



HAL
open science

Prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with non-small cell lung cancer: a randomised trial

Francis Edouard Gravier, Pauline Smondack, Fairuz Boujibar, Guillaume Prieur, Clément Medrinal, Yann Combret, Jean François Muir, Jean Marc Baste, Antoine Cuvelier, David Debeaumont, et al.

► **To cite this version:**

Francis Edouard Gravier, Pauline Smondack, Fairuz Boujibar, Guillaume Prieur, Clément Medrinal, et al.. Prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with non-small cell lung cancer: a randomised trial. *Journal of Physiotherapy*, 2022, 68 (1), pp.43-50. 10.1016/j.jphys.2021.12.010 . hal-03554189

HAL Id: hal-03554189

<https://hal.science/hal-03554189v1>

Submitted on 15 Apr 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Research

Prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with non-small cell lung cancer: a randomised trial

Francis-Edouard Gravier ^{a,b}, Pauline Smondack ^a, Fairuz Boujibar ^{c,d}, Guillaume Prieur ^{b,e}, Clément Medrinal ^{e,f,g}, Yann Combret ^h, Jean-François Muir ^{a,b}, Jean-Marc Baste ^{c,d}, Antoine Cuvelier ^{b,i}, David Debeaumont ^j, Tristan Bonnevie ^{a,b}

^aADIR Association, Rouen University Hospital, Rouen, France; ^bNormandie University, UNIROUEN, UPRES EA 3830, Haute Normandie Research and Biomedical Innovation, Rouen, France; ^cDepartment of Thoracic Surgery, Rouen University Hospital, Rouen, France; ^dNormandie University, UNIROUEN, INSERM U1096, Haute Normandie Research and Biomedical Innovation, Rouen, France; ^eIntensive Care Unit Department, Le Havre Hospital, Le Havre, France; ^fUniversité Paris-Saclay, UVSQ, UR 20201 ERPHAN, Versailles, France; ^gIFMK Saint Michel, Paris, France; ^hPhysiotherapy Department, Le Havre Hospital, Le Havre, France; ⁱPulmonary, Thoracic Oncology and Respiratory Intensive Care Department, Rouen University Hospital, Rouen, France; ^jDepartment of Respiratory and Exercise Physiology and CIC-CRB 1404, Rouen University Hospital, Rouen, France

KEY WORDS

Non-small cell lung cancer
Lung resection
Preoperative care
Exercise training
Prehabilitation



ABSTRACT

Question: In people with non-small cell lung cancer, what is the effect of condensing 15 prehabilitation sessions into a 3-week regimen compared with a 5-week regimen? **Design:** Randomised controlled trial with concealed allocation, intention-to-treat analysis and blinded assessment of the primary outcome. **Participants:** People with diagnosed or suspected non-small cell lung cancer and moderate-to-high risk of postoperative complications. **Intervention:** Fifteen supervised prehabilitation sessions delivered with either a dense regimen of five sessions/week for 3 weeks (experimental group) or a non-dense regimen of three sessions/week for 5 weeks (control group). **Outcome measures:** The primary outcome was the change in cardiorespiratory fitness measured by the $\dot{V}O_{2peak}$ in ml/kg/min. The secondary outcomes were the change in other variables of interest measured during cardiopulmonary exercise testing, non-invasive nutritional markers, quadriceps maximal voluntary isometric contractions, maximal inspiratory pressure, quality of life, adherence and postoperative complications. **Results:** Changes with the experimental regimen were similar to or better than changes with the control regimen for: $\dot{V}O_{2peak}$ (MD 1.2 ml/kg/min, 95% CI -0.1 to 2.6); $\dot{V}E/\dot{V}CO_2$ slope (MD -3.6 points, 95% CI -8.7 to 1.5); and work rate at ventilatory threshold (MD 3.7 W, 95% CI -5.6 to 13.0). The two regimens had similar effects on: peak work rate (MD 1.3 W, 95% CI -6.4 to 9.0), $\dot{V}O_2$ at ventilatory threshold (MD 0.0 ml/kg/min, 95% CI -1.4 to 1.4); body mass index (MD -0.2 kg/m², 95% CI -0.5 to 0.1); and maximal inspiratory pressure (MD -0.7 cmH₂O, 95% CI -9.8 to 8.4). The relative effect was uncertain for quadriceps maximal voluntary isometric contractions, quality of life and complications. **Conclusion:** Condensing prehabilitation sessions led to similar or better improvement in cardiorespiratory fitness and did not decrease adherence or increase adverse events. This could increase the number of patients who can be referred for prehabilitation, despite short presurgical periods. **Trial registration:** NCT03936764. [Gravier F-E, Smondack P, Boujibar F, Prieur G, Medrinal C, Combret Y, Muir J-F, Baste J-M, Cuvelier A, Debeaumont D, Bonnevie T (2022) Prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with non-small cell lung cancer: a randomised trial. *Journal of Physiotherapy* 68:43–50]

© 2021 Australian Physiotherapy Association. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Lung cancer is the most common type of cancer and the leading cause of cancer death worldwide.¹ Lung resection is currently the recommended curative treatment for early-stage non-small cell lung cancer (NSCLC).² Measurement of peak oxygen uptake ($\dot{V}O_{2peak}$) by cardiopulmonary exercise testing is recommended to assess perioperative risk in frail patients.^{3,4} Physical preparation for surgery,

termed prehabilitation, which involves exercise training, support with smoking cessation, nutritional advice, respiratory physiotherapy and postoperative education, is increasingly being prescribed and delivered to this clinical population.

Prehabilitation was initially undertaken to allow patients who were inoperable due to their poor cardiorespiratory fitness to benefit from curative surgery. Today, as evidenced by a growing number of randomised trials from various regions of the world, the challenge is

to offer this intervention to reduce the occurrence and severity of postoperative complications and to shorten length of hospital stay, including in patients with moderate postoperative risk.⁵ Despite these benefits, some teams might be reluctant to offer prehabilitation to operable patients with high/moderate surgical risk so that surgery is not delayed.

Related to this concern, the organisation of prehabilitation must consider both the need for rapid surgery and the need to provide a sufficient training load to obtain physiological benefits. In a preliminary retrospective cohort study, we found that the subgroup of patients who completed ≥ 15 sessions showed more improvement in cardiorespiratory measures after the prehabilitation program than those who performed fewer sessions.⁶ The program was therefore designed to have 15 sessions. Programs involving daily training could provide considerable physiological stimulation in a shorter timeframe compared with a more conventional frequency of two to three sessions per week in pulmonary rehabilitation.⁷ However, such intense training could cause significant fatigue or limit adherence. Patients scheduled for NSCLC resection undergo many preoperative consultations and examinations and may struggle to also participate in prehabilitation.

To date, no study has evaluated the relative effect of condensing the delivery of a fixed number of exercise sessions on the physiological benefits and safety of prehabilitation.

Therefore, the research question for this randomised controlled trial was:

In people with NSCLC, what is the effect of condensing 15 prehabilitation sessions into a 3-week regimen compared with a 5-week regimen?

Method

Study design

This randomised controlled trial was conducted by ADIR Association, Rouen, France, in partnership with Rouen University Hospital. Consecutive adult patients with suspected or confirmed NSCLC and a moderate-to-high perioperative risk at the pulmonary rehabilitation centre of the ADIR Association were screened for eligibility. Eligible, consenting patients were randomly assigned after baseline assessment to one of two prehabilitation regimens: five sessions per week for 3 weeks (experimental group) or three sessions per week for 5 weeks (control group). The 1:1 randomisation sequence was computer-generated before initiation of the trial using the Research Randomizer website and concealed until enrolment in the first prehabilitation session. Before and after prehabilitation, participants underwent cardiopulmonary exercise testing and measurement of non-invasive nutritional markers, quadriceps strength, maximal inspiratory pressure, quality of life and adherence. Complications were assessed postoperatively. A blinded researcher assessed the primary outcome (cardiorespiratory fitness). Analysis followed the intention-to-treat principle. The results of the study are reported according the Consolidated Standards of Reporting Trials (CONSORT) statement.⁸

Participants

The inclusion criteria were suspected or confirmed NSCLC and a moderate-to-high perioperative risk, defined as $\dot{V}O_{2\text{peak}} < 20$ ml/kg/min. The exclusion criteria were: cardiological contraindications to training; neoadjuvant radio-chemotherapy; refusal to carry out a training program; a comorbidity that limited cycling (eg, orthopaedic, vascular or neurologic limitations); exacerbation; or medical recommendation for early cessation of the prehabilitation program.

Intervention

Prehabilitation sessions

All participants in both groups were allocated to receive 15 prehabilitation sessions. Each prehabilitation session lasted approximately 90 minutes. The first session was individual and the following sessions were performed in groups of around six patients. The program was supervised by a physiotherapist. The program included the following four components.

Aerobic endurance training: aerobic endurance training on a cycle ergometer at the ventilatory threshold (VT) determined during the initial cardiopulmonary exercise testing. The first session lasted for 15 to 20 minutes. The duration increased by 5 minutes each session to reach 45 minutes (including a 5-minute warmup and a 5-minute active recovery). The intensity was then increased by 5 or 10 watts, as tolerated.⁹

Peripheral muscle strengthening: peripheral muscle strengthening on weight machines performed at 60 to 70% of the 1-repetition maximum (1RM) (three exercises: whole-leg extension, whole-arm pull down and whole-arm extension). Three sets of 12 movements were carried out for each exercise and the load was increased regularly as tolerated.¹⁰

Inspiratory muscle training: inspiratory muscle training using an inspiratory threshold valve calibrated to at least 30% of the maximal inspiratory pressure (MIP). Patients were encouraged to carry out 15 minutes of independent training daily and to increase the resistance regularly.¹¹

Support and education: smoking cessation support¹² and education regarding mucus clearance techniques, deep-breathing, directed and protected coughing, and postoperative mobilisation.¹³ The last two components were mainly delivered during the first individual session, and reminders and advice were provided during the following 14 group sessions. The exercises were prescribed and progressed by a physiotherapist in accordance with the safety criteria recommended by the physician after cardiopulmonary exercise testing.

Randomised regimens

Participants were randomly assigned to one of two regimens for 15 sessions of prehabilitation. The experimental group was scheduled to attend five 90-minute sessions per week for 3 weeks. The control group was scheduled to attend three 90-minute sessions per week for 5 weeks.

Outcome measures

A comprehensive medical history was collected for each patient. Cardiorespiratory fitness and spirometry were assessed by a physician who was blind to patient allocation before and after the 15 planned prehabilitation sessions. The same physiotherapist, who was not blind to patient allocation, assessed quadriceps strength, maximal inspiratory pressure, and non-invasive nutritional variables at the first and last sessions. A quality of life questionnaire was completed during the first and last sessions.

The primary outcome was the post-training change in cardiorespiratory fitness measured by the $\dot{V}O_{2\text{peak}}$ in ml/kg/min. Secondary outcomes were the post-training change in the other variables of interest measured during cardiopulmonary exercise testing, non-invasive nutritional markers, quadriceps maximal voluntary isometric contractions, maximal inspiratory pressure, quality of life, adherence and postoperative complications.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed on an electromagnetic ergometer^a. A face mask, pneumotach and gas analyser^b were used to assess oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$), breath by breath. Heart rate was continuously monitored using a 12-lead electrocardiogram and perceived exertion was assessed using the Borg scale. After a 3-minute warm-up period, incremental ramp exercise (aimed to last for about 10 minutes using steps from 5 to 15 W/min depending on the physician's evaluation,

the patient's history and usual physical activity levels) was applied to exhaustion.¹⁴ $\dot{V}O_2$ measured during the last fully sustained ramp was defined as the $\dot{V}O_{2peak}$ and expressed as a percentage of the predicted value according to age, weight and sex.^{14,15} Ventilatory threshold was manually identified using a three-criterion discrimination technique.¹⁴ Linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$) generated the $\dot{V}E/\dot{V}CO_2$ slope.

Pulmonary function

Pulmonary function tests were carried out according to the American Thoracic Society and the European Respiratory Society guidelines with a commercial spirometer^c. Values were expressed as percentages of established predicted values for European populations.¹⁶ MIP was measured before and after prehabilitation using an electronic manometer^d.

Quality of life

Quality of life was estimated using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire and modular supplement for Lung Cancer patients (EORTC QLQ-C30 / LC13), a 30-question questionnaire with a 13-question modular specific supplement for patients with lung cancer.¹⁷ Scores range from 0 to 100, and a higher score reflects either better function or milder symptoms.

Nutritional status

Nutritional status was estimated non-invasively by measuring body mass index and bioimpedance analysis^e of fat-free mass calculated as percentage of total body weight. The measurement was carried out before exercise, in a standardised supine position, after urination and 10 minutes of rest.¹⁸ Since the patient then performed the exercise training session, fasting was not required. The pre- and post-prehabilitation measurements were taken at the same time of day.

Quadriceps strength

Bilateral quadriceps maximal voluntary isometric contractions were evaluated with hand-held dynamometry^f according to a standardised methodology.¹⁹ The obtained results were expressed in absolute values and as a percentage of the corresponding theoretical normal values for each lower limb.²⁰

Adherence and adverse event

Adherence to the prehabilitation program was defined as the ratio of the number of sessions attended to the 15 sessions prescribed. Any adverse event during or related to exercise training was recorded.

Postoperative complications

Postoperative complications were collected from the medical records at 30 days and graded according to the Clavien-Dindo classification.²¹

Data analysis

This study aimed to assess the relative effects of a dense and a non-dense supervised outpatient prehabilitation program on improvements in cardiorespiratory fitness measured by the change in $\dot{V}O_{2peak}$. Taking into account an expected between-group difference ($\mu_A - \mu_B$) of zero, alpha of 0.05, power of 80%, a two-sided 95% CI, a smallest worthwhile effect on the change in $\dot{V}O_{2peak}$ of 1.75 ml/kg/min, and a standard deviation of 1.62 ml/kg/min,⁶ it was determined that a total of 30 participants was required, divided into two groups.²² Assuming a 20% dropout risk, the sample size was set to 36 participants.

Categorical data were expressed as numbers (percentages). Continuous data were expressed as means (SD) or median (IQR) according to distribution. Normality was assessed using the Kolmogorov-Smirnov test. Between-group differences were expressed as MD (95% CI). If necessary, skewed data were preliminarily converted into means (SD) with the Luo et al and Shi et al

methods,^{23,24} and the widest estimate was conservatively used before calculating the MDs. Statistical analyses were performed with an intention-to-treat approach using the last observation carried forward method for preoperative variables,²⁵ and no postoperative complication was considered for patients who did not undergo surgery. Commercial statistical software^g was used for analyses.

Results

Flow of participants through the study

Thirty-six participants were recruited between May 2019 and April 2021. The flow of participants through the study is presented in Figure 1. The baseline characteristics of the participants are presented in Table 1 and in the first two columns of data in Table 2.

Primary outcome

The mean between-group difference in the change in $\dot{V}O_{2peak}$ was 1.2 ml/kg/min (95% CI -0.1 to 2.6). The two-sided 95% CI (-0.1 to 2.6) spanned from close to 0 (no between-group difference) to greater than the prespecified smallest worthwhile effect of 1.75 ml/kg/min in favour of the dense training regimen, indicating similar or better benefits from the dense training regimen relative to the control regimen. (Table 2 and Figure 2).

Secondary outcomes

Preoperative outcomes

Changes in the secondary outcomes from before to after prehabilitation for each group and the corresponding between-group comparisons are presented in Table 2. As for primary outcome, the effect from the dense prehabilitation was similar to or better than the control regimen for $\dot{V}E/\dot{V}CO_2$ slope (MD -3.6 points, 95% CI -8.7 to 1.5) and work rate at the ventilatory threshold (3.7 W, -5.6 to 13.0). The dense prehabilitation regimen was estimated to have similar effects to the control regimen on peak work rate (MD 1.3 W, 95% CI -6.4 to 9.0), $\dot{V}O_{2VT}$ (MD 0.0 ml/kg/min, 95% CI -1.4 to 1.4), body mass index (MD -0.2 kg/m², 95% CI -0.5 to 0.1), and maximal inspiratory pressure (MD -0.7 cmH₂O, 95% CI -9.8 to 8.4). Although the mean between-group differences for quadriceps maximal voluntary isometric contractions and quality of life were all too small to be perceived as clinically relevant, the large 95% CIs demonstrate that these estimates had important inherent uncertainty that does not exclude the possibility of worthwhile differences in effect. Individual participant data are presented in Table 3 on the eAddenda.

Adherence and adverse events

The mean adherence rate for scheduled sessions was 86% (SD 11) in the experimental group and 87% (SD 11) in the control group, giving a mean difference of 1% (95% CI -9 to 7). No patient dropped out due to intolerance to the prehabilitation program. Only one patient had to discontinue the program early, because the date of surgery was brought forward. No adverse events occurred.

Postoperative outcomes

Twenty-six participants (72%) underwent surgery at the end of their prehabilitation program (Table 4). Ten surgical interventions (five in each group) were not carried out for the following reasons: three participants had stable nodules under surveillance, three participants had metastases discovered, two participants had unfavourable onco-geriatric opinions, one participant had a benign biopsy result and one participant refused surgery. Six postoperative complications were reported: two in the experimental group and four in the control group, RR 0.5 (95% CI 0.1 to 2.1). Most of the postoperative complications were pulmonary and clinically significant (Clavien-Dindo classification ≥ 2) (Table 5).

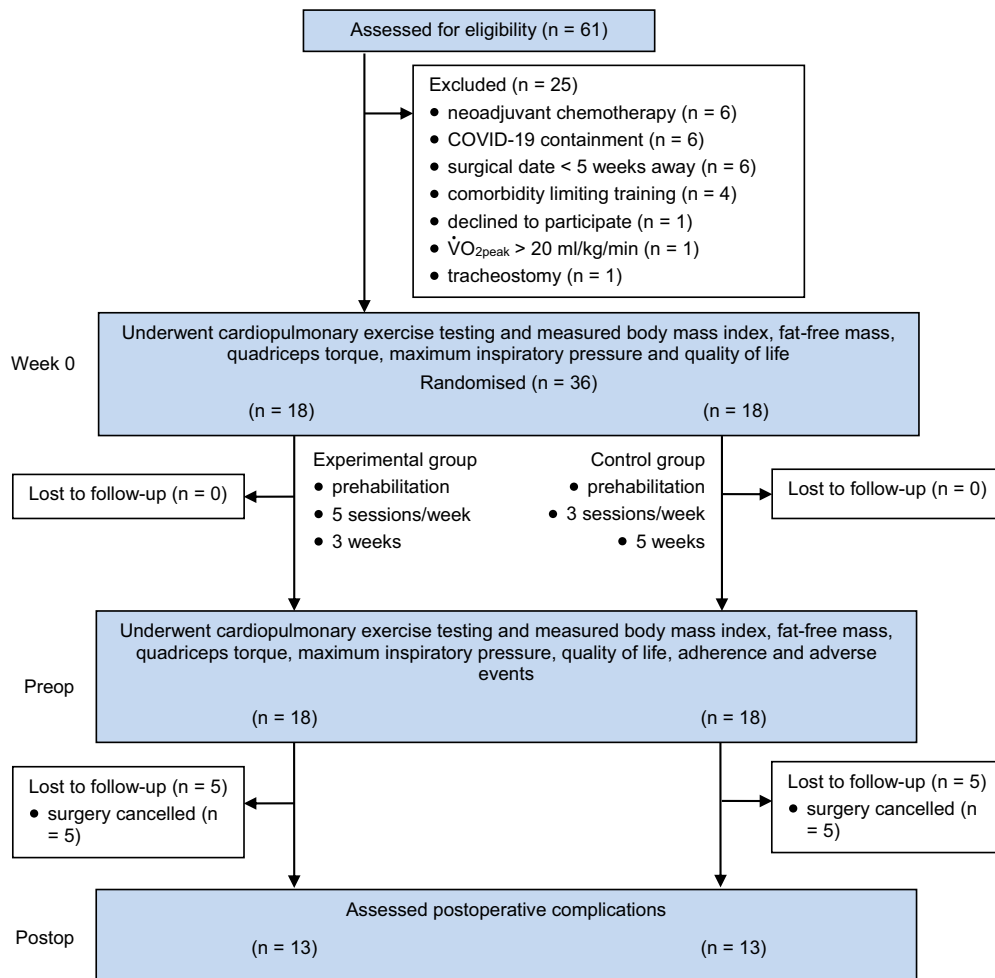


Figure 1. Design and flow of participants through the trial.

COVID-19 = coronavirus disease 2019, CPET = cardiopulmonary exercise testing, $\dot{V}O_{2peak}$ = peak oxygen uptake.

Discussion

The main finding of this study was that a shorter dense prehabilitation program (five sessions/week for 3 weeks) had a similar or better effect than a longer regimen (three sessions/week for 5 weeks) on cardiorespiratory fitness measured with $\dot{V}O_{2peak}$. The between-group difference in change in $\dot{V}O_{2peak}$ was 1.2 ml/kg/min (95% CI -0.1 to 2.6) in favour of the dense regimen, although the uncertainty in that estimate ranged from quite similar to better than control to a clinically worthwhile degree (ie, greater than the prespecified smallest worthwhile effect of 1.75 ml/kg/min). As no relevant smallest worthwhile effect has been published for this clinical scenario, the threshold that was prespecified requires further clarification. This value corresponded to the mean difference previously observed between patients who completed 15 training sessions or more and those who received a lower training load.⁶ Furthermore, this value of 1.75 ml/kg/min is equal to a half metabolic equivalent of task (1 MET = 3.5 ml/kg/min)—a value that can distinguish different levels of functional activity.²⁶ Ultimately, whatever smallest worthwhile effect threshold is chosen, this study provides an estimate that is accurate enough to support that a dense prehabilitation regimen leads to benefits that are at least similar to those achieved with a longer less-dense regimen.

A previous study found that ventilatory efficiency was probably less sensitive than oxygen uptake to prehabilitation.⁶ In the present study, only the experimental group showed a substantial mean reduction in the $\dot{V}E/\dot{V}CO_2$ slope, resulting in a mean difference between the two groups of -3.6 (slope coefficient). Although there is currently no established threshold for a smallest worthwhile effect,

this value represents approximately 10% of the baseline median (Table 2) and can potentially allow some patients to fall below the previously reported postoperative risk threshold of 35.²⁷ However, the uncertainty around this estimate ranges from a very worthwhile reduction in favour of dense prehabilitation regimen through to negligible differences (95% CI -8.7 to 1.5).

The two outcome measures discussed above (ie, $\dot{V}O_{2peak}$ and $\dot{V}E/\dot{V}CO_2$ slope) are powerful predictive markers of complications after pulmonary resection.^{4,27} Given that mean estimates favoured the dense prehabilitation regimen and the confidence intervals indicated that the effects are as good as or better than the control regimen, a reduction in postoperative complications might be anticipated. Unfortunately, the study did not confirm this assumption. Although the overall complication rate in the present cohort (23%) was close to the overall complication rate of 19% reported by the European Society of Thoracic Surgeons from their database, this produced a very uncertain estimate of the relative effect of the interventions on this outcome. Additionally, the distribution of surgical procedures performed did not allow this comparison to be interpreted without possible confounding. Future adequately powered trials are warranted to further explore the effects of prehabilitation density on postoperative complications.

The estimated effect of the dense prehabilitation regimen on peak power on the cycle ergometer (WR_{peak}) was a mean between-group difference of 1.3 W (95% CI -6.4 to 9.0). This can be considered clinically similar to the control regimen, based on a MCID of 10.5 W.²⁸ The upper limit of the confidence interval could perhaps be judged as a worthwhile benefit from the dense regimen, since in clinical practice the variation in Watts on cycle ergometers is generally rounded

Table 1
Baseline characteristics of the study participants.

Characteristic	All (n = 36)	Exp (n = 18)	Con (n = 18)
Age (yr), mean (SD)	66 (8)	68 (8)	65 (8)
Sex, n male (%)	23 (64)	14 (78)	9 (50)
Body mass index (kg/m^2), mean (SD)	29 (6)	29 (7)	29 (5)
$\dot{V}O_{2\text{peak}}$ (% pred), mean (SD)	64 (15)	61 (15)	67 (15)
FEV ₁ (L), mean (SD)	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)
FEV ₁ (% pred), mean (SD)	74 (28)	73 (31)	75 (26)
FVC (L), mean (SD)	3.0 (0.8)	3.2 (0.9)	2.9 (0.8)
FVC (% pred), mean (SD)	90 (22)	90 (26)	90 (19)
DLCO (% pred), median (IQR)	56 (45 to 70)	58 (46 to 70)	55 (45 to 69)
Comorbidities, n (%)			
COPD	22 (61)	14 (78)	8 (44)
hypertension	19 (53)	9 (50)	10 (56)
hypercholesterolaemia	14 (39)	6 (33)	8 (44)
cardiovascular disease	13 (36)	8 (44)	5 (28)
diabetes	10 (28)	6 (33)	4 (22)
anxiety-depression syndrome	5 (14)	2 (11)	3 (17)
orthopaedic/rheumatic disease	8 (22)	4 (22)	4 (22)
Medications (n/patient), median (IQR)	6 (3 to 7)	6 (4 to 7)	5 (3 to 8)
Tobacco use category, n (%)			
non-smoker	2 (6)	1 (6)	1 (6)
smoker	11 (31)	6 (33)	5 (28)
former	23 (64)	11 (61)	12 (67)
Tobacco exposure (pack-yr), median (IQR)	42 (36 to 60)	48 (35 to 60)	40 (34 to 54)
NSCLC stage, n (%)			
I	22 (61)	13 (72)	9 (50)
II	7 (19)	2 (11)	5 (28)
III	3 (8)	1 (6)	2 (11)
IV	1 (3)	0 (0)	1 (6)
NS	3 (8)	2 (11)	1 (6)

Con = control group, COPD = chronic obstructive pulmonary disease, DLCO = diffusing capacity of the lung for carbon monoxide, Exp = experimental, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, NS = not specified, $\dot{V}O_{2\text{peak}}$ = peak oxygen uptake.

off to 5 W higher or lower, and an average gain of 10 W at WR_{peak} generally results in an additional increment during cardiopulmonary exercise testing.¹⁴

Concerning a submaximal marker, the difference in $\dot{V}O_{2VT}$ between the two groups was unimportant (MD 0.0 ml/kg/min, 95% CI -1.4 to 1.4). For WR_{VT} , although the difference was clinically trivial, the uncertainty around this estimate ranged from similar to better in favour of the dense regimen (MD 3.7 W, 95% CI -5.6 to 13.0). Due to uncertainty, further research is needed to clarify the relative effects of different training densities on submaximal cardiorespiratory fitness biomarkers.

The evaluated nutritional markers did not clinically change after prehabilitation in either group, with trivial between-group differences. These measures have not been previously reported in lung cancer patients but the results are consistent with the effect of a similar prehabilitation program in patients with scheduled colorectal surgery.²⁹

To interpret the effects on quadriceps strength, the smallest worthwhile effect of 7.5 Nm (established in patients with COPD³⁰) could be used. Against this threshold, the between-group difference of 0.3 Nm and 4.7 Nm were both clinically trivial (Table 2). The estimates were, however, very imprecise; on the left side, for example, the 95% CI spanned clinically worthwhile differences in either direction. Although there are no data in the literature for NSCLC patients, a meta-analysis reported that healthy untrained subjects benefit more from higher training frequencies with moderate loads rather than low training frequencies with higher resistive load.³¹ Due to uncertainty, further research is needed to clarify the relative effects of more-frequent resistance training on peripheral muscle strength during prehabilitation. Regarding inspiratory muscle strength measured with MIP, a smallest worthwhile effect threshold of 17.2 cmH₂O was used.³² The relative improvement in MIP can be judged as clinically similar because both the main estimate (-0.7 cmH₂O) and its confidence interval (-9.8 to 8.4) are smaller in magnitude than the smallest worthwhile effect. It is worth noting that in addition to the supervised exercise training sessions, participants in both groups also had the opportunity to perform daily unsupervised inspiratory muscle training. Therefore, the control group had the

opportunity to perform more inspiratory muscle training sessions due to the longer duration of the program; however, this did not produce clinically relevant increases in the amount of improvement in maximal inspiratory pressure.

We were concerned that participants undertaking an outpatient training program 5 days per week might experience a reduction in quality of life and/or adhere poorly to the prescribed sessions. Both groups underwent an identical total prescribed training load with a similar rate of adherence: 86% in the experimental group and 87% in the control group. The study produced very imprecise estimates about the relative effects of the two prehabilitation regimens on quality of life. For example, the confidence interval around the mean between-group difference in the EORTC-QLQ-C30 LC13 subscale spanned the published smallest worthwhile effects of a 3-point increase and a 6-point decrease.³³ Therefore, we were unable to draw any clear conclusion about whether and by how much one regimen might be superior to the other for quality of life. This requires further clarification with future trials. However, the current results confirm that it is possible to obtain physiological benefits in a short period of time with a condensed program without generating adverse events or a negative effect on adherence.

The positive effects of prehabilitation in patients scheduled for lung resection for NSCLC are increasingly being scientifically supported; however, these programs are very heterogeneous.⁵ One-week programs with twice-daily training and multimodal management have recently been described, but they involve hospitalisation,^{34,35} which cannot be generalised to a large number of patients in most healthcare systems. The durations of supervised outpatient programs described in prospective trials are ≥ 3 weeks, and training frequencies range from three to five times per week.⁵ Since patients with risk factors frequently require a larger set of examinations, we observed locally that those who benefited from prehabilitation did not have a longer surgical delay, while reducing the incidence and the severity of postoperative complications.³⁶ In order to facilitate the implementation of such prehabilitation programs, this must be considered in parallel with their diagnosis in a global oncological care pathway. As the flowchart shows, a sizeable proportion of patients referred for prehabilitation do not ultimately

Table 2
Mean (SD) of groups, mean (SD) within-group difference and mean (95% CI) between-group difference for outcome measures.

Outcome	Groups				Within-group difference		Between-group difference
	Baseline		Preoperative		Preoperative minus baseline		Preoperative minus baseline
	Exp (n = 18)	Con (n = 18)	Exp (n = 18)	Con (n = 18)	Exp	Con	Exp minus Con
Cardiorespiratory exercise testing							
$\dot{V}O_{2peak}$ (ml/kg/min)	12.9 (3.3)	14.1 (3.2)	15.3 (3.6)	15.3 (3.7)	2.4 (1.8)	1.2 (2.1)	1.2 (-0.1 to 2.6)
$\dot{V}O_{2VT}$ (ml/kg/min)	9.6 (1.8)	9.9 (1.7)	10.4 (1.9)	10.6 (2.0)	0.8 (2.1)	0.8 (2.0)	0.0 (-1.4 to 1.4)
WR_{peak} (W)	73.9 (19.2)	77.2 (26.4)	85.3 (19.6)	87.5 (31.7)	11.1 ^a (12.3)	9.8 ^a (11.3)	1.3 (-6.4 to 9.0)
WR_{VT} (W)	45.0 ^{a,b} (12.8)	43.0 ^{a,b} (17.4)	50.9 ^{a,b} (14.4)	48.5 ^{a,b} (19.7)	10.4 ^a (17.2)	6.7 ^a (10.3)	3.7 (-5.6 to 13.0)
$\dot{V}E/\dot{V}CO_2$ slope	38.9 ^a (10.4)	39.0 (9.9)	35.5 (6.2)	38.8 (11.0)	-3.8 ^a (8.9)	-0.2 (6.6)	-3.6 (-8.7 to 1.5)
Nutrition							
Body mass index (kg/m ²)	29.5 (6.8)	29.3 (5.1)	29.5 (6.7)	29.5 (5.1)	0.0 (0.5)	0.2 ^a (0.5)	-0.2 (-0.5 to 0.1)
Fat-free mass (%)	66.3 (8.4)	62.2 (8.6)	66.0 (7.9)	62.0 (7.9)	-0.3 (1.5)	-0.1 (2.8)	-0.2 (-1.8 to 1.3)
Muscle strength							
QMVIC left (Nm)	82.7 ^c (20.7)	86.7 (42.6)	91.2 ^c (21.8)	94.9 (39.5)	8.5 (12.5)	8.2 (18.3)	0.3 (-10.8 to 11.4)
QMVIC right (Nm)	76.4 ^c (21.7)	83.5 (43.0)	86.1 ^c (22.4)	89.2 (39.2)	10.4 ^a (14.4)	5.7 (13.8)	4.7 (-2.4 to 11.8)
MIP (cmH ₂ O)	60.9 (16.3)	60.5 (20.6)	70.5 (17.1)	68.4 ^a (24.9)	9.6 (9.3)	10.3 ^a (17.3)	-0.7 (-9.8 to 8.4)
EORTC QLQ-30							
Functional score (0 to 100)	78.3 ^a (11.6)	71.1 (23.0)	86.2 (7.3)	81.9 ^a (17.2)	7.7 (8.9)	11.0 (17.1)	-3.3 (-12.6 to 5.9)
Symptom score (0 to 100)	81.3 ^a (11.7)	82.8 ^a (14.0)	83.0 (12.0)	83.9 ^a (14.1)	1.5 ^a (13.8)	4.0 ^a (12.6)	-2.5 (-11.1 to 6.1)
Global score (0 to 100)	59.3 ^a (22.1)	64.7 ^a (20.0)	71.3 (14.1)	74.1 ^a (16.0)	12.5 ^a (25.1)	10.2 ^a (19.1)	2.3 (-12.3 to 16.9)
LC13 score (0 to 100)	85.7 (8.2)	83.6 (12.6)	88.0 (8.2)	84.9 ^a (13.3)	2.3 (5.2)	1.4 (7.5)	1.4 (-8.7 to 6.5)

Small anomalies in subtraction in the unconverted data are due to the effects of rounding. Shaded row = primary outcome.

Con = control group, EORTC QLQ-30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire, Exp = experimental group, FEV₁ = forced expiratory volume in 1 second, FEF₂₅₋₇₅ = forced expiratory flow at 25 to 75% of the expiratory volume, FVC = forced vital capacity, LC13 = lung cancer-specific module of the EORTC QLQ-30, MIP = maximal inspiratory pressure, QMVIC = quadriceps maximum voluntary isometric contraction, $\dot{V}E/\dot{V}CO_2$ slope = linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$), $\dot{V}O_{2peak}$ = peak oxygen uptake, $\dot{V}O_{2VT}$ = oxygen uptake at ventilatory threshold, WR_{peak} = peak power on cycle ergometer, WR_{VT} = power at ventilatory threshold.

^a Data converted.

^b n = 17.

^c n = 16.

undergo their planned surgery. Routine referral of all NSCLC patients to prehabilitation programs may incur expenditure on patients whose planned surgery does not eventuate. However, the clinical benefits that were intended to overcome the surgical and

postoperative stress will help a patient to better tolerate other therapeutic strategies, as suggested by the positive effects of exercise training on exercise capacity and disease-specific health-related quality of life for patients with advanced lung cancer.³⁷ Future work should consider long-term follow-up and analysis of cost-effectiveness in order to answer this issue.

Our current results show that prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with NSCLC. This could increase the number

Table 4
Characteristics of participants' surgery.

Characteristic	All (n = 26)	Exp (n = 13)	Con (n = 13)
Surgical approach, n (%)			
VATS/RATS	20 (77)	12 (92)	8 (62)
thoracotomy	6 (23)	1 (8)	5 (39)
Type of surgery, n (%)			
pneumonectomy/bilobectomy	3 (12)	0 (0)	3 (23)
lobectomy	12 (46)	5 (39)	7 (54)
wedge/segmentectomy	11 (42)	8 (62)	3 (23)

Con = control group, Exp = experimental, RATS = robot-assisted thoracoscopic surgery, VATS = video-assisted thoracoscopic surgery.

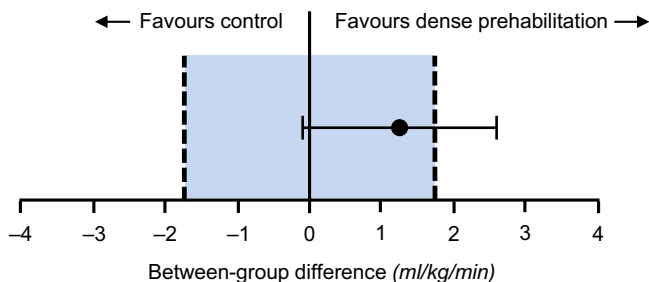


Figure 2. Mean between-group difference (95% CI) between the experimental group (dense regimen; five sessions/week for 3 weeks) and the control group (standard regimen; three sessions/week for 5 weeks) in change in peak oxygen uptake ($\dot{V}O_{2peak}$) after the prescribed 15-session prehabilitation program. The two-sided 95% CI (-0.1 to 2.6) spanned from close to 0 (no between-group difference) to greater than the pre-specified smallest worthwhile effect of 1.75 ml/kg/min, indicating similar or better benefits from the dense training regimen relative to the control regimen.

Table 5
Postoperative complications.

Complications	Exp (n = 13)	Con (n = 13)
Type, n		
subcutaneous emphysema	0	1
arrhythmia	0	0
air leak > 5 d	1	0
pneumonia	1	1
atelectasis	0	1
ARDS	0	1
Clavien-Dindo classification, n		
I	0	1
II	2	1
IIIa	0	1
IVa	0	1

ARDS = adult respiratory distress syndrome, Con = control group, Exp = experimental group.

of patients with postoperative risk who can be referred for prehabilitation, despite short presurgical delays.

This study had several strengths, including compliance with the pre-registered protocol, concealed allocation, blinded assessment of the primary outcome, intention-to-treat analysis and reporting according to the CONSORT recommendations. Moreover, we provided a clinical interpretation of each estimate based on the relative mean between-group difference and its confidence interval. One limitation was that the physiological mechanisms behind the obtained benefits remain to be explored. For both training modalities, the duration can be considered as short with regards to the magnitude of physiological modifications mostly observed in longer periods of rehabilitation in patients with COPD.³⁸ Improvements in muscle strength are described as a combination of neurological and morphological factors, with a predominance of neurological factors during the first weeks of training.^{39,40} However, there are no electromyographical or biological data to support this assumption. In terms of external validity, the results can be transposed to outpatient prehabilitation programs; however, their validity with regard to inpatient or home-based programs is limited.

In conclusion, the effects of a prehabilitation program of 15 sessions performed in a 3-week regimen with five sessions per week are similar to or better than the effects of a 5-week regimen with three sessions per week on cardiorespiratory fitness in patients with NSCLC. Further work is needed to clarify whether such a condensed prehabilitation program leads to superior benefits in people with scheduled lung resection surgery for NSCLC.

What was already known on this topic: Lung resection is currently the recommended curative treatment for early-stage non-small cell lung cancer. Prehabilitation (which involves exercise, education and support) is increasingly being used to physically prepare these patients for surgery. The prehabilitation regimen must consider both the need for rapid surgery and the need to provide a sufficient training load to obtain physiological benefits and thereby reduce the risk of postoperative complications.

What this study adds: In people with non-small cell lung cancer, a course of prehabilitation can be provided with greater frequency in a shortened regimen, with similar or better efficacy. This could increase the number of patients with postoperative risk who can be referred for prehabilitation, despite short presurgical periods.

Footnotes: ^a Ergoline 900, GmbH, Bitz, Germany.

^b Vyntus CPX, Vyair Medical, Mettawa, USA.

^c Masterscreen, Jaeger, Wittsburg, Germany.

^d POWERbreatheKH2, HaB International Ltd, Southam, UK.

^e Bodystat® 1500MDD, Bodystat, Douglas, Isle of Man, UK.

^f MicroFET2®, Hoggan Health Industries, West Jordan, USA.

^g GraphPad Prism 8 software, GraphPad Software, San Diego, USA.

eAddenda: Table 3 can be found online at <https://doi.org/10.1016/j.jphys.2021.12.010>.

Ethics approval: The French ethics committee SUD-EST IV approved this study (n° 19.01.29.69434). All participants gave written informed consent before data collection began.

Competing interests: All the authors have completed the ICMJE uniform disclosure form. Francis-Edouard Gravier declares personal fee from Asten Santé unrelated to this study. Tristan Bonnevie declares receiving grants from Fisher and Paykel, a personal fee from Asten Santé and another from KerNel Biomedical, both unrelated to this study. None of the authors have any conflicts of interest to declare.

Source(s) of support: This work was supported by ADIR Association.

Acknowledgements: We thank Johanna Robertson for language assistance.

Provenance: Not invited. Peer reviewed.

Correspondence: Francis-Edouard Gravier, Pulmonary Rehabilitation, ADIR Association, Rouen, France. Email: f.gravier@adir-hautenormandie.com

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
- Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e278S–e313.
- Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. 2009;34:17–41.
- Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e166S–e190S.
- Gravier FE, Smondack P, Prieur G, Médinal C, Combret Y, Muir JF, et al. Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis. *Thorax*; 2021.
- Gravier FE, Bonnevie T, Boujibar F, Médinal C, Prieur G, Combret Y, et al. Effect of prehabilitation on ventilatory efficiency in non-small cell lung cancer patients: a cohort study. *J Thorac Cardiovasc Surg*. 2019;157:2504–2512.e1.
- Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhon MA, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2015;192:1373–1386.
- Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
- Debigare R, Maltais F, Whittom F, Deslauriers J, LeBlanc P. Feasibility and efficacy of home exercise training before lung volume reduction. *J Cardiopulm Rehabil*. 1999;19:235–241.
- Puhan MA, Schunemann HJ, Frey M, Scharplatz M, Bachmann LM. How should COPD patients exercise during respiratory rehabilitation? Comparison of exercise modalities and intensities to treat skeletal muscle dysfunction. *Thorax*. 2005;60:367–375.
- Ge X, Wang W, Hou L, Yang K, Fa X. Inspiratory muscle training is associated with decreased postoperative pulmonary complications: evidence from randomized trials. *J Thorac Cardiovasc Surg*. 2018;156:1290–1300.e5.
- Pierre S, Rivera C, Le Maître B, Ruppert AM, Bouaziz H, Wirth N, et al. Guidelines on smoking management during the perioperative period. *Anaesth Crit Care Pain Med*. 2017;36:195–200.
- Boden I, Skinner EH, Browning L, Reeve J, Anderson L, Hill C, et al. Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. *BMJ*. 2018;360:j5916.
- Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Brit J Anaesth*. 2018;120:484–500.
- Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(2 Pt 2):S49–S55.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Supplement*. 1993;16:5–40.
- Pompili C, Brunelli A, Xiumé F, Refai M, Salati M, Socci L, et al. Prospective external convergence evaluation of two different quality-of-life instruments in lung resection patients. *Eur J Cardiothorac Surg*. 2011;40:99–105.
- Kyle UG, Bosaes I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. *Clin Nutr*. 2004;23:1430–1453.

19. Beaumont M, Kerautret G, Peran L, Pichon R, Le Ber C, Cabillic M. Reproducibility of strength and endurance measurements of the quadriceps in patients with COPD. *Rev Malad Respir.* 2017;34:1000–1006.
20. Hogrel JY, Payan CA, Ollivier G, Tanant V, Attarian S, Couillandre A, et al. Development of a French isometric strength normative database for adults using quantitative muscle testing. *Arch Phys Med Rehabil.* 2007;88:1289–1297.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205–213.
22. Chow S, Shao J, Wang H. *Sample Size Calculations in Clinical Research.* 2nd Ed. Florida, USA: Taylor & Francis Group, LLC; 2008.
23. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Statist Methods Med Res.* 2018;27:1785–1805.
24. Shi J, Luo D, Weng H, Zeng XT, Lin L, Chu H, et al. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods.* 2020;11:641–654.
25. Streiner D, Geddes J. Intention to treat analysis in clinical trials when there are missing data. *Evid Based Ment Health.* 2001;4:70–71.
26. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Ex.* 2011;43:1575–1581.
27. Brunelli A, Belardinelli R, Pompili C, Xiumé F, Refai M, Salati M, et al. Minute ventilation-to-carbon dioxide output (VE/VCO₂) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg.* 2012;93:1802–1806.
28. Sutherland ER, Make BJ. Maximum exercise as an outcome in COPD: minimal clinically important difference. *COPD.* 2005;2:137–141.
29. Suen M, Liew A, Turner JD, Khatri S, Lin Y, Raso KL, et al. Short-term multimodal prehabilitation improves functional capacity for colorectal cancer patients prior to surgery. *Asia-Pac J Clin Oncol.* 2021.
30. Vaidya T, Beaumont M, de Bisschop C, Bazerque L, Le Blanc C, Vincent A, et al. Determining the minimally important difference in quadriceps strength in individuals with COPD using a fixed dynamometer. *Int J COPD.* 2018;13:2685–2693.
31. Peterson MD, Rhea MR, Alvar BA. Applications of the dose-response for muscular strength development: a review of meta-analytic efficacy and reliability for designing training prescription. *J Strength Cond Res.* 2005;19:950–958.
32. Iwakura M, Okura K, Kubota M, Sugawara K, Kawagoshi A, Takahashi H, et al. Estimation of minimal clinically important difference for quadriceps and inspiratory muscle strength in older outpatients with chronic obstructive pulmonary disease: a prospective cohort study. *Phys Ther Res.* 2021;24:35–42.
33. Hong F, Bosco JL, Bush N, Berry DL. Patient self-appraisal of change and minimal clinically important difference on the European organization for the research and treatment of cancer quality of life questionnaire core 30 before and during cancer therapy. *BMC Cancer.* 2013;13:165.
34. Lai Y, Wang X, Zhou K, Su J, Che G. Impact of one-week preoperative physical training on clinical outcomes of surgical lung cancer patients with limited lung function: a randomized trial. *Ann Translat Med.* 2019;7:544.
35. Lai Y, Su J, Qiu P, Wang M, Zhou K, Tang Y, et al. Systematic short-term pulmonary rehabilitation before lung cancer lobectomy: a randomized trial. *Interact Cardiovasc Thorac Surg.* 2017;25:476–483.
36. Boujibar F, Bonnevie T, Debeaumont D, Bubenheim M, Cuvellier A, Peillon C, et al. Impact of prehabilitation on morbidity and mortality after pulmonary lobectomy by minimally invasive surgery: a cohort study. *J Thorac Dis.* 2018;10:2240–2248.
37. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. *Cochrane Database Syst Rev.* 2019;2:CD012685.
38. Neder JA, Marillier M, Bernard AC, James MD, Milne KM, O'Donnell DE. The integrative physiology of exercise training in patients with COPD. *COPD.* 2019;16:182–195.
39. Folland JP, Williams AG. The adaptations to strength training: morphological and neurological contributions to increased strength. *Sports Med.* 2007;37:145–168.
40. Del Vecchio A, Casolo A, Negro F, Scorcelletti M, Bazzucchi I, Enoka R, et al. The increase in muscle force after 4 weeks of strength training is mediated by adaptations in motor unit recruitment and rate coding. *J Physiol.* 2019;597:1873–1887.

Websites

Research Randomizer. www.randomizer.org