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Rehabilitation in patients with radically treated respiratory cancer: A randomised controlled trial comparing two training modalities

Bihiyga Salhi[a,*], Christel Haenebalcke[b], Silvia Perez-Bogerd[c], Mai D. Nguyen[d], Vincent Ninane[c], Thomas L.A. Malfait[a], Karim Y. Vermaelen[a], Veerle F. Surmont[a], Georges Van Maele[e], Roos Colman[e], Eric Derom[a], Jan P. van Meerbeeck[a,f]

[a] Department of Respiratory Medicine, Ghent University Hospital, Belgium
[b] Department of Respiratory Medicine, AZ Sint Jan, Bruges, Belgium
[c] Department of Respiratory Medicine, CHU St Pierre, Brussels, Belgium
[d] Department of Respiratory Medicine, CHU Sart Tilman, Liège, Belgium
[e] Biostatistical Unit, Faculty of Medicine, Ghent University, Belgium
[f] Thoracic Oncology, Antwerp University Hospital, Belgium

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ABSTRACT

Introduction: The evidence on the effectiveness of rehabilitation in lung cancer patients is limited. Whole body vibration (WBV) has been proposed as an alternative to conventional resistance training (CRT).
Methods: We investigated the effect of radical treatment (RT) and of two rehabilitation programmes in lung cancer patients. The primary endpoint was a change in 6-min walking distance (6MWD) after rehabilitation. Patients were randomised after RT to either CRT, WBVT or standard follow-up (CON). Patients were evaluated before, after RT and after 12 weeks of intervention.
Results: Of 121 included patients, 70 were randomised to either CON (24), CRT (24) or WBVT (22). After RT, 6MWD decreased with a mean of 38 m (95% CI 22–54) and increased with a mean of 95 m (95% CI 58–132) in CRT ($p < 0.0001$), 37 m (95% CI −1–76) in WBVT ($p = 0.06$) and 1 m (95% CI −34–36) in CON ($p = 0.95$), respectively. Surgical treatment, magnitude of decrease in 6MWD by RT and allocation to either CRT or WBVT were prognostic for reaching the minimally clinically important difference of 54 m increase in 6MWD after intervention.
Conclusions: RT of lung cancer significantly impairs patients' exercise capacity. CRT significantly improves and restores functional exercise capacity, whereas WBVT does not fully substitute for CRT.

1. Introduction

A minority of patients with lung cancer receives a treatment with curative intent, consisting of either radical surgery or definitive radiotherapy, administered either as single modality or combined with platinum-based chemotherapy [11,33,34].

These treatments lead to a decrease in QoL, physical activity and enhance their morbidity [10]. Cancer-related fatigue (CRF), which is frequently reported by cancer patients, is defined as an unusual and persistent sense of tiredness, affecting both physical and mental capacity and is unrelieved by rest [35]. The underlying mechanisms are biological (anaemia, pro-inflammatory cytokines, nutritional and fluid imbalances, muscle wasting), functional (reduced aerobic capacity and decreased activity of daily living) and psycho-behavioural (sleep disorders, anxiety, depression, reduced self-efficacy, sleep disorders, distress and difficulty coping). This may lead to a further muscle deconditioning and disuse atrophy [35], which in turn may aggravate the feeling of fatigue [1].

Oncological rehabilitation has most been extensively studied in breast cancer patients [28]. The beneficial effects of rehabilitation in lung cancer patients, were currently limited to a few randomised trials. These trials showed that patients with lung cancer can improve their exercise capacity, muscle strength and QoL, however the results were not consistent [2,9,29].

Whole body vibration training (WBVT) has been proposed as an alternative training modality for resistance training on multigym equipment. WBVT generates vertical sinusoidal vibrations and elicits in short periods reflectory neuromuscular training without much effort [26]. It is assumed that these vibrations evoke muscle

* Corresponding author at: Department of Respiratory Medicine, Ghent University Hospital, De Pintelaan 185, 7K12IE, B-9000 Ghent, Belgium. Tel.: +32 9 332 5536; fax: +32 9 332 2341.
E-mail address: Bihiyga.Salhi@UGent.be (B. Salhi).

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contractions via a tonic vibration reflex [32]. In elderly subjects, WBVT improved both aerobic fitness and muscle strength [4].

The present multi-centre trial, acronamed "REINFORCE" (Randomized Exercise trainINg FOr patients with Radically treated respiratory CancEr), was designed to assess the potential beneficial effect of rehabilitation in lung cancer patients. More specifically, we wanted to address the following questions: (1) does lung cancer therapy affect exercise capacity, muscle strength and QoL; (2) does a 12-week rehabilitation programme improve 6MWD (the primary outcome), maximal exercise capacity, muscle strength and QoL; and (3) are both training methods, WBVT and conventional resistance training (CRT), equally effective in improving 6MWD and other outcome variables?"

2. Materials and methods

Sequential patients with stages I-III lung cancer or mesothelioma, candidate for a treatment with curative intent, were solicited by their attending physician of four departments of Respiratory Medicine to participate in the present study. Radical treatment was defined as either radical resection with or without a perioperative platinum-based chemo-(radio) therapy, or definitive thoracic radiotherapy with or without concurrent or sequential platinum-based induction chemotherapy. Patients were between 18 and 80 years and had a baseline haemoglobin level of at least 8 g/dl. Patients with severe cachexia (a decrease of at least 35% premorbid weight), co-morbidities interfering with exercise training and contra-indications for WBVT, such as a pacemaker, joint prostheses or recently introduced osteosynthetic material and osteoporotic fractures were excluded. All patients provided written informed consent at inclusion. The study was approved by the Ethics Committee of each participating hospital.

This open multi-centre trial consisted of a prospective observational part I, describing the effect of radical treatment and a randomised part II, analysing the effect of the intervention in those patients who were radically treated. In part I, patients were evaluated before (M1) and after (M2) radical treatment. M2 was assessed within 8 weeks of resection or within 2 weeks after the end of the non-surgical treatment. Patients proceeded only to part II, if their treatment was considered radical and if their post-treatment quadriceps force (QF) was either equal or less than 70% of the predicted normal value or showed a decrease of at least 10% from the baseline value [8]. The randomisation procedure was conducted directly after the M2 evaluation.

Patient randomisation was conducted by a blinded, web-based platform using a minimisation technique with surgery, COPD and centre as stratification variables and with random allocation to either a control group (CON), a CRT-group and a WBVT-group. Patients allocated to CON were discouraged to improve their exercise tolerance with professional help. Patients allocated to either CRT and WBVT received 20 min of aerobic training on the bicycle and treadmill at 70% of the respective maximal workload (Wmax) and speed, observed at M2. Thereafter, CRT-group received resistance training on multigym equipment starting with three sets of eight repetitions for each exercise at 50% one-repetition-maximum (1RM) (Appendix 1). WBVT-group performed exercises on the vibration platform (FITVIBE, Gymna, Belgium), starting with three sets of 30 s for each exercise at 27 Hz. Rehabilitation started within 8 days after randomisation. Patients trained three times a week for 12 weeks, whereafter they were re-evaluated (M3). The investigator was unblinded for the intervention and its evaluation.

The Charlson comorbidity index was used to reflect comorbidities [7]. Spirometry, diffusion capacity (DL,CO) and 6MWD with continuous oxygen saturation monitoring were measured according to existing guidelines and expressed as percentage predicted [5,19,23,30]. A change of at least 54 m in 6MWD was considered as the minimally clinically important difference (MCID) [24]. Maximal exercise capacity was assessed by Wmax and VO_2 peak using an incremental symptom-limited cycle ergometer test and compared with normal values [18]. A change exceeding 10 W was considered as MCID [25]. QF was assessed using an isometric handheld dynamometer (Microfet; Biometrics, Almere, the Netherlands) attached to a knee pendicular bank. Extension peak torque was evaluated at 60° of knee flexion, by performing a 5 s maximal isometric contraction. The best out of three attempts was retained. Health-related QoL was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30) and more specifically the item physical functioning (PF) [14]. Fatigue was assessed by the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) [6,37]. Pain and dyspnoea were scored with visual analogue scales (VAS) [13].

The adherence of the trial was defined as the percentage of patients completing the intervention. It was calculated as ratio between the number of patients, who did not drop out and the total number of patients who were randomised to the active intervention. The attendance was defined as the percentage of attended sessions of the proposed 36 sessions. At each supervised training session, the study-intervention-related adverse events were recorded.

Statistical analysis

Baseline patient characteristics are expressed as medians with ranges. The effect of radical treatment was analysed in all participants completing part I (sample 1). The primary endpoint of the trial is the change in 6MWD (m) in those patients who proceeded to part II (sample 2). The null hypothesis is that neither CRT nor WBVT would result in an increase of at least 54 m in 6MWD, the proposed MCID [24]. To refute this, a sample size of 57 patients (19 patients in each group) is needed (α: 0.05; power: 0.80) [3]. Assuming a dropout rate of 50% of patients after part I, 114 participants had to be included in the study.

The primary endpoint was analysed by performing an intention-to-treat (ITT)-analysis on sample 2. A per protocol (PP)-analysis on patients who completed part II, defined as sample 3, was also conducted. For the ITT-analysis, missing observations at M3 were predicted by applying multiple imputations using monotone linear regression (Proc MI in SAS 9.3). Linear regression was applied on 50 imputed datasets and the results were combined using SAS Proc Mianalyse to calculate means with 95% confidence intervals (CI) [38]. Bonferroni corrections were applied to correct for multiple pairwise comparisons.

The effect of radical treatment and the combined effect of radical treatment and intervention, both expressed as changes in exercise capacity, muscle strength and QoL, were analysed with the paired-*T* test for differences within, and by one-way ANOVA for differences in-between groups. These results were expressed as means with 95%CI (SPSS version 20, Chicago IL). In order to analyse variables predictive for reaching the MCID in 6MWD, the allocation to either CRT or WBVT, together with relevant clinical factors, were combined in a multiple logistic regression model on sample 3. All comparisons were done with the use of a two-sided α level of 0.05.

3. Results

3.1. Patient population

Between January 2009 and February 2012, 121 consecutive patients were recruited (Fig. 1). Eighty-six patients completed part

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