Study Protocol

Project title:
Effects and mechanisms of online delivered singing training (Singing for Lung Health) vs usual care in patients with persistent symptoms 6-18 months after surgical resection for non-small cell lung cancer (NSCLC) – a multi-centre cross-over randomised controlled trial

Approved by:
The Scientific Ethical Committee Region Zealand, Denmark

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1. Short summary

People who have undergone curative surgery for non-small cell lung cancer (NSCLC) often experience reduced quality of life (QoL), a high burden of symptoms, and physical deconditioning. Current Danish rehabilitation offers are heterogeneous and inconsistent and not tailored to the specific needs of this population. Additionally, some patients continue to suffer from persistent physical symptoms months or even years after surgery, yet no targeted support is currently available for them.
Singing - delivered as a structured form of training - has shown benefits in improving both physical and psychological outcomes in individuals with chronic obstructive pulmonary disease (COPD). Although singing has not yet been studied in NSCLC patients, the two conditions share overlapping symptoms and characteristics. Therefore, this study aims to explore whether a singing-based intervention can help reduce symptom burden and improve physical function and QoL in NSCLC patients 6 to 18 months post-surgery. To test this, we will conduct a multi-centre, cross-over randomised controlled trial (RCT), comparing a singing intervention to usual care. Given that travel and distance often pose significant barriers to participation, the intervention will be delivered online.

2. Background

2.1 Prevalence and impact

Lung cancer is now the most common cancer in Denmark (incidence 5000 new cases/year), representing 13% of total cancer incidences. At the same time, 5-year survival is increasing along with the prevalence of long-term survivors [1–5]. The main curative treatment for non-small cell lung cancer (NSCLC) is surgical resection of low-stage lung cancer i.e., localised disease with no metastatic spread. Curative treatment may also be achieved by stereotactic radiation therapy (low-stage disease) or concomitant radio-chemotherapy (locally advanced disease) [2, 6].

However, compared to age-matched controls, patients with lung cancer have persistently reduced quality of life (QoL), decreased psychological well-being, reduced physical and social activity, deconditioning, symptom clusters (e.g., dyspnoea, cough, pain, fatigue, dysphonia). In addition, many are affected by comorbidities (some, but not all, tobacco-related) [2–4, 7], with a particular frequent overlap between lung cancer and COPD [2, 4, 8].

2.2 Follow-up programme after NSCLC surgery

Usual procedure after NSCLC surgery consists of follow-up consultation with conversation, computed tomography (CT) scan after three months, and e.g., lung function testing. Subsequently, CT scans will be performed every three months in two years (for low stage cancer, however, every six months) and CT scans every six months in the next three years [9].

Besides, the recommended follow-up programme after NSCLC surgery includes rehabilitation with e.g. exercise training, smoking cessation, education, and self-management as key components [2, 4, 8, 10, 11]. The programmes are, however, heterogeneous and there is currently no lung cancer-specific community-based rehabilitation programme available that addresses the long-term decline in physical capacity, QoL, and social activity after curative intended treatment in NSCLC [4, 7, 12].
Most commonly, people after NSCLC surgery are offered a general rehabilitation programme in a municipal setting [7, 12, 13], but may also be referred for e.g., pulmonary rehabilitation (PR), which is a multidisciplinary, multi-faceted, and comprehensive intervention based on

evidence-based activities, recommended by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) to reduce symptoms, increase quality of life, and to optimise functional capacity [2, 4, 14, 15].

It is recommended that the rehabilitation offer for lung cancer includes a combined intervention consisting of aerobic training and strength training, either alone or combined with respiratory muscle training [16]. A Cochrane review (Cavalheri, et al., 2019) concluded high evidence that rehabilitation with exercise training improved physical capacity and physical fitness, and suggested low-moderate evidence regarding improved Health-Related QoL and dyspnoea [17]. Additionally, in 2025, a Core Outcomes Set, based on a Delphi consensus study (Edbrooke, et al., 2025), concluded that critical outcomes are: physical function, HRQoL, breathlessness, activities of daily living, emotional and mental well-being and pain [18]

Our recent study (Kaasgaard, et al., 2024) about availability, type, and content of Danish community-based rehabilitation offers (n=100), confirmed that the rehabilitation programme is offered as heterogeneous models including cancer rehabilitation (across different cancer diseases), individual training, online training, or pulmonary rehabilitation (PR) [19]. Nevertheless, a disease-specific offer was related to improved QoL and to higher satisfaction and experienced relevance [19]. Barriers to offering such model may, however, include lack of attention towards the disease-specific needs, a limited number of lung cancer patients in each municipality, and transportation issues [19].

2.3 Long-term symptom burden after NSCLC surgery

In our recent study [19] we, moreover, found that a large proportion of patients experience persistent symptoms five to six months after their NSCLC surgery and that the symptoms were mostly physiological-oriented, based on a researcher-developed questionnaire: Fatigue (78%), hyper-vigilance (74%), dyspnoea (65%), and pain (47%), although psychological-oriented symptoms were also present: Worry about the future (40%), depressive symptoms (35%), and anxiety symptoms (29%). In addition, 27%, experienced having vocal problems. This pattern was confirmed in our subsequent cross-sectional study on QoL and symptom burden 6-12 months after NSCLC surgery (Kaasgaard, et al., 2025, under preparation for submission (approval numbers Region Zealand: 57069; Southern Region: 24/511. Study protocol available at Open Science Framework: osf.io/vmpft)), based on the The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [20, 21] and clinically relevant cut-off score for any item: ≥ 2 [22], e.g.: Fatigue (58%), sleep disturbances (54%), and dyspnoea (69%).

These findings are in line with the findings in other recent Danish studies that a considerable proportion of patients experience persistent symptoms long-term after their NSCLC surgery, such as fatigue, dyspnoea, pain, and cough [13, 23]. In addition, a systematic review found that a modest, yet significant, proportion of patients experience poor mental health-related QoL after their NSCLC surgery [24] and, moreover, persistent symptoms of dyspnoea and pain have been observed up to one year after surgical treatment in NSCLC patients [7, 23].

Taken together, this implies signs of a neglected population of people who continue to experience persistent symptoms following surgical treatment for NSCLC. Yet, there is no standard offer available to support this subgroup of patients.

2.4 Singing in respiratory disease

Singing has become increasingly popular for people with respiratory diseases [25–28] being an activity which both comprises elements of physiological training and psychosocial aspects [28–31] and, therefore, also seems likely to be able to address the unmet needs of lung cancer patients.

Previous studies have suggested that lung patients gain a physiological training effect from participating in singing training [28–30, 32] and that singing training leads to increased respiratory control, less dyspnoea, improved QoL, and reduced anxiety and depression [26, 33–38]. Moreover, singing is suggested to confer physiological training effects [28–30, 32] with work load equivalent to brisk walk pace [30, 39]. Furthermore, studies report that singing is perceived as a relevant and beneficial activity that improves well-being, and builds joy, meaning, and social cohesion [25, 28, 31, 32, 40, 41]. However, the vast majority of studies have overall mostly been small and heterogenous, though, and with contradictory findings, as clinical studies have widely not been able to confirm reportings of anecdotal-oriented studies [42] and as there is an substantial lack of knowledge about the underpinning mechanisms of singing in people with respiratory diseases [30, 43].

Moreover, there are different approaches to singing in people with respiratory diseases, both in general and used in scientific studies. However, mainly a traditional choir approach is adapted [25–27, 29]. The currently most well-documented, best-practice approach is Singing for Lung Health (SLH) which has been developed within a multidisciplinary healthcare setting in the UK since 2008 [28, 30]. SLH is a disease-specific approach that aims to target the specific challenges in respiratory diseases and provide health-promoting benefits through the use of exercises and songs as tools for purpose and further includes movement and dancing while singing [27, 28, 30–32].

In our recent multicentre-RCT in COPD - Sing-a-Lung 1.0 -, we demonstrated that PR with SLH improved functional capacity and QoL in a dose-response manner and was non-inferior to PR with usual care delivery of PExT [44]. Furthermore, the trial suggested that SLH was related to improved respiratory strength and dyspnoea control [43, 44]. This RCT was conducted within a real-life community-based setting. It was the largest study on singing so far, had sufficient power to detect change (n=270), and, thus, represents a proof-of-concept study [44].

Post-hoc explorations, further, indicated that singing was associated with relevant physiological improvements, e.g., respiratory strength and control, dyspnoea control, and heart-rate response. However, surprisingly, clinically relevant improvement in physical capacity and QoL were not significantly correlated [43].

2.5 Singing in NSCLC?

Singing has not yet been investigated in patients after NSCLC surgery, but a qualitative study exploring impact of group singing for patients with breast or colorectal cancer suggests that singing is a feasible activity that may improve resilience, confidence, and mood, and builds social support [45].

However, given that several epidemiological and common pathogenetic factors are shared between chronic obstructive pulmonary disease (COPD) and NSCLC patients [46] and that the incidence of lung cancer and COPD is often overlapping [2, 4, 8], results from Sing-a-Lung 1.0 are likely to be transferrable specifically to people with lung cancer, and may address important needs of this overlooked group.

However, the limited number of lung cancer patients in each municipality and the heterogeneity of the current rehabilitation offer [19], lead to critical barriers and compromise the feasibility of an RCT equally to the one of Sing-a-Lung 1.0 with participants collected in groups of approximately 10 receiving SLH or PExT in their local community close to their home. Therefore, given that a substantial proportion of patients experience long-term persistent symptoms and given that singing may address these specific symptoms, we aim to focus on this group. Given that there is no programme available to support this patient group, we will compare singing with usual care using a cross-over RCT design. Additionally, we will conduct the study with online delivery of the singing intervention to account for the barriers regarding distance and transportation.

2.6 Online delivery of singing

Previous studies of singing for lung patients have mostly been based on face-to-face delivery, however, a number of studies have also investigated singing for lung patients (or with respiratory-related symptoms) based on online delivery [47–51] and found that online delivery is feasible and well-accepted [47, 48, 51].

3. Aims and Hypotheses

In the main study, we aim to investigate whether a 10 weeks' course of online singing training (delivered as SLH) improves key physiological and psychosocial outcomes, as well as reduces symptom burden compared to usual care in patients who display long-term symptoms 6-18 months after curative intended NSCLC surgery.

In an exploratory study of a sub-cohort, we aim to investigate the underpinning mechanisms of singing compared to usual care, both in NSCLC alone and taking the NSCLC-COPD overlap into account. Specifically, we aim to explore the physiological adaptations and to explore the correlation between objective and subjective improvements.

In the main study, we hypothesise that:
SLH provides relevant and beneficial improvements in both physiological and psychological parameters and is superior to usual care, and.
SLH relieves symptom burden and is superior to usual care.

In the exploratory sub-study, we hypothesise that:
SLH improves physical fitness, oxygenation, and inflammation and is superior to usual care.

4. Materials and Methods

4.1 Study design

We will conduct a cross-over randomised controlled trial in patients with persistent symptoms 6-18 months after NSCLC surgery, i.e., after completion of any municipal rehabilitation offer shortly after surgery. Moreover, we will conduct an exploratory study in a sub-group of participants with additional advanced assessments of the physiological adaptations to singing.

Participants will be randomised 2:1 in blocks of five to either Group 1, receiving 10 weeks' online SLH or Group 2, receiving 10 weeks' usual care followed by – to enhance willingness to participate - 10 weeks' online SLH.

For overview of groups, please see 4.5 Randomisation procedure, and for overview of the overall study, please see Figure 3.

Additionally, we will include a qualitative documentation (in the form of a visual production) on the intervention and on patient perspectives, specifically focusing on the experience of participating in the intervention and how the tools are adapted/integrated, e.g., related to change in breathing pattern, control over the respiratory muscles, symptom management, and capability to perform physical exercise. The visual production will be facilitated by photograph and producer, David Kahr (https://www.davidkahr.dk).

4.2 Setting
The overall project will be run between Q4 2025 and Q4 2028 with active intervention phase between Q4 2025 and Q3 2027.

The intervention will be held via a video conferencing application (Zoom Video Communications, 'Zoom'), delivered by three specialised singing teachers.

The following sites are involved in the project:
Site 1: Department of Medicine, Zealand University Hospital, Roksilde and Næstved, Næstved Hospital, Ringstedgade 61, DK-4700 Naestved.

Site 2: Department of Respiratory Medicine, Bispebjerg Hospital, Bispebjerg Bakke 23, DK-2400 København NV.

Site 3: Department of Respiratory Medicine, Lillebaelt Hospital, Vejle, Kabbeltoft 25, DK-7100 Vejle, respectively (with assistance from Department of Oncology, Lillebaelt Hospital, Kabbeltoft 25, DK-7100 Vejle).

Site 4: Department of Respiratory Medicine, Odense University Hospital, J. B. Winsløws Vej 4, DK-5000 Odense (with assistance from Department of Oncology, Odense University Hospital, J. B. Winsløws Vej 4, DK-5000 Odense).

Site 5: August Krogh Section for Molecular and Human Physiology, Department of Nutrition, Exercise and Sports, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 3, DK-2100 København Ø (August Krogh Section for Molecular and Human Physiology is a research site with comprehensive experience with planning and conduct of all procedures related to clinical research, including recruitment, basic and advances data collection, analysis, and dissemination).

See 4.4 and 4.5 for description of procedures and data collection at the sites.

4.3 Participants
Patients who display persistent symptoms 6-18 months (+/- one month) after surgical resection of localised lung cancer with video-assisted thoracoscopy (VATS) will be invited to participate in the study.

Inclusion criteria for the study include:
Persistent symptoms, i.e., an EORTC-QLQ-C30 symptom domain score (in any item) of ≥2 (= "clinically relevant symptom or problem that should have healthcare professional attention")[20–22],

Surgery for stage I lung cancer 6-18 months (+/- one month) earlier,
Motivated for participating in the project (and acceptance of randomisation procedure),
Access to a computer or a tablet with internet access,
Ability to speak and understand Danish,
Acceptance of the scheduled times of the singing intervention twice a week.

Exclusion criteria include:
1) Unstable coronary diseases,
2) Severe cognitive disabilities (e.g., dementia),
3) Indication for adjuvant chemotherapy or other antineoplastic therapy,
4) Signs of lung cancer recurrence at regular follow-up CT scan.

No previous singing experience or musical competence is required. Participants will be informed that they are allowed to participate in additional offer of structured or unstructured offer physical exercise training and/or singing along with the project.

4.4 Recruitment procedure
Participants will be recruited using the following methods:

Retrospectively: At study onset: Participants from our recent cross-sectional study (Kaasgaard, et al., 2025, under preparation for submission) who provided consent and indicated to be interested in being part of the study, will be contacted and receive information about the project, directly via telephone or secure video-link by the study coordinator (doctor or nurse) at Site 1 and 2, respectively. If interested, patients will be screened according to EORTC-QLQ-C30 symptom domains and cut-off for any item: ≥ 2 (see inclusion criteria 1).

Retrospectively: At study onset: Each site retrieves patient lists from the Danish Lung Cancer Registry (DLCR) and/or from patient records related to their own, local patients having undergone NSCLC surgery within the past 6-18 months. Based on study inclusion criteria 2-5 and exclusion criteria 1-4, eligible patients will be contacted and receive information about the project, directly via telephone or secure video-link by the study coordinator at each site. If interested, patients will be screened according to EORTC-QLQ-C30 symptom domains and cut-off for any item: ≥ 2 (see inclusion criteria 1).

Prospectively: Ongoingly: Identification at each site of own, new local patients having undergone NSCLC surgery, based on patient records related to their own, local patients (i.e., if not identified as part of recruitment procedure point 2). Based on study inclusion criteria 2-6 and all exclusion criteria, eligible patients will be contacted and receive information about the project, directly in person, via telephone, or by secure video-link by the study coordinator at each site. If interested, patients will be screened according to EORTC-QLQ-C30 symptom domains and cut-off for any item: ≥ 2 (see inclusion criteria 1).

Patients will be offered to receive the information on another day and to bring a relative. After the oral information, patients will receive informed written information about the project and about their basic rights, either directly or via digital mail (“e-boks”) and will be able to read the relevant information materials at home. 2-3 days after receiving the written information, patients will be contacted via telephone or secure video-link by the study coordinator at each site and asked whether they will provide consent to participate.

Procedure specific to the involved sites:

Site 1 is responsible for recruitment and data collection for the main study concerning patients from own site who live close to Næstved and/or who prefer to be assessed there.

Patients from Site 2 (and patients from Site 1 living close to Copenhagen area and/or who prefer to be assessed in Copenhagen) will be screened and identified according to in- and exclusion criteria (see above) in connection with telephone calls for information from recent CT control. Patients will receive provisional information about the study via telephone. Patients will be able to provide provisional oral consent to be contacted by Site 5 and to receive the written information materials and a link to study questionnaires via "e-boks". Site 5 will then contact the patients by telephone within one week and arrange a date and time for receiving of the full information about the project, via telephone, by secure video-link, or – if the patient prefers so - directly in person. Subsequently, Site 5 is responsible for recruitment and data collection for the main study and for the exploratory sub-study. In case that the patient does not wish to confirm the oral consent, the patient is considered screen failure, and all information about name, telephone number, and any entered data from study questionnaires will be deleted.

Site 3 is responsible for recruitment and data collection for the main study concerning patients from own site.

Site 4 will collaborate with the local Department of Oncology who will screen and identify patients according to in- and exclusion criteria in connection with standard telephone calls with patient information concerning their recent CT control. If considered eligible, patients will receive provisional information about the study. Patients will be able to provide provisional oral consent to be contacted by Site 4 and to receive the written information materials and a link to study questionnaires via "e-boks". Site 4 will then contact the patients within one week by telephone and arrange a date and time for receiving of the full information about the project via telephone, by secure video-link, or – if the patient prefers so - directly in person. Subsequently, Site 4 is responsible for the final recruitment (retrieval of written consent) and data collection for the main study. In case that the patient does not wish to confirm the oral consent, the patient is considered screen failure, and all information about name, telephone number, and any entered data from study questionnaires will be deleted.

In all cases, before signing the written informed consent, participants will - if requested - be offered extra time to consider participation in the project. Moreover, they will be able to receive further information about the project. For detailed descriptions of procedures, please see Appendix 4.1, 4.2, and 5 to the protocol for the scientific ethics committee (Region Zealand, Denmark).

Provided written informed consent gives the project responsible, sponsor and sponsor's representatives, and possibly the relevant control authority, direct access (according to the Scientific Ethical Committees Act §3, stk. 3 and according to Danish health legislation ("Sundhedsloven") §46, stk. 1) to retrieval of relevant data from databases and medical journals on: Age, lung function, prescribed medication, hospitalisations, "performance status" after NSCLC surgery (Eastern Cooperative Oncology Group (ECOG) performance status scale), lung cancer stage and type (TNM; tumor, nodule, metastasis), and co-morbidities. These data will provide information about the patient's health conditions, which is a necessary for conduct of the research project, data analyses, and for mandatory control purposes, including self-control, quality control, and monitoring.

Patients with surgical TNM above stage I or non-NSCLC pathology are considered screen failures and will be excluded.

The study coordinators inform the patients about the dates and times for the next intervention group onset and inform the principal investigator about the status of recruitment ongoingly. The patient will receive a thorough written guide with instructions for entering the Zoom platform.

Every month (the first week in the month), a new intervention group will be starting with recruited patients since last intervention group onset. If the number of recruited patients is less than four, however, the intervention group onset is postponed until the following month.

4.5 Randomisation procedure
Included study participants will be block randomised (using sealed envelopes) by the PI to either:

Group 1: 10 weeks' online SLH, or
Group 2: 10 weeks' usual care followed by 10 weeks' online SLH.

Participants are informed about the randomisation immediately after the first baseline assessment by the local study coordinator. If assigned to Group 1, participants are also informed about the time for the intervention (weekdays and times during the 10 weeks).

Each site will collect patients ongoingly during the trial period or until number needed to treat (total including expected drop-out: n=100) is reached (see 4.10 Analysis).

4.6 Data collection procedure
Study participants will be assessed by a local study nurse or by a research assistant.

Study coordinators are responsible for contacting the local study participants and arranging time for assessments (with physical show-up). See descriptions of site-related procedures concerning recruitment and data collection under 4.4.

The participants will be assessed at the following time points:

Group 1:
T0: Baseline (at randomisation),
T1: Follow-up 11-14 weeks later).

Group 2:
T0: Baseline (at randomisation),
T1: Follow-up 11-14 weeks later).
T2: Follow-up: Withing three weeks after the SLH intervention (approximately 11-14 weeks after T1).

Given that there is no structured, active ingredient in the usual care component, a wash-out period between crossing of interventions is not needed.

The assessors will be blinded to randomisation all time points and participants are instructed not to speak to the participants about the randomisation.

The assessors are responsible for entering data. For data collection and data storage, we will use web-based, software and secure database, SurveyXact by Ramboll (Rambøll Management Consulting, Aarhus, Denmark) or metadata-driven database (EDC software, REDCap (Research Electronic Data Capture, Vanderbilt University, USA)). A research assistant will assist in data cleaning, validation, and management.

Each site receives its own closed profile (data access group) for data entry and data collection and is responsible for anonymisation (pseudonymisation) of site-specific data. The PI will not be able to access data directly in REDCap until data is fully anonymised. The anonymised data will be sent via encrypted e-mail and accessed by Site 1-researchers for combined analysis, reporting, and publication of results.

In case of detection of significant depressive symptoms at any time point (assessed by Hospital Anxiety and Depression Scale (HADS), sub-scale depression, max 21, cut-off ≥11), the assessor will inform the local study coordinator (or doctor) who will then contact the patient directly and refer to hospital psychologist or general practitioner to evaluate any need for treatment of depression.

4.7 Intervention: Singing training (Singing for Lung Health (SLH))

The study intervention is singing training, which will be conducted according to an intervention protocol based on the SLH-approach [28–31] (see also the main RCT article; Supplementary Materials, Appendix S2 and S3 for specific descriptions of content, methodology, and approach of SLH [29], reported and described using the Consensus on Exercise Reporting Template (CERT) tool [52]). The singing training will be delivered by three professional singing teachers specifically trained and experienced within the SLH-approach.

Sessions will be held online, lasting for 1½ hour twice a week during the 10 weeks' intervention phase. Sessions will include physical, vocal, and breathing exercises and musical repertoire, specifically designed to improve strength, endurance, and flexibility of the respiratory muscles. Besides, the intervention will include movement, dancing, and artefacts for playful games along with singing. Each session will consist of 20 minutes of physical warm-ups, 20 minutes of vocal warm-up with rhythm and pitch games, 40 minutes of singing (including a 5 minute-break), and 10 minutes of cooling down, e.g., mindfulness or relaxation.

The singing teachers will be supervised during the intervention phase by Associate Professor, Mette Kaasgaard, in collaboration with the SLH-team, and a logbook will be kept for documentation and to ensure programme fidelity.

4.8 Control: Usual care

The control group will receive usual care, i.e., no specific additional intervention above those which the person usually engages with.

4.9 Outcomes and measures

At baseline, basic characteristics will be collected, including sex, age, BMI, socio-demographics, smoking history, health care utilisation, exacerbations, medicine consumption, comorbidities, and expectations towards benefits of singing.

Primary study outcome is change in physical capacity, assessed with the Six Minute Walking Test (6MWT). Secondary outcomes include both objective outcomes and subjective, patient-reported outcomes, e.g., QoL symptom burden, symptoms of anxiety and depression, airway physiology, activity of daily living, health care usage, adherence, and drop-out-rate.

Specific outcomes and measures are displayed in the tables below:

4.9.1 Baseline characteristics

Characteristics/Status	Information
Status retrieved from Danish Lung Cancer Registry (DLCR)	CPR-number Date of surgery Lung cancer stage Lung cancer type Pathology classification Surgery type Localisation Risk factors Complications Lung function before surgery (Forced Expiratory Volume (FEV1% of predicted) and diffusion capacity for carbon monoxide (DLCO% of predicted)) BMI Former lung cancer surgery Admission
Status retrieved from patient record	Comorbidities Medicine consumption (prescriptions)
Self-reported information	Socio-demographic characteristics Municipality Smoking history, smoking status Information about previous attended rehabilitation after surgery (setting, type, content, duration, intensity, adherence, perceived benefits, perceived satisfaction/relevance) Co-morbidities and medicine consumption Disease-related GP and hospital visits Expectations towards benefits of singing

4.9.2 Outcomes and measures in the main study

Study outcomes	Measures
Primary outcome	Measures
Physical Capacity	Six Minute Walking Test (6MWT) [53, 53]. Perceived exertion (BORG dyspnoea scale) [53, 54]
Secondary outcomes	Measures

Quality of Life	EORTC 30 item Quality of Life Questionnaire (QLQ-C30) (QoL domains) [20, 21]). The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Lung Cancer Module Questionnaire (QLQ-LC13) (QoL domains) [20, 55]. St. George's Respiratory Questionnaire (SGRQ) [56, 57].
Symptom burden	EORTC 30 item Quality of Life Questionnaire (QLQ-C30) (symptom domains [20, 21]). EORTC Quality of Life Lung Cancer Module Questionnaire (QLQ-LC13) (symptom domains) [20, 55]. Breathing vigilance (Breathing Vigilance Questionnaire). Dyspnoea (mMRC (Modified Medical Research Council) Dyspnoea Scale) [58].
Symptoms of anxiety and depression	Hospital Anxiety and Depression Scale (HADS) [59]. Consumption of psychoactive drugs (yes/no; self-reported).
Airway physiology	Lung function (Body Plethysmography): Forced Expiratory Volume (FEV1 in litres and % predicted), Forced Vital Capacity (FVC in litres and % predicted), FEV1%/FVC% ratio [65]. Diffusion capacity for carbon monoxide (DLCO % predicted). Hyperinflation (RV, TLC, operating lung volumes).
Adherence and drop-out	Continuously registered by the singing teachers and study nurses.
Adverse events	Any adverse events registered continuously

4.9.3 Additional outcomes and measures in sub-study of physiological mechanisms

Study outcomes	Measures
Primary outcome	
Aerobic fitness/Maximal oxygen uptake	VO2-max (Cycling Test for VO2 Max Estimate; 70% of maximum heart rate for 20 minutes continuously)
Secondary outcomes	Measures
Perceived exertion	BORG dyspnoea scale [53, 54]
Peripheral oxygenation	Peripheral oxygenation (SpO2) (pulse oximeter)
Respiratory muscle strength	In- and expiratory pressures (MIP and MEP) (PowerBreathe) [65]. In- and expiratory muscle strength and endurance [65]
Heart rate	Maximum and recovery
Blood samples: Metabolism, oxygenation, stress response, inflammation, and inflammatory drivers.	Lactate dehydrogenase (LDH) Acid/base Saturation Catecholamines Inflammatory markers (TNF-α, IL-1β, IL-6) C-reactive protein (CRP) Leukocyte differential count JAK2V617F mutation

4.10 Analysis

An a priori statistical power analysis calculation showed that the needed sample size is n=78 study participants and including an expected drop-out-rate of 20%, an overall total sample of n=100 study participants is needed. In the power analysis, we considered data from previous studies on the primary study outcome, 6MWT distance, with a minimal important difference of ≥ 30 m [29, 66–68], with the final calculation based on findings from our previous RCT on singing for COPD with a pre-post difference of mean 13.1±36.3 m after 10 weeks of singing in pulmonary rehabilitation for COPD [44].

Statistical power analysis calculations; primary study outcome: 6MWD
Estimated sample size for two-sample comparison of means Test H0: n1 = n2, where n1 is the mean in population 1 and n2 is the mean in population 2
Assumptions: α (two-tailed) 0.05 β 0.2 Effect size Group 1: 5 m; Group 2: 15 m SD 15
Estimated required sample sizes (based on power: 80 %): n1 = 26 n2 = 52

Quantitative data from questionnaires and closed question fields will be described with number and percentage (categorical data) and either mean +/- standard deviation (normally distributed continuous data) or median and range (not normally distributed continuous data). Differences in within-groups and between-groups effects will be investigated with relevant test for continuous (independent samples, paired-samples, related-samples), and categorical data (Chi2 or Fischer's test) and differences quantified and reported with p-values and 95% Confidence Intervals (CI). Findings related to primary and secondary outcomes will be stratified in reaching of MID/MCID or not (reported as number and percentage). Association and independence between objective and subjective outcomes will be explored using Cochran-Mantel-Haenszel test for 2x2 tables. Multivariable mixed-effects regression models will also be included to elucidate any relevant correlations and associations. Missing data will be handled using multiple imputation and sensitivity analyses performed using the principles of last observation carried forward or next observation carried backward [69].

Data will be analysed at Site 1: Department of Respiratory Medicine, Zealand University Hospital, Næstved, Ringstedgade 61, DK-4700 Naestved. Main analyses will be performed by Associate Professor Mette Kaasgaard, and advanced analyses of physiological parameters will be performed in collaboration with Associate Professor Morten Hostrup.

Blinded results (presented as Treatment 0 compared to Treatment 1) of the study will be presented to the research group, who will interpret and discuss the blinded results [70].

In the discussion, we will include experiences from recent mappings on cancer rehabilitation from the Danish Cancer Society and REHPA (Da: "Videncenter for rehabilitering og palliation") [12, 71, 72] and findings from our previous studies on lung cancer rehabilitation [19] and QoL and symptom burden after NSCLC surgery (Kaasgaard, et al., 2025, under

preparation for submission). Besides, experiences and reports from e.g. the European Lung Foundation will be included.

CONSORT 2010 Statement checklist for randomised controlled trials [73] will be used for study reporting. Statistical analyses will be performed using statistical software STATA 18.1, StataCorp LLC, Texas, USA, and SPSS 31.0, IBM, New York, USA). Statistical significance will be reported as $p < 0.05$.

5. Organisation

The project facilitates cross-disciplinary research (respiratory medicine, oncology, surgery, respiratory physiology, physiotherapy, rehabilitation medicine, qualitative research, health economics, and "Arts-in-Health"-aspects).

The following institutions, researchers, and stakeholders will be involved in the project:

- Pulmonary Research Unit Zealand (PLUZ), Department of Respiratory Medicine, Zealand University Hospital, Roskilde and Naestved Hospital: Associate Professor, PhD, Mette Kaasgaard; Professor, head of research, respiratory consultant, PhD, Uffe Bødtger.
- Department of Respiratory Medicine, Lillebaelt Hospital, Vejle: Professor, DMSc, respiratory consultant, Ole Hilberg; Professor, DMSc, respiratory consultant, Anders Løkke; Associate Professor, respiratory consultant, PhD, head of "Lungepakken" at Lillebaelt Hospital, Morten Hornemann Borg.
- Respiratory Research Unit (ODIN), Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark (Christian Borbjerg Laursen, Professor, head of research, respiratory consultant, PhD).
- Department of Respiratory Medicine, Bispebjerg Hospital & Department of Clinical Medicine, Faculty of Health Sciences, Copenhagen University: Respiratory consultant, Pernille Kristiansen; Respiratory consultant, PhD, Anne Orholm.
- Department of Oncology, Lillebaelt Hospital, Kabbeltoft 25, DK-7100 Vejle.
- Department of Oncology, Odense University Hospital, J. B. Winsløws Vej 4, DK-5000 Odense
- August Krogh Section for Molecular and Human Physiology, Department of Nutrition, Exercise and Sports, Faculty of Health and Medical Sciences, University of Copenhagen: Associate Professor, physiologist, MD, PhD, Morten Hostrup.
- Danish Research Center for Lung Cancer: Professor, DMSc, respiratory consultant, Ole Hilberg.

Several international collaborations with world leading experts - including concerning methodological framework of the singing approach applied – was established during Sing-a-Lung 1.0 (and this will be continued and expanded during the present project), e.g., with:

- Stephen Clift, Professor Emeritus, Sidney De Haan Research Centre for Arts and Health, Canterbury Christ Church University. Visiting Professor, International Centre for Community Music, York St John University. Visiting Professor, School of Music, University of Leeds. Professorial Fellow, Royal Society for Public Health, UK.

6. Involving of patients

We aim to involve patients in all phases of the project. Patients have already been involved in the process of final designing the study protocol in terms of defining relevant and preferred outcomes of rehabilitation, via the updated Core Outcomes Set for pulmonary rehabilitation for patients with lung cancer (Edbrooke, L., et al., 2025) [18]. Furthermore, patients have been involved in terms of their view on potential benefits of singing and any interest and concerns regarding participating in a study (in the cross-sectional study, Kaasgaard, et al., 2025, under preparation for submission). Subsequently, we aim to involve patients in the development and qualification for the recruitment procedure, comprising written information materials as well as enactment-training concerning oral information provided by the health-professionals. Further, the assessment procedure will be tested in patients before onset of the study.

In the mandatory training of disease-specific methodology for singing teachers (facilitators of the intervention), patient perspectives will be included. Here, we will gain first-hand experience directly from a number of patients with lung cancer, who will visit the training workshop and provide important perspectives on the impact and challenges of the disease and feedback on exercises, repertoire, and approach.

Besides, the qualitative documentation (in the form of a visual production) will be made to involve patient-perspectives, focusing on the experience of participating in the intervention and how the tools are adapted/integrated, e.g., related to change in breathing pattern, control over the respiratory muscles, symptom management, and capability to perform physical exercise. In addition, the visual production will serve as documentation about the project for future use in dissemination situations (e.g., presentation at scientific conferences) and will provide insight into the project and the intervention. This will be useful to health-professionals, facilitators, politicians, health authorities, media, and for future research, including implementation research.

7. Possible risks

The research group is not familiar with any side-effects related to participation in the intervention, SLH. Previous studies have described singing as a safe and well-accepted activity [28, 29, 33, 38] and the research group is not familiar with any side effects of participation in the intervention and we expect that the participants will benefit positively from the intervention.
Any adverse events that do arise will be addressed in regular research group meetings, with strategies for the future mitigation of these events strategised in collaboration with the local ethics committee, where necessary.

8. Ethics

Approvals will be sought at the local scientific ethics committee (Region Zealand, Denmark) and The Danish Data Protection Agency. The study will be conducted in accordance with the Helsinki Declaration and according to the General Data Protection Regulation and The Danish Data Protection Act. Study participants are covered by the Danish Patient Compensation.

9. Dissemination

The trial protocol will be registered in a relevant public database (e.g. ClinicalTrials.gov) and all results, positive, negative or inconclusive, will be reported in accordance with recommendations from The International Committee of Medical Journal Editors (ICMJE) and made publicly available in peer-reviewed journals, social media channels, news media, and at conferences, scientific meetings, seminars, etcetera. Results will be reported based on relevant EQUATOR guidelines, and authorship will be awarded according to Vancouver regulations ("Uniform Requirements").

10. Funding

Currently, funding for salaries, equipment and running cost has been obtained from The Danish National Research Center for Lung Cancer, Danish Cancer Society (DKK 150,000), The Danish Health Foundation (DKK 500,000), The Danish Lung Foundation (DKK 150,000), Region Zealand (DKK 342,857), Danish Cancer Society (DKK 1,750,000 kr.), Novo Nordisk Foundation (DKK 3,707,217). Further funding has been applied for (awaits feed-back). In case of further funding obtained, the Ethical Committee will be informed, and the patient information (Appendix 5.1) will be updated.

Funding will be used for salaries (PI/Ass. Professor (Mette Kaasgaard), project nurses, research assistants, statistical advice, and singing teachers), for equipment (measurement devices, digital pianos, singing books, and computer hardware and software), and for running costs (analyses, information materials, training of singing teachers, travel, conference, publication, and overhead). Participants will not receive economic compensation for participation. No member of the research group has any financial or personal conflict of interest in the project or in connection to the funding bodies.

A detailed budget has been made and additional funding for all salaries, equipment, and running expenses will be sought throughout the course of the project.

11. Expected results and perspectives

Overall, we expect that singing training supports and strengthens physiological and psychological/existential parameters, relieves symptom burden, and, moreover, may break the vicious circle of loneliness, isolation, and hopelessness which many people with lung diseases – including patients with lung cancer – experience.

If the study demonstrates that singing is an effective, relevant, and feasible modality for patients with lung cancer, the study may form the basis for further research. Furthermore, the project may generate hypotheses for future studies applying other research approaches.

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