A Randomized, Controlled Pilot Study to Evaluate the Immediate Effect of Targeted Exercise Therapy on Cancer-Related Fatigue in Cancer Survivors: The FatiGO Study

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Keywords
Cancer survivors · Chronic fatigue · Exercise intervention · Fatigue assessment

Abstract

Objectives: Cancer-related fatigue (CRF) is a clinically relevant side effect that impairs cancer survivors after treatment cessation. Exercise interventions have proven effective; however, specific exercise modalities remain untested. The purpose of this study was to evaluate the feasibility of daily fatigue screenings and to show the impact of various exercise interventions on CRF. Methods: The randomized controlled pilot study ran for 4 weeks with 3 training sessions per week, in 5 groups: endurance versus strength (moderate- and vigorous-intensity levels for each) compared to a non-active control group. The primary outcome was feasibility; more specifically, it was evaluated whether the documentation with the Numerical Rating Scale (NRS) on a daily basis and the Multidimensional Fatigue Inventory (MFI) on a weekly basis are usable assessments to generate information about CRF. Results: Over the course of the 4-week intervention, 8.3% of the participants \((n = 3)\) dropped out. Thirty-three of the initial 36 participants completed the exercise sessions with an adherence of 95%. Measurements of daily fatigue were collected three times per day, 85% of which were completely filled out. In regard to weekly fatigue, all but one of the questionnaires were submitted \((99.5\%)\). Neither during the intervention nor during the tests did any serious adverse events occur within the FatiGO study; hence, the exercise intervention is considered to be feasible for participants. Conclusions: This pilot study showed the feasibility of close-meshed daily fatigue screening. Preliminary data indicate that cancer survivors are able to train in high-intensity ranges with tendencies toward decreased fatigue. Therefore, practicability of the study design is shown. Further results are expected within the prospective multicenter trial.

Introduction

Cancer-related fatigue (CRF) is one of the most common side effects of cancer and cancer therapy. The symptoms are nonspecific, complex and range from self-assessed complaints to issues with concentration and mem-
It has been defined by the National Comprehensive Cancer Network as a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [2]. Common recovery mechanisms will not help overcome this feeling of exhaustion. Furthermore, sleep does not lead to the desired regeneration or provide relief [3]. Fatigue is a clinically relevant limitation that impairs patients persistently, in spite of the completion of medical therapy [3]. Even years after surviving cancer therapy, fatigue can occur and cause an enormous reduction in quality of life. A research group diagnosed fatigue symptoms in 61% of patients, years after being cancer-free [4]. Chronic CRF reduces the patient’s ability to return to work [5]. In order to re-establish a social life and to reduce the burden of symptoms, adequate therapeutic approaches must be established [2, 6].

Several reviews and meta-analyses have shown that exercise therapy is an appropriate and effective approach for reducing CRF. A meta-analysis of 113 randomized controlled trials (RCTs) with 11,525 patients estimated the effect of exercise therapy on CRF and concluded that exercise interventions were significantly more effective than pharmaceutical options [7]. Another meta-analysis showed that exercise reduced CRF in patients with a wide variety of malignancies [8]. A meta-analysis of individual patient data from 31 RCTs on exercise interventions also showed its significant beneficial effects on fatigue [9]; specifically, supervised interventions demonstrated larger effects than unsupervised interventions. A Cochrane review, which included 56 RCTs, demonstrated decreased fatigue and improved fatigue scores at 12-week follow-up, with the most improvement seen in patients enrolled in the exercise group [10]. Furthermore, over 100 randomized controlled studies have shown the effectiveness of exercise therapy in oncological patients [11]. Exercise or physical activity shows the strongest evidence for decreasing the burden of fatigue in cancer survivors [12]. As long as the exercise and treatment period are individually adjusted, the exercise training can be increased progressively while fatigue symptoms decrease [13]. Despite this knowledge, a study by Smith et al. [14] revealed that very few cancer survivors meet the Centers for Disease Control and Prevention (CDC) guidelines for physical activity.

Regardless of the patients’ motivation to be active, the symptoms are rarely treated in everyday clinical practice [15, 16]. With regard to the possible chronification of CRF, there are only few studies which have adequately evaluated the symptoms and the burden on the patients. Moreover, studies that examine which type of physical activity has the best immediate effect on CRF in the follow-up care of oncology patients are lacking. Furthermore, it is not clear which exercise modalities (e.g., strength or endurance training) and which intensity (moderate or vigorous) are the most effective at achieving immediate effects on CRF.

It was against this background that the randomized, controlled FatIGo study was designed with four intervention groups, varying in exercise modality and exercise intensity, and a non-active control group. In addition to comparing different exercise modalities, the aim of this pilot study was to determine if a comprehensive fatigue assessment and extensive training at moderate and high intensities is feasible for cancer survivors.

Materials and Methods

This randomized, controlled pilot study was the preliminary work for a multicenter prospective trial with five arms, comparing a 4-week exercise intervention with a control group. The trial has been registered in the German Clinical Trials Register (DRKS-ID: DRKS00007798) and did not receive any external funding for the preliminary work. The Ethics Commission of the German Sport University Cologne (reference number 43/2015), as well as the Ethics Commission of Cologne University’s Faculty of Medicine (reference number 17–157), approved the study. All participants submitted written informed consent before entering the study. Participants were screened for eligibility between 2017 and 2019 at the University Hospital of Cologne. Inclusion criteria were history of malignancy of any tumor entity, completion of cancer therapy at least 1 year and not longer than 5 years ago, within follow-up care, age 18–69 years, and the diagnosis of a chronic fatigue syndrome. Exclusion criteria were defined as ongoing cancer therapy, local tumor recurrence, progression of tumor, age <18 and >69 years. Patients who met the inclusion criteria and agreed to participate in the study were randomly assigned to one of five groups. An independent research assistant performed the randomization by using an envelope with random numbers for the five groups.

In order to examine the feasibility of targeted exercise therapy under professional supervision on fatigue syndrome, five arms, including four intervention groups and one control group, were implemented. The training took place three times a week for 30 min over a period of 4 weeks at the Center for Integrated Oncology in Cologne. The exercise frequency was higher than the CDC guidelines suggest for muscle-strengthening activity, which demonstrates the willingness of participants to attend the intervention. Therefore, feasibility of the training schedule was confirmed. The endurance groups exercised on a cross-trainer or bicycle ergometer; meanwhile, the strength groups used weight machines (leg extension, bench press, seated row, abdominal, leg curl, back trainer); intensities vary in reference to the exercise group. 50–60% of V̇O_2 max or hypothetical one-repetiotion maximum test (hIRM), respectively, indicated moderate intensity, and vigorous intensity was defined as 70–80% of V̇O_2 max or hIRM. The choice of the high-intensity level is scientifically new to cancer survivors with CRF and must be checked for feasibility.

The assessment at baseline (week 0) and post-intervention (week 4) included fatigue (Multidimensional Fatigue Inventory [MFI-20] [17], Numerical Rating Scale [NRS] [18]), anxiety, and depression (Hospital Anxiety and Depression Scale [HADS] [19]), physical activity behavior (Freiburg Physical Activity Questionnaire [20]), muscle strength (hIRM), and peak oxygen consumption. Also, demographic data (sex, age, body mass index) and medical history (cancer diagnosis, medical treatment) were surveyed at
baseline and post-intervention. This comprehensive assessment requires a substantial effort from the participants, which in turn is an indication of feasibility. Additionally, serious adverse events were documented and defined as follows: death, cardiovascular event, or substantial disability.

Within this pilot, feasibility of the study design was of primary outcome. In order to document the fatigue as closely as possible, patients were asked to document their fatigue status with the NRS three times per day, as well as before and after exercise training, and the MFI-20 in weeks 1, 2, and 3.

### Statistical Analysis
The statistical data analysis was carried out with descriptive statistical methods from the SPSS Statistics 26 software by IBM. The pilot study was planned to generate a reliable study design which shows the potential possibility of reducing individual fatigue status. The arithmetic mean, median, standard deviation, and range of the characteristics with minimum and maximum value were calculated for the descriptive statistics. In addition, the course-related results in group comparison were included. Within the pilot study, a per protocol analysis was performed. A presentation via inference statistics was renounced due to the small size in each group (<10 participants).

### Results

#### Study Population and Characteristics
Among the potential participants, 40 were interested and contacted the study team. Cancer survivors who were eligible according to age (18–69 years), diagnosis, and treatment criteria were screened for their current exercise behavior. Two participants refused to provide written informed consent, one did not meet inclusion criteria, and one canceled due to medical complications. Thirty-six of these underwent randomization and baseline assessment. Overall, 33 participants completed the intervention and could be evaluated; hence, three participants (8.3%) dropped out during the intervention (Fig. 1). 21.2% (n = 7) of the participants were randomized to the endurance training group of moderate intensity, 15.1% (n = 5) to the strength training group with moderate intensity, 21.2% (n = 7) to the endurance training group with vigorous intensity, 18.2% (n = 6) to the strength training group of vigorous intensity, and 24.2% (n = 8) to the control group. 39.4% of the participants were male, and 60.6% were female (Table 1). The average age was 57.6 years, ranging from 30 to 69 years. 39.4% of the patients had a breast carcinoma (n = 13), followed by 9% with colorectal cancer (n = 3), 9% with lymphoma (n = 3), and 9% with a prostate carcinoma (n = 3). Further diagnoses included: esophageal carcinoma (n = 1), bronchial carcinoma (n = 1), ovarian carcinoma (n = 1), cancer of unknown primary origin (n = 2), and carcinomas of other entities (n = 6). The diagnosis date was within the past 5 years for 76% (n = 25) of the participants, whereas 24% (n = 8) of the respondents dated the diagnosis of cancer back more than 5 years.

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Fig. 1. CONSORT flow diagram.
Primary Objective/Outcome
The primary objective of this pilot study was to test the feasibility of the 4-week exercise intervention. Out of 36 participants, 8.3% \( (n = 3) \) patients dropped out of the study. Reasons for dropout were documented as change of residence \( (n = 1) \) and discontinuation without stating a reason \( (n = 2) \).

In order to further express the feasibility of the study, adherence to the protocol was examined. Out of 300 planned exercise sessions, 94.7% were completed. A total of 25 participants were assigned to the intervention group, each of whom trains 3 times per week over a period of 4 weeks. It was not investigated whether there was an influence of social and environmental factors on the training adherence.

The focus was on the fatigue assessment in order to evaluate the feasibility of the close-meshed daily fatigue screening. The query of the daily number scale was filled out 2,352 times. In total, that represents 85%. These questionnaires had to be filled out three times a day. When examining the completion of the weekly MFI, a percent-age of 99.2% was achieved. In both surveys, all 33 participants had to fill out the questionnaires over a time span of 4 weeks.

During the pre- and post-measurements, both a measurement of the hypothetical maximum and spiroergometry were carried out, which showed a participation rate of over 98%. Only one spiroergometric measurement could not be carried out. In addition, 1 patient was unable to take measurements on the rowing machine due to a limited range of motion.

Neither during the intervention nor during the tests were any serious adverse events reported within the Fatigo study. Additionally, the fatigue assessment was tested in order to be applied as a preliminary investigative tool for the multicenter prospective trial.

Fatigue Outcomes
The results of the MFI-20 can be separated into five subcategories, which are presented for the five groups in Table 2. The parameters general fatigue and physical fatigue showed the greatest differences in the pre-post-

### Table 1. Patient characteristics \( (n = 33) \)

| Parameter                                      | Results                          |
|-----------------------------------------------|----------------------------------|
| Age (AV±SD), years                           | 57.6±9.75                       |
| BMI (AV±SD), kg/m²                            | 26.5±4.85                       |
| Gender                                        |                                 |
| Male                                          | 13                               |
| Female                                        | 20                               |
| Time of initial diagnosis, years              |                                 |
| <5                                            | 25                               |
| 6–10                                          | 6                                |
| >10                                           | 2                                |
| Diagnosis                                     |                                 |
| Breast carcinoma                              | 13                               |
| Colorectal carcinoma                          | 3                                |
| Prostate carcinoma                            | 3                                |
| Esophageal carcinoma                          | 1                                |
| Lymphoma                                      | 3                                |
| Cancer of unknown primary origin              | 2                                |
| Bronchial carcinoma                           | 1                                |
| Ovarian carcinoma                             | 1                                |
| Carcinoma of other entities                  | 6                                |
| Treatment                                     |                                 |
| Chemotherapy                                  | 26                               |
| Radiotherapy                                  | 27                               |
| Surgery                                       | 26                               |
| Hormonotherapy                                | 10                               |
| Stem cell transplant                          | 1                                |
| Immunotherapy                                 | 1                                |
| Duration of treatment (AV±SD), months         | 12.39±7.65                      |
| Participation in rehabilitation               |                                 |
| Yes                                           | 16                               |
| No                                            | 2                                |
| n/a                                           | 15                               |

\( n \), number of patients; AV, average value; SD, standard deviation; n/a, not available.
When comparing the groups, the vigorous-intensity strength training group showed the highest improvement by decreasing the values by 4.4 and 5.0 points, respectively. The variable mental fatigue did not show relevant changes, independent of group affiliation. The endurance training group with moderate intensity and the control group showed consistent values. Regarding reduced motivation, the vigorous-intensity strength training group profited the most, when comparing pre- and post-intervention. In contrast to the control group, which showed slight to no change during the intervention time, the intervention groups showed beneficial changes.

Table 2. MFI pre-post-comparison of the subgroups

| Fatigue subscales         | Endurance training group of moderate intensity | Strength training group of moderate intensity | Endurance training group of vigorous intensity | Strength training group of vigorous intensity | Control group |
|---------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------|
| General Fatigue           | Pre: 14.2 (3.77) Post: 14.7 (4.02)             | Pre: 15.4 (3.51) Post: 12 (2.16)               | Pre: 14.6 (3.95) Post: 11.9 (4.33)             | Pre: 14.6 (1.90) Post: 10.2 (2.14)             | Pre: 15.0 (3.20) Post: 13.3 (3.57) |
| Physical Fatigue          | Pre: 15.1 (3.93) Post: 13.5 (3.69)             | Pre: 15 (2.91) Post: 11.8 (2.06)               | Pre: 12.1 (4.29) Post: 10 (4.69)               | Pre: 13.7 (2.42) Post: 8.7 (2.58)              | Pre: 14.1 (2.42) Post: 14 (3.37) |
| Reduced Activity          | Pre: 15.4 (2.93) Post: 15.7 (3.09)             | Pre: 16 (3.08) Post: 13.5 (1.29)               | Pre: 13.4 (4.85) Post: 10.9 (4.25)             | Pre: 12.3 (3.35) Post: 10.3 (2.50)             | Pre: 13.9 (3.37) Post: 13.3 (4.41) |
| Reduced Motivation        | Pre: 10.7 (3.45) Post: 10.8 (2.47)             | Pre: 9.2 (2.58) Post: 8.8 (2.87)               | Pre: 9.4 (3.73) Post: 8.1 (3.18)               | Pre: 9.9 (2.19) Post: 7.2 (1.94)               | Pre: 10 (3.16) Post: 11.1 (3.39) |
| Mental Fatigue            | Pre: 13.6 (3.41) Post: 14.3 (3.68)             | Pre: 13.8 (3.96) Post: 13.3 (3.04)             | Pre: 11.6 (3.99) Post: 10.6 (2.29)             | Pre: 12.4 (3.31) Post: 10.7 (5.35)             | Pre: 11.8 (4.71) Post: 11.8 (4.35) |

Values are mean (SD). MFI, Multidimensional Fatigue Inventory; M, median; SD, standard deviation.

The NRS was assessed three times per day to generate a differentiated presentation of fatigue symptomatology over the course of the exercise intervention. Figure 2 contains the daily course over the 4-week intervention period. Three of the four intervention groups showed a reduction effect immediately after the start of training. The greatest difference appeared for the strength training group with vigorous intensity. On day 1, the median of the group was at 5.5, and over the course of the 4-week intervention, the subjective fatigue symptomatology decreased by 1.8 points. A similar progress was determined for the moderate intensity strength training group. The endurance-based exercise intervention groups had more divergent NRS values. The vigorous-intensity endurance training group increased 1.5 points compared to the control group on day 7. On day 20, the NRS values were higher than the values of the control group as well. The endurance training group with moderate intensity started with
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The values peaked on days 12 and 27. By day 14, all groups showed a positive trend in terms of fatigue, with the exception of the moderate intensity group which leveled off with relatively constant values of 4–5.

In order to display the specific intervention modes for the course-related fatigue symptoms, two diagrams were created. Figure 3 shows the vigorous strength intervention group in comparison to the control group. To show the discrepancy, the differences were calculated over the course of the intervention. The same procedure was also applied to the vigorous endurance intervention group. With the help of a trend line, the immediate change can be seen. Because the NRS was taken three times at every testing point, the group median of the respective time of testing was determined, and the arithmetic mean was calculated.

On day 1 of the intervention, the accumulated vigorous strength group had an advantage of 0.3 points opposed to the control group. Overall, there are 4 days, on which the control group had lower fatigue values (days 3, 4, 9, and 14). From day 15 onward, the strength group had a positive development which, on average, exceeded the control group with a difference of 1. The maximum difference for a given day reached 2.0 points. Compared to the strength intervention group, the trend of the endurance intervention group was not as steep because the values of the endurance intervention group did not show as large a change as the strength group. Taking a closer look at the vigorous endurance group, it also showed a positive trend regarding reduced fatigue (Fig. 4).

**Discussion**

Several systematic reviews and meta-analyses show the importance of exercise therapy and its effectiveness at reducing CRF [7, 9, 12]. However, it is unclear which exercise modality best benefits survivors with CRF.

The FatiGO pilot study was the preliminary work for a multicenter trial, which to our knowledge will be the first investigation concentrating on the optimal effect of exercise on CRF by comparing four groups with different exercise modalities and intensities (endurance vs. strength training of both moderate and vigorous intensity) to a control group. The close-meshed documentation and the extensive training program should be verified with regard to method and process. Therefore, the primary objective...
of this pilot study was feasibility since it has never been conducted before. The dropout rate of 8.3% shows that the 4-week intervention is indeed feasible, even though the training frequency with three sessions a week is higher than other exercise interventions. In total, three participants dropped out of the study, two of which did not state a reason. Other supervised exercise interventions in cancer survivors with CRF demonstrated comparable dropout rates [21–23]. The exercise adherence rate of 95% was considered high in comparison to other reported RCTs [24] which also emphasizes the feasibility of this study. No adverse events were reported within this study. Moreover, the feasibility of this close-meshed fatigue assessment is demonstrated by the high response rate (85%). State-of-the-art literature limits their findings by assuming a bias because of usually lower feedback. Hinz et al. [25] (59.1%) queried the general population; however, Bjerkset et al. [26] gave out questionnaires to cancer survivors only, yet anonymously, and generated a response rate of 63%. The method of a supervised study design may have caused the high percentage in the present pilot study and therefore reinforces the methodology for the planned multicentric trial.

In addition to the questionnaire response rates, the adherence to the exercise interventions is also crucial for the feasibility of the pilot. In previous studies that examine exercise interventions for cancer patients suffering from fatigue, Kim et al. [27] as well as Pagola et al. [28] describe an adherence of 83% and 90%, respectively. Exceeding these amounts, the rate of 94.7% in the present study confirms excellent adherence to the program. High-intensity trainings are therefore considered to be feasible.

Physiological outcomes, such as cardiorespiratory fitness and strength, were assessed within the pilot study and considered feasible. Within the main study, one of the key areas of interest will be the effect of the physiological parameters on the fatigue syndrome.

There are only a few RCTs which have examined training intensity in relation to fatigue symptoms. Kampshoff et al. [23] showed improved MFI subscales in both the high- and low-to-moderate-intensity exercise groups but no significant differences between the groups. Pagola et al. [28] did not find significant differences regarding the fatigue outcome between high- and moderate-intensity training programs. A systematic review and meta-regression by Dennett et al. [12] support the recommendation of moderate-intensity aerobic training in exercise programs for cancer survivors.

Recruitment for the multicenter FatiGO study started in April 2021 at the University Hospital of Cologne, the
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University Hospital Wuerzburg, and the University Medical Center Hamburg-Eppendorf. For the prospective multicenter trial, the study protocol has been revised regarding the assessment. Considering the development of fatigue assessments in general, the more commonly used fatigue module of the EORTC QLQ-C30 the EORTC QLQ F-12 was selected as the primary outcome within the main study. This is based on the fact that the fatigue assessment is being developed further during the time of the study, as well as the complex display of the three forms of the fatigue syndrome (physical, emotional, and cognitive) and the proven validity of the EORTC QLQ-FA 12 [29]. An assessment for sleep quality (Pittsburgh Sleep Quality Index [PSQI]) [30] has also been included against the background that participants reported a subjective improvement of their sleep quality associated with exercise training. Several studies show an improvement of the sleep quality in cancer survivors after an exercise intervention [31, 32]. The primary outcome of the main study will be measured with the fatigue module of the EORTC QLQ-FA 12 [29]. There are also plans to implement an online/app-based assessment for the documentation of the daily fatigue symptoms.

The main limitation of the FatiGO pilot study is the limited number of patients. Therefore, the evaluation of the pilot study was carried out without focusing p values. Accordingly, due to the small sample size, all results were considered tendencies. Concerning feasibility, it cannot be stated how fast participants can be recruited. Therefore, there is no information on how long it will take to conduct a multicentric study that is representative for its aim.

However, there is a lack of exact exercise recommendations for cancer survivors with fatigue. The intention of the main follow-up FatiGO study will be used to suggest a screening method for patients with fatigue and to give clear training instructions. The NRS assessment should give information about the immediate training effect with the intention to target the exercise training directly.

Conclusion

The present pilot study evaluated the feasibility of a close-meshed daily fatigue screening and of an extensive training protocol considering various exercise intensities on cancer survivors over a 4-week period. A high response rate and an above-average high adherence of the exercise interventions confirm the feasibility. All participants of the strength training groups demonstrated a decrease of fatigue over the course of the study. These important findings from this pilot study served as the foundation for the newly initiated multicentric study, which is currently underway.

Statement of Ethics

The study was approved by the Ethics Commission of the German Sport University Cologne (reference number 43/2015) as well as the Ethics Commission of Cologne University’s Faculty of Medicine (reference number 17–157) and has been registered in the German Clinical Trials Register (DRKS-ID: DRKS00007798). During the course of the study, personal data, treatment data, and information about the disease from all participants, who provided written informed consent, were collected. These data, specifically diagnostic findings, are bound to professional discretion as well as data protection rules. A legal basis for working with the collected data comes from within the General Data Protection Regulations (GDPR), the Declaration of Helsinki, and the Good Clinical Practice Guidelines. Participation in this study is voluntary and refusing to participate did not have any disadvantages for the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Freerk Theeagnus Baumann is the principal investigator of the study. Stefanie Siebert, Franziska Byrtus, Jennifer Lesnik, and Anne Kollikowski recruited patients and conducted the intervention. Stefanie Siebert, Carrie-Ann Minto, Freerk Theeagnus Baumann, and Jannike Salchow drafted the manuscript. Stefanie Siebert, Freerk Theeagnus Baumann, and Jannike Salchow performed the statistical analysis. All the authors read and approved the final manuscript.

Data Availability Statement

The datasets generated at the University Hospital of Cologne during the current pilot study are not public but are available upon reasonable request to Prof. Dr. Baumann, the principal investigator of the study.

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