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Effects of exercise training programs on physical performance and quality of life in patients with metastatic lung cancer undergoing palliative chemotherapy—A study protocol

Wiebke Jensen [a,*], Karin Oechsle [a], Hans Jörg Baumann [a], Anja Mehnert [b], Hans Klose [a], Wilhelm Bloch [c], Carsten Bokemeyer [a], Freerk T. Baumann [c]

[a] Department of Oncology/Hematology/Bone marrow Transplantation/Pneumology, University Medical Center Eppendorf, Hamburg, Germany
[b] Section of Psychosocial Oncology, Department of Medical Psychology and Medical Sociology, University Medical Center, Leipzig, Germany
[c] Department of Molecular and Cellular Sport Medicine, Institute of Cardiovascular Research and Sport Medicine, German Sport University Cologne, Cologne, Germany

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ABSTRACT

Purpose: The aims of the study protocol are to investigate different adapted physical training programs in patients with advanced lung cancer undergoing palliative chemo- or radiotherapy and to evaluate their effects on physical performance, quality of life, symptom burden, and efficacy of oncologic treatment.
Methods: Patients will be randomized into three study arms: interventional group 1 performing aerobic exercise, interventional group 2 performing resistance training, and a control group without specific physical training. Interventional training will be performed for 12 weeks consisting of two supervised and one self-instructed training sessions per week each. Respiratory therapy over 12 weeks is provided in all three study arms as an established supportive therapy in lung cancer patients.
Primary efficacy endpoint is physical performance measured by peak oxygen consumption (VO_2peak). Secondary efficacy endpoints include additional parameters of physical performance (resistance, lung function, perceived exertion, level of physical activity and IPAQ-questionnaire), health-related quality of life (EORTC QLQ C30-questionnaire), disease and treatment related symptoms (Memorial Symptom Assessment Scale), biologic parameter (e.g. body composition, blood values of immune system, chronic inflammation, glucose and lipid metabolisms), and parameter of efficacy of oncologic treatment.
Discussion: The results of this study will offer an overview over possible effects of specific training interventions on health related quality of life, physical and psychological symptoms, and on the efficacy of oncologic treatment. The primary aim of this study is to detect adapted intervention programs for metastatic lung cancer undergoing palliative chemotherapy.

1. Introduction

The positive effects of physical training programs on physical performance and quality of life in oncologic patients in rehabilitation after completion of curative chemotherapy are well known [1–3]. Clinical investigations have demonstrated that specific training programs are feasible in patients during chemo- or radiotherapy despite disease- or treatment-related symptom burden [4–7]. These trials have shown beneficial effects of specific physical training not only on the patients' physical performance, but also on their quality of life and disease- or treatment-related symptoms, e.g. pain, nausea and fatigue [4–7]. Different trials demonstrated a positive impact of

* Corresponding author at: Dept. of Oncology/Hematology/BMT with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. Tel.: +49 40 7410 0; fax: +49 40 7410 58841.
E-mail address: w.jensen@uke.de (W. Jensen).

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physical activity in cancer patients on immune function [8,9], glucose and lipid metabolism [10–12], tumor-associated chronic inflammatory reactions [13,14], as well as tumor proliferation and apoptosis [15–17].

While most of these studies were performed in patients undergoing curative treatment, only a small number of clinical studies have evaluated the impact of physical training programs in patients with incurable cancer undergoing palliative chemotherapy. These studies suggest that physical programs are feasible even in these severely ill patients and have beneficial effects on their quality of life, symptom burden, and physical functioning [18–20].

Due to the development of new cytostatic drugs and targeted therapies, life expectancy of patients with incurable malignancies has been extended considerably in many tumor entities. Improvement of quality of life and reduction of physical and psychological symptoms in this additional life time represent the main targets of oncologic and supportive treatment [21]. A stable performance status and at least tolerable symptoms are of enormous relevance for the feasibility of palliative oncologic treatment providing an improved survival. Therefore, the evaluation of possible positive effects of training programs on symptoms, health related quality of life, physical performance, and feasibility of oncologic treatment are of particular relevance in patients undergoing palliative chemo- or radiotherapy.

Patients with metastatic lung cancer typically suffer from severe physical and psychological symptoms very early after initial diagnosis, especially dyspnea, pain, fatigue, and weakness, as well as anxiety and depression [22–24]. Palliative chemotherapy frequently causes further symptoms, including nausea, emesis, polyneuropathy, anemia, and immune deficiency, leading to a continuous impairment of quality of life, functionality, mobility, and social function [25,26]. Most patients with advanced lung cancer present with significantly reduced physical performance at an early time point of their disease and are unable to perform standardized training programs established in lung cancer patients, e.g. for postoperative rehabilitation [27–31].

Data on feasibility and efficacy of training programs in patients with advanced lung cancer are rare and specific recommendations for daily practice are lacking [31–39]. Today, respiratory training represents the only supportive training modality with proven benefit on dyspnea as well as on other symptoms, and on quality of life in patients with advanced lung cancer [40–42].

Therefore, the aims of the underlying study are to investigate different physical training programs in patients with advanced lung cancer undergoing palliative oncologic therapy and to evaluate their effects on physical performance, health related quality of life, symptom burden, and efficacy of oncologic treatment.

2. Methods/design

2.1. Study design

This prospectively conducted, randomized, controlled clinical intervention study will include patients with advanced lung cancer (stage IIIb–IV) currently undergoing palliative oncologic treatment, which could consist of chemo-, radio- or targeted therapy. This trial was approved by the local ethics committee of the Medical Association Hamburg (PV4101).

Patients with advanced lung cancer undergoing palliative oncologic treatment will be screened at the University Medical Center Hamburg-Eppendorf and the University Medical Center Cologne. Patients could enter this study at the beginning of every new treatment line: at first-line therapy with newly diagnosed advanced cancer, at second- or further-line therapy at relapse after prior remission or in case of tumor progression during a previous line of chemotherapy. Additional inclusion and exclusion criteria are described in Table 1.

Patients will be randomized 1:1:1 in three study arms to prospectively compare the effects of two different physical training interventions with each other and with a non-interventional control arm. The interventional group 1 will perform aerobic exercise, the interventional group 2 will exercise resistance training, and the control group will not perform any specific physical training.

Respiratory training representing an established supportive treatment modality in lung cancer patients [40–42] will be provided in all three study arms to reduce a methodological bias due to more intensive psychosocial support in patients undergoing intervention training compared with patients in the control group. The study flow is presented in Fig. 1.

2.1.1. Interventional group 1: aerobic exercise training and respiratory training

The aerobic training group will exercise twice weekly for 12 weeks in supervised training sessions of 45 min duration, including warm-up and cool-down periods (with a break of at least one day) plus an instructed home-based aerobic

Table 1
Inclusion and exclusion criteria of the study.

Inclusion criteria	Exclusion criteria
– Advanced lung cancer undergoing palliative oncologic treatment – Age ≥18 years – Karnofsky performance status ≥70 – Given written informed consent – Willing to attend 24 training dates (at least 75% = 18 training dates)	– Expected life expectancy <6 months – Already ongoing chemo- or targeted therapy – Symptomatic brain metastases or – Symptomatic uncontrolled cardiovascular disease – Severe ventilatory or pulmonary insufficiency ($PaCO_2$ > 50 mm Hg and/or PaO_2 < 60 mm Hg breathing oxygen) – Symptomatic heart failure (≥NYHA III) – Insufficiently controlled coronary heart disease – Insufficiently controlled arterial hypertension – Higher grade of peripheral arterial occlusive disease – Insufficiently controlled metabolic diseases

Abbreviations:
$PaCO_2$ = partial pressure of carbon dioxide in arterial blood.
PaO_2 = partial pressure of oxygen in the blood.
mm Hg = millimeters of mercury.
NYHA = New York Heart Association class.