Enhanced COPD Management in Suspected Lung Cancer Patients - Improving Outcomes Through timely Intervention

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Study overview

Identifying and treating COPD in patients undergoing lung cancer evaluation is crucial. Early intervention could lead to better management of both diseases, improving health status, reducing healthcare costs, and potentially increasing survival rates.

This study aims to assess the impact of early diagnosis and optimal treatment of COPD on clinical outcomes in patients under evaluation for lung cancer. The study will combine information through an open-label RCT at the Lung Cancer Investigation Unit at Lillebaelt Hospital Vejle.

The findings could inform clinical practice by emphasizing the importance of integrated care approaches for patients with coexisting COPD and lung cancer, ultimately leading to better health outcomes.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) and lung cancer frequently coexist due to shared risk factors, most notably smoking, which is the leading cause of both conditions [1]. COPD, characterized by persistent airflow limitation and chronic inflammation of the airways [2, 3], is a major contributor to morbidity and mortality worldwide [4]. Similarly, lung cancer is one of the most common and deadliest cancers [5], with a significant overlap in the patient populations affected by COPD [6]. Studies suggest that individuals with COPD are at an increased risk of developing lung cancer [6], with rates estimated to be four to six times higher than in the general population [7]. This overlap is not merely coincidental but is thought to be influenced by chronic inflammation, oxidative stress, and impaired immune responses in the lungs of patients with COPD, which can promote carcinogenesis [6].

Despite the frequent coexistence of COPD and lung cancer [1, 6], patients are usually not investigated for COPD as usual care, therefore, COPD often remains underdiagnosed or is diagnosed late [8], particularly in patients being evaluated for lung cancer [9, 10]. Delayed diagnosis and untreated COPD can negatively affect a patient's overall prognosis, complicating the management of lung cancer [10, 11]. At the same time, some patients with COPD are incorrectly diagnosed [12] and suboptimal treated [12, 13, 14] resulting in progressive deterioration of health status [15, 16]. Deterioration of health status including lung function is contributed by comorbidities in patients with COPD especially cardiovascular diseases [17, 18].
Overall, patients with COPD tend to have poorer tolerance to lung cancer treatments, including surgery, chemotherapy, and radiotherapy, due to compromised lung function [6]. In contrast, early detection and optimal management of COPD, including pharmacotherapy, smoking cessation, and pulmonary rehabilitation, may improve lung function [19, 20], enhance treatment tolerance, and reduce complications during cancer therapy [6, 19, 20].

Given the high prevalence of both COPD and lung cancer in individuals with a history of smoking, identifying and treating COPD in patients undergoing lung cancer evaluation is crucial. Early intervention could lead to better management of both diseases, improving health status, reducing healthcare costs, and potentially increasing survival rates. This study aims to assess the impact of early diagnosis and optimal treatment of COPD on clinical outcomes in patients under evaluation for lung cancer. Specifically, it will explore how timely COPD management affects cancer treatment tolerability, postoperative recovery, hospitalization rates, and overall survival in this high-risk population. The findings could inform clinical practice by emphasizing the importance of integrated care approaches for patients with coexisting COPD and lung cancer, ultimately leading to better health outcomes.

Aim and objectives

To assess the impact of early COPD diagnosis and optimal treatment on health status outcomes in patients undergoing lung cancer work-up and to evaluate the effect of early COPD diagnosis and optimal treatment on COPD-related health status in patients undergoing lung cancer work-up.

Design and methods

Effect of optimised COPD treatment alongside lung cancer workup: a randomized open-label trial

Aim

To evaluate the impact of tailored COPD consultations and optimised treatment on health status outcomes in patients undergoing evaluation for suspected lung cancer who also present with COPD.

Trial design

The study is a randomized, controlled, open label trial. Patients referred for diagnostic evaluation of suspected lung cancer, who exhibit obstructive airflow limitation, defined as $FEV_1/FVC < 75$ % or $FEV_1 < 80$ % on pulmonary function testing, will get redirected to participate in the trial alongside the lung cancer investigation. The participants who meet the criteria for COPD [21] will be randomized to receive either tailored COPD consultations alongside their lung cancer investigation or usual care (lung cancer investigation only) with an equal allocation ratio 1:1 using a computer-generated table of random numbers in REDcap. The study protocol is reported in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [22].

Setting

The RCT will be conducted at the Lung Cancer Investigation Unit, Lillebaelt Hospital Vejle, which evaluates approximately 1,000 patients for suspected lung cancer and diagnoses approximately 500 lung cancer cases each year. All patients referred for suspected lung cancer undergo routine spirometry. Patients diagnosed with lung cancer are referred for thoracic surgery at the

Department of Thoracic Surgery, Odense University Hospital, or for oncological treatment at the Department of Oncology, Lillebaelt Hospital Vejle. If lung cancer is ruled out, patients are either discharged or followed up with CT imaging as appropriate.

Inclusion criteria

- Age ≥ 18 years
- Undergoing diagnostic evaluation for suspected lung cancer
- Spirometry showing obstructive airflow limitation ($FEV_1/FVC < 75$ %, $FEV_1 < 80$ % and no reversibility) at the first outpatient visit at the lung cancer evaluation

Exclusion Criteria

- Presence of significant comorbidities that may interfere with diagnostic procedures or spirometry
- Pregnant or breastfeeding women.

Intervention

Eligible patients will be randomized 1:1 to either the intervention group or usual care (Figure 1). Participants in both arms will undergo standard diagnostic evaluation for suspected lung cancer in timely manner. In the intervention group, patients will additionally receive tailored COPD consultations at the COPD clinic of Lillebaelt Hospital Vejle during diagnostic work-up. These consultations will include assessment and treatment according to GOLD guidelines [21], including:

- Pharmacological management
- Smoking cessation support
- Referral to pulmonary rehabilitation as appropriate
- Referral for nutritional assessment and optimization when appropriate
- Referral to cardiovascular evaluation when appropriate
- Referral to sleep apnea evaluation when appropriate

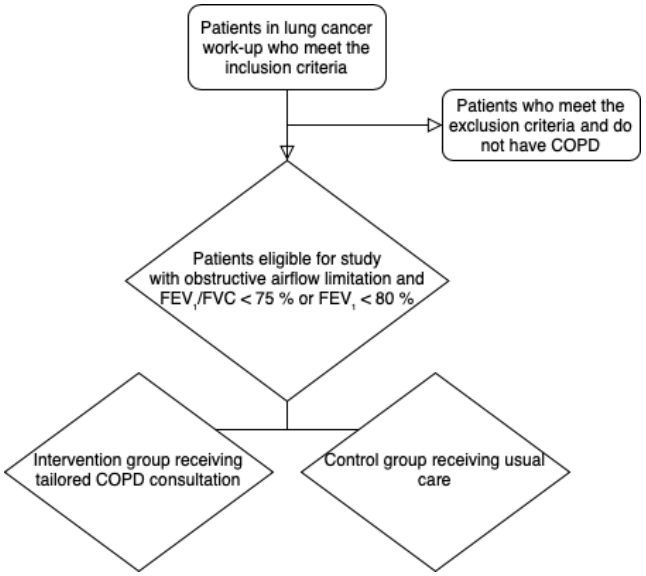

Figure 1: Participant flow chart

Data collection

An overview of the data collection for this study can be found in Table 1. The primary outcome is the change in COPD Assessment Test (CAT score) over 6 months. CAT consists of a questionnaire with eight items with the possibility of scoring 0-40 on respiratory symptoms. Participants will be tested at baseline, and after a follow-up period of 3 and 6 months after enrollment of the study. The baseline visit and the 6 months follow-up will be a physical meeting whereas the 3 months follow-up will be a conversation through a phone call conducted by the PhD-student.

The participants will be asked about new medication, the results of the lung cancer evaluation of treatment plans along with disease-related information. The information will be checked through the participant's electronic medical journal if access at the baseline visit is granted. This information is important to further and better clarify COPD consultations effect on disease-related outcomes. Secondary outcomes will be disease-related information, change in BMI, change in 1 min sit-to-stand test, the proKOL questionnaire, the HADS questionnaire and smoking cessation rates. Covariates include the participants characteristics (e.g. sex, age, risk factors, comorbidity).

	T1, baseline visit in lung cancer investigation unit	T2, 3 months' follow-up	T3, 6 months' follow-up
Sociodemographic info	X		
Body Mass Index (BMI)	X		X

Spirometry and reversibility testing	X		
Smoking history and status	X	X	X
ProKOL [23] to clarify treatment and rehabilitation needs (includes CAT [24])	X	X	X
1 min sit-to-stand test [25]	X		X
Disease-related information (exacerbations, mortality, hospitalisations, cancer treatment tolerability, postoperative recovery, overall survival)	X	X	X
Hospital Anxiety and Depression Scale (HADS) [26]	X	X	X
Cardiovascular investigation (coronary calcium scan)	X		
Sleep apnea investigation	X		

Tabel 1: Chart of data collection

Sample size calculation

The sample size calculation is based on the CAT score, aiming to detect a difference of 3 based on a standard deviation (SD) of 7.7, with a power of 80% and a significance level of 5%. The SD is calculated from a similar previous Danish study optimizing COPD treatment in patients with lung- or head and neck cancer [27]. Accounting for a 25% dropout rate, the sample size is calculated to be 280 participants. The estimated lung cancer rate of 50 % is not taken into account when calculating the sample size because lung cancer will be presented as subgroup analysis.

Statistical Analysis

Patients will be categorized based on their assignment to either the usual care group or the intervention group. The randomisation will be stratified to ensure equal distribution of known or unknown COPD and the median of baseline CAT score. The median of baseline CAT score is perceived to be 12.7, found from similar studies [27, 28, 29, 30, 31, 32, 33, 34]. The randomisation group will be distributed in three strata according to the CAT score as mild (0-9), moderate (10-20) or high (21-40) symptom burden.

Every participant in the intervention group will receive tailored COPD consultations by the PhD-student minimizing significant variation between the interventions. Baseline characteristics will be analyzed descriptively. In case of significant differences between the study groups on key characteristics, multivariate analyses will be performed adjusting for potential confounders such as sex, age and smoking status [27, 32]. Primary and secondary outcomes will be evaluated using appropriate statistical tests, including ANCOVA. The primary outcome is a CAT score difference from baseline to the 6 months' follow-up for the intervention group compared to the control group. If the 6 months' data is missing due to death, the 3 months' data will be used to calculate a surrogate for the CAT score. As a secondary analysis, the test will be performed without the missing data. A sensitivity analysis will be performed on the difference of the two analysis methods. Subgroup analyses will be performed to explore differences in intervention effects among patients with known COPD and patients with newly diagnosed COPD. Additionally, subgroup analyses and adjusted analyses will be performed to account for the potential effects of lung cancer diagnosis on study outcomes as well as kaplan-meier analysis. All the statistics will be performed using Stata.

Ethical Considerations

The study protocol was approved by The Health Research Ethics Committee 2, Region of Southern Denmark (Project-ID S-20250091). The study will adhere to the Declaration of Helsinki [35].

The eligible patients are recruited at the day of their first visit in the Lung Cancer Investigation Unit, Lillebaelt Hospital Vejle, after the usual consultation by a doctor and a nurse including lung function testing. Identification focuses on patients who may have diagnosed or potential COPD and are obtained by the clinical nurse who has performed the lung function testing. Initial contact are conducted by the PhD-student who are located at the Lung Cancer Investigation Unit. At this stage, the patient is briefly informed about the study, including its purpose to investigate the impact of early diagnosis and optimal treatment of COPD on clinical outcomes in patients undergoing lung cancer evaluation. Patients are asked whether they are interested in receiving further information about participation. Before consent is obtained, the PhD-student will perform thorough oral and written information in a consultation room in the Lung Cancer Investigation Unit. The information is given in a private and undisturbed setting to ensure confidentiality and allow sufficient time for

discussion. The patients are allowed to bring along their desired companions when the information is given. It is ensured that the information interview takes place without interruptions by conducting the conversation in a closed room and allocating adequate time for questions and reflection. Patients are encouraged to ask questions involving the companion if they wish. The oral and written information includes a description of the study design, as well as the potential benefits and risks associated with early COPD diagnosis and treatment, participant rights, and data handling procedures. Informed consent is obtained after the patient has confirmed their willingness to participate in the same setting as the first visit at the Lung Cancer Investigation Unit. The patients will provide written and informed consent prior to inclusion obtained by the PhD-student and receive usual care independent of the allocated group.

The consent will include permission to collect questionnaire content and allowance to store data from the study as described above. The consent allows the PhD-student, the sponsor and the sponsor's representatives as well as any supervisory authority, direct access to obtain information from the patient's medical records, etc., including electronic medical records, for the purpose of reviewing information about the trial subject's health status that is necessary for the conduct of the research project, as well as for control purposes, including self-monitoring, quality control, and monitoring, which they are obliged to carry out. It is always possible to withdraw consent.

The collection and storage of personal data will comply with the Data Protection Act and the GDPR. The results of the project will be treated confidentially. The results will be stored on a secure server controlled by the Region of Southern Denmark. The results will only be disclosed in pseudonymised (de-identified) form, where neither your name, date of birth, address, nor the like will be disclosed. The results from the project will be published in an anonymous form.

This study's risk of harm are considered as time used by the patient to participate in the study, use of mental capacity in an already difficult situation and side-effects to the medical inhalators or medication for smoking cessation. The study will not introduce trial based medication, medical procedures or additional blood tests to the participants. The participants are informed to contact the PhD-student if any side-effects to the new medication appear. At the follow-up visits, the participants will be asked about side-effects and any inconvenience regarding the study participation. The second follow-up visit is physical, meaning a minor inconvenience for the participants. It is possible to schedule the second follow-up visit with the PhD-student at the same time as other visits to the hospital. Overall, the study is assessed to carry low risk, which is proportionate to the anticipated benefits in terms of improved disease understanding, better management, and potentially improved health outcomes and prognosis for participants. If any serious adverse events happens, the study will not proceed without a thorough investigation including a risk/benefit analysis.

Every patient will receive usual care regarding lung cancer evaluation. A possible cancer diagnosis or treatment will not be delayed by the intervention. The intervention will be a thorough evaluation to find the right parts of intervention for the individual. Therefore, the study trial appears as a quality improvement of usual care. The patients are entitled to compensation due to injuries from healthcare treatments or side effects to drugs due to the Danish Patient Compensation.

Dissemination of Results

The project protocol and conclusions of any kind will be published by www.clinicaltrials.gov. It must be stated that positive, negative, as well as inconclusive results will be published. Our strategy for dissemination of the results involves three levels:

1) Local: The project group will inform local collaborators about the study and present the progress and preliminary results at local department- and interdisciplinary meetings. If the study shows positive results it may continue in clinical practice at the Lung Cancer Investigation Unit at Lillebaelt Hospital Vejle.

2) National: The project group will present the study protocol and the results at national meetings of relevant scientific societies and, at meetings for relevant patient organizations and in mainstream media for the broad public.

3) International: The project group aims to present the results at meetings in international scientific societies and at international conferences. Results will be published in peer-reviewed journals. Participants will receive a summary of the study findings.

Impact

This study aims to improve outcomes for patients with both COPD and lung cancer by focusing on early COPD diagnosis and treatment during lung cancer evaluation. The frequent coexistence of these conditions, driven by shared risk factors, most notably smoking, often results in late COPD diagnosis, complicating cancer treatment. Early intervention could improve lung function, enhance cancer treatment tolerance, reduce hospitalizations, and potentially increase survival.

By addressing this gap, the study may lead to integrated care approaches that improve health status and reduce healthcare costs. Findings could inform clinical guidelines for managing COPD in lung cancer patients, highlighting the value of early diagnosis. The inclusion of cost-effectiveness analysis will also provide insights into the economic benefits of early COPD treatment, supporting better healthcare resource allocation.

The research has the potential to shift clinical practice by reinforcing the need for integrated management of COPD in patients with lung cancer, leading to better overall health outcomes.

Timeline

	2025		2026				2027				2028	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Preparation and Recruitment												
- Planning	x											
- Initiation		x										
- Recruitment			x	x								
Data Collection and Follow-up												
- Complete recruitment					x	x						
- Follow-up							x	x				
Analysis and Dissemination												
- Data analysis									x	x		
- Dissemination											x	x

Tabel 2: Timeline

References

1. Taucher E et al. Implications of the Immune Landscape in COPD and Lung Cancer: Smoking Versus Other Causes. Front Immunol. 2022;13:846605. Implications of the Immune Landscape in COPD and Lung Cancer: Smoking Versus Other Causes - PubMed
2. McDonough JE et al. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2011;365:1567-1575. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease - PMC
3. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Imminol. 2016;138(1):16-17. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease - ClinicalKey
4. Ferrera MC, Labaki WW, Han MK. Advances in Chronic Obstructive Pulmonary Disease. Annu Rev Med. 2021;72:119-134. Advances in Chronic Obstructive Pulmonary Disease - PMC
5. Siegel RL et al. Cancer Statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21708
6. Qi C, Sun S, Xiong X. From COPD to Lung Cancer: Mechanisms Linking, Diagnosis, Treatment, and Prognosis. Int J Chron Obstruct Pulmon Dis. 2022;17:2603-2621. From COPD to Lung Cancer: Mechanisms Linking, Diagnosis, Treatment, and Prognosis - PMC
7. Skillrud DM, Offord KP, Miller RD. Higher Risk of Lung Cancer in Chronic Obstructive Pulmonary Disease: A Prospective, Matched, Controlled Study. Ann Intern Med. 1986;105(4):503-7. https://www.acpjournals.org/doi/10.7326/0003-4819-105-4-503?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
8. Martinez CH et al. Undiagnosed Obstructive Lung Disease in the United State. Associated Factors and Long-term Mortality. Ann Am Thorac Soc. 2015;12(12):1788-1795. https://pmc.ncbi.nlm.nih.gov/articles/PMC4722830/
9. Scott N et al. Stigma as a barrier to diagnosis of lung cancer: patient and general practitioner perspectives. Prim Health Care Res Dev. 2015;16(6):618-22. https://www.cambridge.org/core/journals/primary-health-care-research-and-development/article/stigma-as-a-barrier-to-diagnosis-of-lung-cancer-patient-and-general-practitioner-perspectives/00DCD12CBBDCBC4517DCD678924BC277
10. Friedemann Smith C et al. Smokers are less likely than non-smokers to seek help for a lung cancer 'alarm' symptom. Thorax. 2016;71(7):659-661. https://pmc.ncbi.nlm.nih.gov/articles/PMC4941149/#s5
11. Butler SJ et al. Association between COPD and Stage of Lung Cancer Diagnosis: A Population-based Study. Curr Oncol. 2023;30(7):6397-6410. https://pmc.ncbi.nlm.nih.gov/articles/PMC10377848/#sec5-curroncol-30-00471

12. Spyratos D et al. Underdiagnosis, false diagnosis and treatment of COPD in a selected population in Northern Greece. Eur J G Pract. 2021;27(1):97-102. https://pmc.ncbi.nlm.nih.gov/articles/PMC8158270/
13. Yang T et al. REALizing and improving management of stable COPD in China: results of a multicentre, prospective, observational study (REAL). Ther Adv Respir Dis. 2023;17:17534666231178692. https://pmc.ncbi.nlm.nih.gov/articles/PMC10285602/#section21-17534666231178692
14. Pinto CR et al. Management of COPD within the Brazilian Unified Health Care System in the state of Bahia: an analysis of real-life medication use patterns. J Bras Pneumol. 2019;45(1):e20170194. https://pmc.ncbi.nlm.nih.gov/articles/PMC6534407/#sec11
15. Rossi A et al.Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research – a consensus document from six scientific societies. Int J Chron Obstruct Pulmon Dis. 2017;12:2593–2610. https://pmc.ncbi.nlm.nih.gov/articles/PMC5587130/#sec19
16. Janjua S et al.Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2021;2021(9):CD013381. https://pmc.ncbi.nlm.nih.gov/articles/PMC8425588/#CD013381-sec-0092
17. Negewo NA, Gibson PG, McDonald VM. COPD and its comorbidities: Impact, measurement and mechanisms. Respirology. 2015;20(8):1160-71. https://onlinelibrary.wiley.com/doi/10.1111/resp.12642
18. André S et al. COPD and Cardiovascular Disease. Pulmonology. 2019 May-Jun;25(3):168-176. https://www.sciencedirect.com/science/article/pii/S2531043718301508?via%3Dihub
19. Makino T et al. Long-acting muscarinic antagonist and long-acting β2-agonist therapy to optimize chronic obstructive pulmonary disease prior to lung cancer surgery. Mol Clin Oncol. 2018 Mar 26;8(5):647–652. https://pmc.ncbi.nlm.nih.gov/articles/PMC5920355/#abstract1
20. Bölükbas S et al. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial. Eur J Cardiothorac Surg. 2011 Jun;39(6):995-1000. https://academic.oup.com/ejcts/article/39/6/995/380499?login=false
21. Agusti A et al. 2024 Global Strategy for Prevention, Diagnosis and Mangement of COPD. Global Initiative for Chronic Obstructive Lung Disease. 2024. https://goldcopd.org/
22. Chan A et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med. 2013;158(3):200–207.
23. proKOL?

24. Jones PW et al. Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. Chest. 2012;142(1):134-140. https://pubmed.ncbi.nlm.nih.gov/22281796/
25. Vaidya T et al. Is the 1-minute sit-to-stand test a good tool for the evaluation of the impact of pulmonary rehabilitation? Determination of the minimal important difference in COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2609–2616. https://pmc.ncbi.nlm.nih.gov/articles/PMC5079690/
26. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70. https://pubmed.ncbi.nlm.nih.gov/6880820/
27. Gottlieb M et al. Optimizing COPD treatment in patients with lung- or head and neck cancer does not improve quality of life – a randomized, pilot, clinical trial. Eur Clin Respir J. 2020 Mar 2;7(1):1731277. https://pmc.ncbi.nlm.nih.gov/articles/PMC7067155/#s0003
28. Zhou R et al. Effect of dual bronchodilators plus preoperative rehabilitation in operable LC & chronic obstructive pulmonary disease. Future Oncol. 2024 Nov 28;20(40):3471–3476. https://pmc.ncbi.nlm.nih.gov/articles/PMC11776851/#s0003
29. Deng D et al. Application of GOLD 2023 Initial Inhalation Therapy Recommendations in COPD patients: a real-world adherence and prognosis analysis. J Glob Health. 2025 Nov 28;15:04324. https://pmc.ncbi.nlm.nih.gov/articles/PMC12662025/#sec11
30. Huang C et al. Chronic obstructive pulmonary disease assessment test for the measurement of deterioration and recovery of health status of patients undergoing lung surgery. Thorac Cancer. 2022 Jan 6;13(4):613–623. https://pmc.ncbi.nlm.nih.gov/articles/PMC8841704/#tca14306-sec-0006
31. Illini O et al. Effectiveness of Outpatient Pulmonary Rehabilitation in Patients with Surgically Resected Lung Cancer: A Retrospective Real-World Analysis. Cancers (Basel). 2022 Jul 18;14(14):3479. https://pmc.ncbi.nlm.nih.gov/articles/PMC9322504/#sec2-cancers-14-03479
32. Shin S et al. Longitudinal changes in pulmonary function and patient-reported outcomes after lung cancer surgery. Respir Res. 2022 Aug 30;23:224. https://pmc.ncbi.nlm.nih.gov/articles/PMC9429784/#Sec2
33. Vagvolgyi A et al. Effectiveness of perioperative pulmonary rehabilitation in thoracic surgery. J Thorac Dis. 2017 Jun;9(6):1584–1591. https://pmc.ncbi.nlm.nih.gov/articles/PMC5506174/#sec6
34. Huang C et al. Pulmonary rehabilitation improves exercise capacity, health-related quality of life, and cardiopulmonary function in patients with non-small cell lung cancer. BMC Cancer. 2024 Feb 15;24:211. https://pmc.ncbi.nlm.nih.gov/articles/PMC10870628/#Sec12
35. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4.