intervention effects varied by cancer entity. Patients with lung cancer improved in the intervention group only. In patients with GI cancer, patients of the intervention and usual care group reported improvement by week 12. The authors suggest that EIPC may be most effective for patients with newly diagnosed incurable cancers, especially if targeted to the specific needs of each patient population [97].

An unexpected result was the maintenance of walk distance of 6MWT in both the CMPC-arm and the EIP-arm regarding ITT and also subgroup analyses. There was some progression both in the CMPC- and EIP-arm, however, far below previous reported results. Dhillon et al. 2017 found no improvement in physical capacity overall, however, patients doubled the walk distance of 6MWT of baseline performance [25]. The relevance and importance has been numerously described [12, 16]. The importance of an increase of the walk distance regarding MID (medical important difference, introduced by Granger et al. and Bohannon et al 2003) and overall survival (as described by Jones et al. [53] and Kasymjanova et al. [55]) has been described previously.

For muscle strength performance, stagnation was observed with sometimes a slight progression in mainly the EIP-arm. The results overall showed no decrease of strength capacity over the intervention period of 24 weeks. In upper limbs, there was no change in progression between the two groups. In lower limbs, the observed progressions were in favor of the EIP-arm. Significant between group differences from T0 to T1 were observed in knee extension. The results of the MVIC reflect the results of previous results of physical exercise intervention programs in patients with advanced cancer, also demonstrated in literature reviews on exercise in patients with advanced cancer. In patients with lung cancer, however, pilot trials have proven not only safety and feasibility but also beneficial effects on resistance capacity. The pilot trial of the POSITIVE study (Part I) covered eight weeks instead of 24 weeks. Within in the POSITIVE study (Part III), less supervised exercise sessions within the inpatient setting due to a change in treatment regimen were provided. The within Part II of the POSITIVE study [59] continuously, three times weekly provided exercise input may have contributed to an extraordinary increase in physical performance. With regard to the results shown in the cross sectional baseline data analysis, physical performance and exercise attendance was low and even decreased more with diagnosis. A performance decline was prevented by the intervention program, even if both groups have taken benefit from it. (Partly) home-based exercise program was proven safe and feasible in cancer patients and it was proven safe and feasible for patients with advanced lung cancer [59]. In this study, patients were required to exercise at least three times per week, 1x in the training facility and 2x at home with use of the exercise manual. With no option to control the exercise session or the individual intensity, in patients with no exercise experience a home-based exercise program may not be very essential.

Before each training session, patients were asked to self-assess pain, fatigue, emotional status, and distress to choose the appropriate exercise volume category. Patients were instructed to rate the individual intensity of the exercise sessions according to the Borg Scale (12-14 for endurance exercise, 14-16 for resistance exercise). However, the results showed almost none significant between group differences in upper and lower limbs. Thus, the applied training intensity may not be efficient enough or high enough. It must be considered that a home-based exercise program may not provide the required intensity. Another research group has also failed to proof clear benefit of physical exercise programs in patients with advanced lung cancer [25]. Results of a similar trial - the previously introduced EXHALE-study [80] - are pending.

Patients of this population showed a relatively low level of education and most patients were smokers or former smokers. This may contribute to a generally reduced understanding of a healthy lifestyle. In many cases, patients did not get support from their family members to be involved in a physical exercise study. Educational aspects should be considered in future studies to advise patients and relatives on the beneficial effects of exercise and physical activity.

Generally, patients of the EIP-arm provided feedback including good acceptability of the exercise program and improvement in self-efficacy. Unfortunately, this was not covered in the physical performance assessments. Thus, the question remains to what extend patients establish a connection between the exercise program and the self-reported improvement in physical well-being, quality of life and self-efficacy.

It must be assumed that predominantly side effects - either therapy-related or caused by the disease itself - lead to reductions of the adherence to the intervention program. Adequate and good adherence was provided in less than 50% of patients of the EIP-arm. Patients with brain radiation were not able to get to the training facilities as they were not allowed to drive. Others did not feel well enough to exercise with other patients or healthy patients. This indicates the support for an individualized and very adapted exercise program to take patients' concerns into account. Supervised exercise sessions worked out very well both at the clinic as well as in training facilities in or near the patients' hometown. Even patients who had no experience in exercising and/or training facilities showed good adherence. Some patients did not show the required understanding in being able to do something or themselves by exercising and were therefore barely motivated.

In treatment-related analyses, percentage change of walk distance, knee extension, and elbow flexion was shown. From T0 to T1, performance of 6MWT of patients with RT only improved most - the CMPC-arm even higher compared to the EIP-arm. In knee extension and elbow flexion, patients of the EIP-arm with RT only improved while patients of the CMPC-arm declined in performance. The lowest percentage change was observed for patients with chemotherapy only. From T0 to T2, the percentage change of performance of walk distance of 6MWT showed overall higher increase in the CMPC-arm compared to the EIP-arm. In knee extension and elbow flexion, the EP-arm improved performance with higher values of percentage change. With regard to treatment-related evaluations, completion rates of chemotherapy will play an important role in pending analyses. In previous studies, it has been observed that patients with better physical capacity showed lower complication rates and higher completion rates of chemotherapy [23, 68, 105, 106].

Sarcopenia and loss of muscle mass in patients induced by anticancer treatment will constitute an essential discussable point in the future [7, 15, 73, 95]. Beyond this, the rising application of immunotherapy supplements in lung cancer may change treatment regimen completely and offers new insights in treatment-related side-effect management.

Strengths of the POSITIVE study (Part III) include the high standard of reliability and validity of a randomized controlled trial with application of standardized questionnaires and assessment tools for physical performance. The study population offered a homogenous population of non-operable patients with lung cancer undergoing palliative treatment.

Limitations of the study must be considered in a possible contamination of the control arm as physical activity (e.g. brief walks) were performed in most patients throughout the intervention and exercise behavior was assessed only once at study enrolment. However, according to the weekly phone calls practiced by the advanced practice nurse, an exercise program including structured resistance and endurance exercise was only performed on very few patients of the control arm. The assessor of physical performance testing procedures was not blinded what may be considered as a bias factor. Further, the weekly phone calls included often more than just a simply record of side-effects and symptom according to the ESAS. Moreover, many patients, regardless of the study arm, found help, support, and encouragement in the weekly provided contact what may also result in a bias factor against other study populations.

What this study adds

- Patients with good adherence and regular supervised exercise sessions showed significantly better performance in knee extension after 12 weeks.
- Treatment-related progress of physical performance was observed in endurance and resistance parameters.
- Uptake and amount of physical exercise sessions decrease in the course treatment.

- Previously reported benefits of physical exercise intervention programs cannot be confirmed in this patient setting.

4.5 Conclusion

With increasing evidence in other cancer entities that support beneficial effects of physical exercise on fatigue, quality of life and physical performance, studies investigating the effects of physical exercise in patients with advanced lung cancer remained rare. The third part of the POSITIVE study - in extension of the POSITIVE study (Part I) and (Part II) - adds to current knowledge on feasibility and safety but moreover on impact on various outcome parameters in patients with inoperable lung cancer. The results presented within this work do not consistently support the hypothesis that an exercise intervention program beneficially effects physical performance in these patients. It has to be considered that in these patients, psychosocial support may play a more important role that also affects quality of life and physical well-being. Therefore, psychosocial support was provided to all study patients.

For the future, a valuable finding of the baseline analyses revealed an alarmingly reduction of physical activity and exercise behavior shortly after diagnosis. This supports an early integration of physical exercise during anti-cancer treatment. The impact of a physical exercise intervention program should induce on accompanying and helping patients to maintain independent functions as long as possible. To provide more support by relatives and family members, it may be necessary to integrated these in exercise sessions to additionally provide social support and physical contact. With the effects observed in patients with good adherence and regular attendance in supervised training sessions, the exercise intervention program resulted in measureable benefits and should therefore be implemented in the clinical setting.

In the POSITIVE study (Part III) further analyses are yet in progress as well as under preparation. The results of the primary endpoints after 12 weeks of the intervention (quality of life, physical well-being, and physical fatigue) are pending as well as analyses of immunological parameters. Beyond this, evaluations of CT scans with regard to cachexia and sarcopenia are yet in preparation as well as overall survival analyses. The clinical parameters will offer new insights in beneficial effects on immune functions caused by physical exercise. Furthermore, analyses will include overall survival with regard to quantitative evaluations of body composition recorded on computer tomography scans and individual response to the exercise program in blood markers.

Future studies in patients with lung cancer should consider psychosocial support in addition to a physical exercise intervention program. Furthermore, amount and intensity of the exercise sessions should be individually tailored to a patient’s condition and shape. Supervised exercise sessions should be integrated to ensure efficient intensity and appropriate extent of the respective training session.

5. Summary

Patients with advanced lung cancer suffer of incurable disease with limited prognosis and experience multidimensional impairments during their course of disease. In the field of exercise oncology, increasing evidence previously supported the implementation of exercise programs in various cancer entities. The evidence includes mainly patients with early stage cancer and/or cancer survivors. However, there is also growing evidence that physical exercise is safe and feasible for advanced cancer patients but knowledge is limited. Also as a part of this thesis, a comprehensive literature search was carried out to provide an overview of randomized controlled physical exercise programs implemented in patients with advanced cancer undergoing palliative treatment. Six studies provided data of 590 cancer patients with advanced disease. Beneficial effects of the exercise interventions were reported for both physical and psychological outcomes. General exercise recommendation for patients undergoing palliative treatment cannot be derived from the analyzed studies due to the large heterogeneity of the applied exercise programs.

As one of the largest RCTs worldwide in patients with advanced lung cancer, the POSITIVE study (Part III) was implemented to add to current knowledge. The cross-sectional baseline analyses revealed reduced physical performance, especially in strength capacity in lower extremities and endurance. However, these results showed promising potential for a structured combined, individually tailored resistance and endurance exercise program in this patient population. The observed decrease in physical activity and exercise shortly after diagnosis supports the importance of an early implementation of exercise interventions in oncology.

The intervention program was conducted for 24 weeks in which all study patients, regardless of the study arm, were contacted once weekly by the study personnel. The results showed significant differences in strength performance after 12 weeks, especially with regard to subgroup analyses. Within the second 12 weeks and overall the 24 weeks no significant effects were observed. Patients' adherence to the exercise program differed from the first to the second 12 weeks of the intervention due to treatment and/or disease related side-effects resulting in decreasing condition.

It remains unclear why no beneficial effects on physical performance of the individually tailored exercise program have been observed in this patient population. It must be considered that the intensity of the exercise program was not efficient enough. Other reasons may be considered with regard to insufficient adherence to the exercise program in order to a lack of motivation and/or therapy-related side-effects. Nevertheless, patients' feedbacks support the importance of a complementary supplement to treatment including the exercise program and the continuous contact.

Based on the observed subgroup analyses including patients with good adherence, physical exercise should be implemented early in patients undergoing palliative treatment to support patients to maintain independent functions as long as possible.

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7. Publications

7.1 Peer-reviewed publications

- Wiskemann J/Hummler S, Diepold C, Keil M, Abel U, Steindorf K, Ulrich CM, Steins M, Thomas, M. POSITIVE Study: Physical Exercise Program in Non-Operable Lung Cancer Patients Undergoing Palliative Treatment. BMC Cancer, 2016 Jul 19; 16:499.
- Titz C, Hummler S, Thomas M, Wiskemann J (2016) Physical Exercise in Advanced Cancer Patients Undergoing Palliative Treatment. Expert Rev Qual Life Cancer Care 1: 433–442
- Titz C, Hummler S, Schmidt ME, Thomas M, Steins M/Wiskemann J (2017). Physical Exercise Behavior and Performance Status in Patients With Advanced Lung Cancer. (Supp Care Can, under review)
- Wiskemann, J, Titz C, Schmidt ME, Steindorf, K, Ulrich, CM, Steins M, Hummler S/Thomas M, (2017). Effects of Physical Exercise in Non-operable Lung Cancer Patients Undergoing Palliative Treatment. (in preparation)
- Titz C, Hummler S, Schmidt ME, Thomas M, Steins M, Wiskemann J (2017). Effects of a 24-week Physical Exercise Program in Patients with Advanced Lung Cancer. (in preparation)

7.2 Other publications

- Titz C & Hummler S (2017). Körperliches Training beim Lungenkarzinom. Prävention und Rehabilitation.

7.3 Oral presentations

09/2017 Symposium „Kardiologie meets Pneumologie“, Heidelberg, „Körperliches Training bei Lungenkarzinom“

07/2017 European College for Sports Science Congress (ECSS), Essen, “Physical performance in patients with advanced lung cancer after a

12-week exercise intervention: preliminary results of the POSITIVE study Part III"

05/2016 Lung Cancer and Exercise Symposium, Kopenhagen, „Group Heidelberg: The POSITIVE study (Physical exercise program in non-operable lung cancer patients undergoing palliative treatment)"

02/2016 32. Deutscher Krebskongress, Berlin, „Physical exercise program in non-operable lung cancer patients undergoing palliative treatment: preliminary report of recruitment rates and feasibility of the POSITIVE study Part III"

11/2015 Thoraxonkologisches Symposium, Münnerstadt, „Sport in der Onkologie – was bringt ein Trainingsprogramm beim Bronchialkarzinom?"

10/2015 22. Hochschultage, Deutsche Vereinigung für Sportwissenschaft, Mainz, „Herausforderungen in der Rekrutierung von Lungenkrebspatienten im fortgeschrittenen Erkrankungsstadium in eine Sportinterventionsstudie"

03/2015 Arbeitstage der Deutschen Gesellschaft für Palliativmedizin, Erlangen, „POSITIVE Studie: Auswirkungen von strukturierter Symptomerfassung auf die Lebensqualität von Lungenkrebspatienten"

7.4 Poster presentations

10/2017 Sport und Krebs - Kongress, München

05/2017 5. ASORS-Jahreskongress der Deutschen Krebsgesellschaft, München

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