

# BMJ Open Effect of an intensive 3-week preoperative home rehabilitation programme in patients with chronic obstructive pulmonary disease eligible for lung cancer surgery: a multicentre randomised controlled trial

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**To cite:** Laurent H, Galvaing G, Thivat E, *et al.* Effect of an intensive 3-week preoperative home rehabilitation programme in patients with chronic obstructive pulmonary disease eligible for lung cancer surgery: a multicentre randomised controlled trial. *BMJ Open* 2017;**7**:e017307. doi:10.1136/bmjopen-2017-017307

► Prepublication history for this paper is available online. To view please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-017307>).

Received 22 April 2017

Revised 22 September 2017

Accepted 5 October 2017



CrossMark

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## ABSTRACT

**Introduction** Surgery is the standard curative treatment for lung cancer but is only possible in patients with local tumour and preserved exercise capacity. Improving fitness before surgery can reduce postoperative complications and mortality. However, preoperative rehabilitation remains difficult to implement for several reasons. We aim to investigate the effectiveness of an intensive 3-week home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance in patients with chronic obstructive pulmonary disease (COPD) who are eligible for lung cancer surgery.

**Methods and analysis** We designed a multicentre randomised controlled trial. The randomisation sequence will be generated and managed electronically by a research manager independent of assessments or interventions. We will recruit 90 patients with COPD and a diagnosis of lung cancer from four university hospitals. The rehabilitation group (R group) will receive a standardised preoperative home exercise programme for 3 weeks, combining both high-intensity training and usual physical therapy. The R group will perform 15 training sessions over 3 weeks on a cycloergometer. A physical therapist experienced in pulmonary rehabilitation will visit the patient at home and supervise one session a week. The R group will be compared with a control group receiving preoperative usual physical therapy only. The primary outcome will be hospital discharge ability assessed with a 10-item list. Secondary outcomes will be postoperative course (complication rate and mortality) as well as pulmonary function, exercise capacity and quality of life assessed 1 month before and the day before surgery.

**Ethics and dissemination** This protocol has been approved by the French health authority for research (2016-A00622-49) and the research ethics committee/institutional review board (AU1267). Adverse events that occur during the protocol will be reported to the principal investigator. The results will be published in an international peer-reviewed journal.

## Strengths and limitations of this study

- This is a multicentre randomised controlled trial.
- The trial will include a large number of participants (n=90 patients).
- The trial will include patients with chronic obstructive pulmonary disease presenting lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy).
- There is no assessor or patient blinding.

**Trial registration number** NCT03020251.

## INTRODUCTION

Lung cancer is the fourth most frequent cancer in the world but the first cause of cancer-related death worldwide.<sup>1 2</sup> Among treatments, surgery is conducted with a curative intent generally in patients with early TNM (tumour, node, metastases) disease stages (stages I, II and IIIA) and preserved exercise capacity.<sup>3</sup> However, only 25% of patients are considered suitable for surgery because of advanced-stage disease or poor functional status.<sup>4</sup>

Despite the operative risk assessment, the incidence of postoperative respiratory complications and overall complications is respectively 15% and 30% after lung resection for cancer.<sup>5</sup> Patients with a complicated postoperative course have a longer hospital length of stay, more frequent stay in an intensive care unit (ICU) and higher mortality rate.<sup>5</sup>

Furthermore, peak oxygen uptake ( $VO_{2peak}$ ) is reported to be the strongest independent predictor of surgical complications and survival rates with non-small cell lung cancer (NSCLC).<sup>6</sup> Performance during field tests is equally a major determinant of morbidity and mortality after lung resection.<sup>6</sup> Surgery itself leads to a 13%–28% decrease in  $VO_{2peak}$ ,<sup>7</sup> lasting up to 24 months after resection.<sup>8</sup> The existence of chronic obstructive pulmonary disease (COPD) or cardiovascular comorbidities may further decrease  $VO_{2peak}$ .<sup>7</sup> Chemotherapy and/or radiotherapy are associated with additional impairment of exercise capacity.<sup>8</sup>

The beneficial effects of preoperative rehabilitation are objectified by physiological parameters and surgical outcomes, but the level of evidence is deemed insufficient.<sup>9–11</sup> A recent Cochrane review emphasised the disparities between studies and the need for larger high-quality randomised controlled trials (RCT) in this area.<sup>11</sup> Future research must focus on patient-tailored exercise programmes and determine the influence of coexisting comorbidities on outcomes. Moreover, preoperative exercise therapy and exercise modalities including timing and training volume should be detailed and compared. Preoperative home rehabilitation should be particularly investigated to make readaptation programmes more accessible and to reduce costs for inpatient and/or outpatient programmes. The feasibility, safety and effectiveness of preoperative interventions performed in a home setting for a short period have been demonstrated.<sup>12 13</sup>

Additionally, rehabilitation programmes are not yet substantially developed, primarily because of fear of tumour progression by delaying surgery and the difficulty in organising such programmes or the lack of experienced physical therapists.

In light of the current literature, we implemented a multicentre RCT of an intensive 3-week preoperative home rehabilitation programme for patients with COPD eligible for lung resection. We aim to investigate the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance.

## METHODS

### Setting

This prospective, multicentre, open-label RCT will be conducted in four French university hospitals.

### Participants

#### Inclusion criteria

We will include patients with the following conditions:

- ▶ Lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)
- ▶ COPD stages from 2 to 4 by the Gold classification ( $FEV_1/FVC < 70\%$ ,  $FEV_1 < 80\%$  of predicted value)

- ▶ Exertional dyspnoea stage mMRC (modified Medical Research Council)  $\geq 1$
- ▶ Receiving written information and giving signed consent
- ▶ Affiliated with the French social health insurance

#### Non-inclusion criteria

We will exclude patients with the following conditions:

- ▶ COPD stage 1 by the Gold classification ( $FEV_1 \geq 80\%$  of predicted value)
- ▶ Contraindication to surgery based on the initial cardiopulmonary exercise test (CPET)<sup>6</sup>
- ▶ Cardiac or vascular contraindication to the rehabilitation programme
- ▶ Living alone at home (to ensure safety during the training sessions)
- ▶ Under ventilator assistance at home (oxygen therapy or non-invasive ventilation (NIV))
- ▶ Exercise hypoventilation ( $PaCO_2 > 45$  mm Hg)
- ▶ Cognitive impairment
- ▶ Legally incapacitated
- ▶ Pregnancy

#### Details of the intervention and control

##### Rehabilitation group

The rehabilitation group (R group) will undergo both a standardised preoperative high-intensity training programme performed at home and standardised physical therapy sessions according to usual care. Over 3 weeks, the patients will perform 15 sessions of rehabilitation (5 days/week) including 1 supervised session performed per week. The cycloergometer will be installed by the service provider who will organise home care in each centre. These training sessions will be supervised by physical therapists familiar with these programmes. The study will not lead to delay in the treatment and the surgical management.

The rehabilitation programme will involve endurance cycloergometer training with heart rate (HR) monitoring.

The first week of training (W1) will consist of a continuous endurance training regime. W1 will allow for assessing the patient's ability to complete the training course and to teach them how to perform it well. The session will include a 5 min warm-up cycloergometer workload fixed to the ventilatory threshold determined during the CPET or at 60% of maximum workload, if the ventilatory threshold was not detectable. The exercise session will last at least 30 min, which can be separated by rest periods.

Weeks 2 and 3 of training (W2 and W3) will consist of a high-intensity interval training regime. The reduced volume of training and shorter session duration required with high-intensity interval training to obtain physical benefits versus continuous training should be more acceptable for patients still engaged in several preoperative exams and preoperative care.<sup>14</sup> The longer rest period between each high-intensity interval training session will optimise recuperation time and favour adherence.<sup>14</sup> The

course of high-intensity sessions will be at least 10 repetitions of 30 s at maximum workload and 60 s at the ventilatory threshold level.

The intensity of the exercise and number of repetitions will be adjusted weekly to maintain the targeted HR within 5 beats/minute.

A physical therapist experienced in pulmonary rehabilitation will visit the patient at home and supervise one session per week (at the beginning of each of the 3 weeks: the 1st, 6th and 11th exercise sessions). The therapist will check the initial intensity and progression of the training sessions. Non-supervised sessions will be performed during the week and not during the weekend to allow for email or phone contact with the physical therapist. The patient will complete a diary to collect the duration and intensity of the cycling exercise, mean HR and number of repetitions. We will record the number of exercise session(s) performed and the reason(s) for not performing exercise.

The rehabilitation programme will also include muscle strengthening exercises for upper arms and standardised usual physical therapy.

Upper arm exercises will be performed on the same days after the cycling exercise. A rest period will be respected according to patients' needs between the endurance and the strength training workouts. Shoulder (deltoid, pectoral and dorsal muscles), elbow (biceps and triceps muscles) and wrist (flexors and extensors muscles) muscles will be trained with elastics or dumbbells. For each muscle groups, 3–5 sets of 8–10 repetitions will be performed starting with the lowest resistance. Depending on the patient perception, the resistance will be increased.

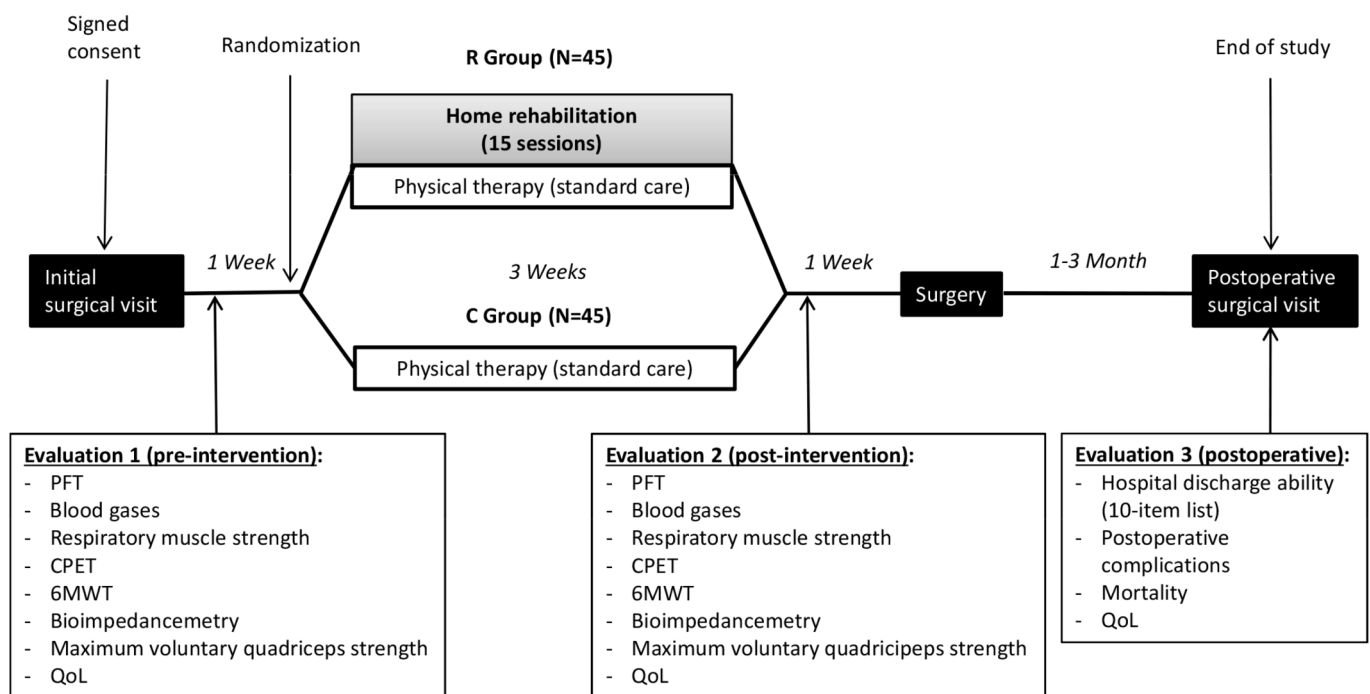
### Control group

A control group (C group) will perform 15 standardised preoperative physical therapy sessions according to usual care. The sessions will consist of 30 min of standardised preoperative physical therapy performed 5 days/week for 3 weeks. They will be standardised with a written prescription and will include airway clearance techniques, deep breathing exercises emphasising inspiration and thoracic stretching. According to current recommendations, the C group will be advised to be physically active.

### Primary and secondary outcome measures and assessment point

Measurements are presented in figure 1. The primary outcome will be hospital discharge ability assessed by a 10-item list. The secondary outcomes will be postoperative course (complication rate and mortality), pulmonary function, exercise capacity and quality of life (QoL). Surgical complications and survival rate with NSCLC are predicted by  $VO_{2peak}$ , a surrogate of patient fitness.<sup>6</sup> Thus, postoperative morbidity should be improved by the exercise training programme.<sup>9 10</sup>

Participants will undergo all assessments in the physiology laboratory on the same day so as to limit transport and fatigue. Baseline assessments will be performed 1 month before surgery (preintervention or first evaluation) and will be repeated the day before surgery (postintervention or second evaluation). To ensure reproducibility of the assessments, the order will be standardised: pulmonary function tests (PFT), maximal respiratory pressure measurements, CPET, bioimpedancemetry, maximum voluntary isometric quadriceps strength measurement, 6 min walk test (6MWT) and



**Figure 1** Design and outcomes. 6MWT, 6 min walk test; CPET, cardiopulmonary exercise test; PFT, pulmonary function test; QoL, quality of life.

**Box 1 The 10-item list to assess the hospital discharge ability****The criteria considered for hospital discharge ability will be as follows:**

- ▶ No chest tube for at least 24 hours
- ▶ Autonomy for feeding
- ▶ Autonomy for rising from bed
- ▶ Autonomy for toilet
- ▶ Autonomy for urinating and defecating
- ▶ Patient able to walk (two lanes 30 m) without desaturation <90% on room air
- ▶ Patient able to go up and down one flight of stairs without desaturation <90% on room air (except handicap in which we consider the return to preoperative status)
- ▶ Satisfactory healing (parietal, thoracic and bronchopulmonary)
- ▶ No infusion
- ▶ No oxygen therapy

QoL. The rest period will be respected according to patients' needs.

**Primary outcome**

We will consider hospital discharge ability assessed by a 10-item list that reflects clinical assessments. Our 10-item list assessing hospital discharge ability was developed by a panel of therapists including thoracic surgeons, physiologists, a physical medicine physician and physical therapists. We considered this outcome to be more relevant than true hospital length of stay, which is affected by circumstances non-related with patient condition (eg, possibility or not for discharge during the weekend, therapeutic care facilities at home, transfer to a rehabilitation centre). The period considered for discharge ability will be the interval between the day of surgery (D0) and the day (Dn) when the 10 items are satisfied (box 1). It will be recorded daily by the therapists of the surgical staff in charge of the patient.

**Secondary outcomes****Postoperative course**

The postoperative course will be assessed daily by the therapists of the surgical staff in charge of the patient and by information from the patient's file. We will record the number of postoperative complications (pulmonary, cardiovascular, infectious and general—see box 2 for respective definitions<sup>15 16</sup>) observed during the stay in surgery or ICU departments, mortality rate, hospital length of stay, chest tube duration, number of NIV sessions, ICU length of stay and reasons.

**Pulmonary function test**

The test will determine static pulmonary volumes and flow rates (flow/volume curve) according to international recommendations by use of a body plethysmograph (Bodybox Jaeger CareFusion, USA).<sup>17</sup> A measure of the alveolar-capillary diffusion capacity for carbon monoxide will involve the apnoea method. All measurements will be expressed as a percentage of reference

**Box 2 Definitions for postoperative complications****Respiratory postoperative complications:**

- ▶ Atelectasis: systematised ventilatory disorder objectified by chest radiography requiring enhanced management such as additional physical therapy sessions, bronchoscopy associated or not with non-invasive ventilation (NIV), maintenance or transfer to an intensive care unit (ICU)
- ▶ Significant bronchial congestion characterised by difficult or spontaneous expectoration of bronchial secretions requiring enhanced management such as additional physical therapy sessions, bronchoscopy with or without NIV, maintenance or transfer to an ICU
- ▶ Bronchospasm: occurrence or aggravation of dyspnoea, wheezing at auscultation requiring a specific treatment
- ▶ Respiratory failure requiring management in an ICU for NIV or intubation

**Cardiovascular postoperative complications:**

- ▶ Pulmonary embolism proven by angio-CT scan
- ▶ Acute coronary syndrome
- ▶ Circulatory failure defined by the need for specific inotropic treatment
- ▶ Rhythm disorder requiring specific treatment

**Infectious postoperative complications:**

- ▶ Tracheobronchial infection, suspicion of pulmonary infection requiring antibiotic treatment, fever >38.5°C, dirty sputum, hyperleukocytosis >10 000/mm<sup>3</sup>, dubious radiological image, absence of pathogenic germs after culture of sputum and/or endobronchial samples
- ▶ Postoperative pneumopathy: pulmonary infection requiring specific antibiotic treatment due to the presence of a pathogenic germ found after culture of sputum and/or endobronchial samples, associated with at least two other signs (a fever >38.5°C, dirty sputum, hyperleucytosis >10 000/mm<sup>3</sup>, dubious radiological image)
- ▶ Pneumopathy considered to be nosocomial (occurring after the fifth postoperative day)
- ▶ Pleuritis requiring puncture or redrainage for lobectomies

**Other postoperative complications:**

- ▶ Empyema
- ▶ Bronchopleural fistula
- ▶ Other (eg, urinary tract infection, bleeding)

values.<sup>18</sup> Arterial blood gases (PaO<sub>2</sub>, PaCO<sub>2</sub> and pH) at rest will be measured by arterial sampling or arterialisated capillary sampling at the ear lobe.<sup>19</sup> Maximum respiratory pressures (inspiratory and expiratory pressures at mouth, and nasal inspiratory pressure) will be measured in accordance with the American Thoracic Society and European Respiratory Society recommendations<sup>20</sup> and compared with predicted values.<sup>21</sup>

**Cardiopulmonary exercise test**

The patient will perform a standardised incremental test following the American Thoracic Society and American College of Chest Physician guidelines.<sup>22</sup> The test will be performed on a cycleergometer until exhaustion, with continuous recording by 12-lead ECG and breath-by-breath expired gas analysis (CPX MedGraphics, St Louis, USA).<sup>22</sup> The workload increments will be defined

according to predicted maximal power output ( $W_{max}$ ), with a first stage of warm-up corresponding to 30%  $W_{max}$  and 10 following stages to complete the test in 12–15 min. The ventilatory threshold will be determined by the Beaver method.  $W_{max}$  and  $VO_{2peak}$  will be measured at the end of the last exercise level maintained for at least 30 s. Symptoms will be rated on a 10-point Borg scale. Blood gases will be measured at the end of the test. Reference values for exercise testing values will be from Jones.<sup>23</sup>

#### *6 min walk test*

The 6MWT will be conducted according to the American Thoracic Society and European Respiratory Society recommendations in 30 m corridor.<sup>24</sup> Patients will be instructed to cover the longest distance possible in 6 min with or without stopping. During the test, only standardised encouragement will be given to the patient. Pulsed oxygen saturation ( $SpO_2$ ) and HR will be measured continuously during the test and recorded each minute with a digital oximeter. The absolute and relative distance (6MWD),  $SpO_2$ , HR, rating of modified dyspnoea Borg scale, walking duration if cessation occurs before 6 min and reasons for this cessation will be recorded. Distance will be compared with predicted values.<sup>25</sup> A rest duration of at least 45 min will be respected between CPET and 6MWT.

#### *Bioimpedancemetry*

Body composition will be assessed by a multifrequency bioelectrical impedance analysis under standardised conditions (Bodystat impedancemeter, UK).<sup>26–28</sup> The patient will be placed in a supine position for determining fat-free mass, dry fat-free mass and fat mass.

#### *Maximum voluntary isometric quadriceps strength*

The patient will sit on a recumbent chair (lower limb training bench) with slight kyphosis and arms crossed over the chest.<sup>28 29</sup> The dominant lower limb will be tested with the knee placed at 90° flexion and a force gauge (Dynatrac strain gauge, Electronic Conseil, France) attached to the ankle. The instruction provided by an experienced assessor will be standardised to obtain maximal contraction. The sustained time of contraction will be 5 s each, and a resting period of 60 s will be respected between each test. The first two attempts will be learning ones. A minimum of 4 and a maximum of 10 attempts will be made to ensure three values varying less than 10%. The maximum value obtained will be recorded. Strength will be compared with predicted values in kilograms.<sup>30</sup>

#### *Quality of life*

We will record QoL with two validated questionnaires for patients with lung cancer. Cancer-related QoL will be assessed by the self-reported EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) including the lung cancer-specific questionnaire QLQ-LC13.<sup>31</sup>

#### *Feasibility and safety*

To evaluate the feasibility of this protocol, we will consider recruitment and adherence rates.<sup>13</sup> Recruitment rate will be defined as the ratio of patients who agree to participate in the study to those who are eligible. Adherence rate will be defined as the ratio of the number of completed training sessions to the number of expected sessions. Adherence will be considered acceptable with performance of 11 of the 15 expected exercise sessions. Adverse events will be systematically tracked during the study period and follow-up.

#### **Ethics**

Recruitment will be conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trials) recommendations for non-pharmacological trials.<sup>32 33</sup> The same applies for the implementation of changes introduced by amendments. All patients will receive an information form and be required to provide their written consent before entering this study protocol and performing any specific procedure. After the first surgical visit and the verification of eligibility, patients eligible for this protocol will be asked to participate. Patients agreeing to participate and having signed informed consent will be directed to the physiology lab for the first assessment visit (preintervention) before being assigned to one of the two study groups.

Pursuant to the provisions concerning the confidentiality of data that are available to persons responsible for quality control of biomedical research and pursuant to the provisions on confidentiality of information, persons with direct access will take all necessary precautions to ensure the confidentiality of information in particular as regard to the identity of patient and to results achieved. For biomedical research or its outcome, the data collected on people who are suitable and transmitted to the sponsor by the investigator will be made anonymous.

#### **Randomisation and allocation procedures**

Randomisation performed after the recruitment procedure will involve a 1:1 ratio, stratified by centre, centralised and in blocks of 5. The randomisation sequence will be generated and managed electronically by a research manager independent of assessments or interventions. Allocation will be transmitted through emails sent to all assessors and therapists involved. Allocation concealment is not possible in such an exercise training trial, and especially in a multicentre study, the physical evaluation and intervention could not be blinded.

#### **Masking and blinding**

In such a clinical experiment, blinding is not possible for patients and therapists or assessors. However, the C group receiving only usual care will allow for demonstrating the beneficial effect of the intervention in the R group. To limit bias, we will ensure that assessors and therapists will be different during the trial period. Moreover, we will ensure that participants do not meet each other.

### Anticipated date of trial commencement and completion

The study started in April 2017 and will be completed in July 2019. The enrolment period is 24 months and patient's participation duration is 3 months.

### Statistical analysis including sample size calculation

Previous studies found a 4-day reduction in length of stay in patients completing an exercise training programme compared with usual care.<sup>34 35</sup> We chose a more conservative effect of the intervention. Our hypothesis is based on a one-sided decrease of 2 days' duration of hospital length of stay and considering an SD of 3 days. With 90% power and a one-sided 5% type 1 error, 39 patients per group are required. Given a risk of dropout or incomplete programme adherence (less than 11 sessions performed), we plan to increase the sample by 15% (ie, 45 patients per group (total number=90 patients)).

The analysis will be performed according to the intent-to-treat principle. Patients' characteristics per allocation group will be described by means, SD, and range for quantitative outcomes or median and interquartile intervals with non-Gaussian distribution. For categorical parameters, counts and frequencies will be reported. The balance of main clinical parameters between allocation groups will be studied to verify randomisation efficacy. The equilibrium of missing data will be checked to assess whether any attrition bias could lower the quality of conclusions. The primary outcome being hospital discharge ability, Student's t-test (unpaired) or Kruskal-Wallis H-test and Mood test (in case of abnormal distributions and/or heteroscedasticity) will be used to test the intergroup difference. Other quantitative outcomes (PFT, maximal respiratory pressures, CPET, body composition, maximum quadriceps voluntary strength, 6MWD and QoL) will be analysed by using the same tests. The intergroup difference for postoperative complication and mortality rates will be tested by  $\chi^2$  test or Fisher's exact test. Multivariate analysis of factors affecting hospital discharge ability or morbidity/mortality will involve analysis of variance (mixed model) and logistic regression, respectively. The standard two-sided  $p < 0.05$  will be used as significance cut-off. Clinsight software will be used for randomisation and data management (Ennov Clinical V.7.5, Ennov Group, Paris, France), and SEM software for statistical calculation.<sup>36</sup>

### Data collection, quality management and dissemination

Data from the study will be collected by the clinical research associate (CRA) in charge of the study, under the responsibility of the physician coordinator of the study. For each patient enrolled, an electronic case report form must be completed and signed by the principal investigator or authorised delegate from the study staff. Data entry will be in Ennov Clinical. A CRA mandated by the promoter will ensure the successful completion of the study, the collection of data generated in writing, documentation, record and report in accordance with the standard operating procedures and

the good clinical practice and current French laws. The data set will be the property of the sponsor. However, the principal investigator, the project manager and the statistician (data monitoring committee) will have full access to the final data set. The results will be presented at an international congress and published in a peer-reviewed journal.

### DISCUSSION

An improvement in physical fitness and decrease in complications were well shown after an exercise programme in this setting.<sup>9-11</sup> Improving the preoperative physical fitness in this specific population should limit the loss of postoperative respiratory function and exercise ability.<sup>12 37</sup> This is the real challenge of all staff taking care of these patients. The beneficial effect of a short preoperative rehabilitation programme on length of stay after lung cancer resection in patients with COPD remains to be robustly demonstrated as emphasised by the recent Cochrane review.<sup>11</sup> Other studies are needed to demonstrate that patients who undergo preoperative rehabilitation have better QoL and longer survival after lung surgery.<sup>12</sup>

Mechanisms underlying decreased hospital discharge ability or postoperative complication rate need further investigation.<sup>11</sup> Nevertheless,  $VO_{2peak}$  is the strongest independent predictor of surgical complications and survival rates in NSCLC.<sup>6</sup> We hypothesise that increasing presurgical physical fitness and  $VO_{2peak}$  should decrease hospital length of stay, postoperative complications and mortality in this population. Moreover, recent systematic reviews demonstrated these important outcomes.<sup>9-11</sup> Even more, a home-based programme should improve adherence to the programme without delaying the surgical treatment and limit costs. In the future, it could permit to make eligible to surgery a more important number of COPD patients with NSCLC. Despite a short time course, the effectiveness of preoperative physical conditioning would increase and could explain the benefits on morbidity.

The safety and feasibility of such a standardised preoperative programme conducted at home should be strengthened because to the best of our knowledge, only an uncontrolled trial has been published to date.<sup>13</sup>

Our study has some strengths. This is the first multi-centre RCT with a large sample (n=90 patients) implementing short course preoperative high-intensity training at home in COPD patients with NSCLC. All the lung resection procedures are considered: lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy. We acknowledge that the main limitation of our study is that patients and assessors will not be blinded to the intervention arm. However, we will ensure that assessors and therapists will be different during the trial period. Concerning exercise training, blinding is not worth considering, but the comparison to the C group should demonstrate the effectiveness of the rehabilitation programme. Finally, we cannot exclude that as part of the rehabilitation programme the visits of the physical

therapist could provide psychological support to patients and would help with the improved condition before surgery.

The results of this original multicentre RCT of home-based rehabilitation could strengthen the effectiveness of a short intensive home-based intervention for patients with COPD eligible for lung cancer surgery. They could change practice before lung cancer resection thereby enabling preconditioning without delaying surgical treatment.

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**Acknowledgements** We warmly thank the Elivie society for organising the home training supervision.

**Contributors** HL, RR, FK, FC and MF designed the study and wrote the protocol. GG, ET, EC and SA read and corrected the drafts. HL, FK, FC, MF, GG and ET collected and managed the data. HL, FK, FC, MF, GG and ET analysed and interpreted the data.

**Funding** This work was supported by the French Health Ministry (Programme Hospitalier de Recherche Clinique Interrégional de Rhône-Alpes Auvergne).

**Competing interests** None declared.

**Ethics approval** The study protocol was approved by the French regulatory authority for research (Agence Nationale de Sécurité du Médicament et des Produits de Santé, registration no. 2016-A00622-49) and the Research Ethics Committee/ Institutional Review Board (REC/IRB: Comité de Protection des Personnes Sud-Est VI France, Human Research Ethics approval no. AU1267).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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