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NCT Number NCT06730685
Unique Protocol Id PHILUCA

PHILUCA: The Development of Muscle Mass, Muscle Strength, and Muscle Function in Patients With Lung Cancer During Cancer Treatment

Updated power considerations and sample size

The sample size calculation was originally based on a pooled estimate from prospective cohorts of patients with advanced-stage lung cancer, assuming a hazard ratio for mortality of 2.38 and a sarcopenia prevalence of 50%. With power set at 90% and a two-sided alpha of 0.05, a final sample of 130 patients with advanced-stage lung cancer was required for the primary analysis.

Initially, an expected study withdrawal rate of **28%** was assumed, corresponding to a required baseline inclusion of **180 patients** with advanced-stage lung cancer to ensure 130 patients available at 3-months follow-up.

However, based on observed study retention during recruitment, the actual withdrawal rate has been lower than anticipated. As of **05 February 2026**, among the first **153 included patients**, the observed dropout rate was **19%**. Under this empirically observed retention rate, inclusion of **160 patients** with advanced-stage lung cancer is sufficient to ensure the required final sample size of 130 patients.

Accordingly, the target sample size for patients with advanced-stage lung cancer has been revised from 180 to **160 patients**, without compromising the statistical power of the study.

Update to data collection timepoints

The study protocol was amended with respect to the timing of follow-up assessments.

Due to logistical and time constraints in the clinical setting, it was not possible to assess changes in muscle parameters or health-related quality of life beyond **three months after inclusion**. Furthermore, repeated assessments of muscle parameters at each chemotherapy cycle during first-line treatment could not be performed, as these timepoints coincided with treatment administration and clinical workflows that did not allow for additional study procedures.

As a result, follow-up assessments were limited to a single post-baseline timepoint. Assessments are intended to be performed approximately **three months after inclusion**, which in routine clinical practice usually corresponds to the timepoint immediately **prior to the first control imaging scan**. This timing ensures clinical relevance while maintaining feasibility and minimizing participant burden.

These changes do not affect the primary study objectives but define the scope of longitudinal analyses accordingly.

Study Protocol

Original English title:

PHILUCA: The development of muscle mass, muscle strength, and muscle function in patients with lung cancer during cancer treatment

Original Danish title:

PHILUCA: Udviklingen af muskelmasse, muskelstyrke og muskelfunktion hos patienter med lungekræft under kræftbehandlingen

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Declaration from investigators and collaborators

The investigators and collaborators of this trial declare no conflicts of interest and that the trial will be conducted in accordance with the Declaration of Helsinki, and the respective rules and regulations in Denmark.

Authorships

This protocol was authored by abovementioned study group. First- and co-authorships of the scientific publications with experiences and findings from the project will follow the Vancouver guidelines.

2.0 Introduction

Low socioeconomic position (SEP) is strongly associated with lung cancer incidence and survival. Barriers related to receiving recommended treatment among lung cancer patients with low SEP may include adverse health behavior, long distances to the hospital, and limited physical and psychosocial resources. Other biological barriers related to treatment receipt include the development of sarcopenia, which is the natural degeneration of the body with a gradual reduction in muscle mass and physical performance. A cancer disease and treatment can further accelerate sarcopenia substantially, thus enhancing the risk of cancer cachexia, which involves sarcopenia along with weight loss. Sarcopenia and cachexia are highly prevalent among patients with lung cancer, and emerging evidence suggests an association between these factors and worse treatment outcomes. Progressive cancer-related sarcopenia and cachexia is multifactorial and self-enhancing and with current knowledge incompletely explaining underlying mechanisms, an efficient management strategy is lacking. Exploring these factors as well as patient-related barriers to treatment may provide an

opportunity to improve lung cancer treatment receipt and tolerance and thus prognosis by informing the treatment plan and intervening timely and appropriately to prevent or improve sarcopenia and cachexia.

3.0 Background

Lung cancer has one of the worst prognoses among cancers, especially for patients with low SEP and advanced disease [1-3]. Differences in received treatment, stage, and comorbidity may explain a large proportion of the social inequality in lung cancer prognosis both among early-stage and advanced-stage patients [2]. Thus, both disease-related factors as well as social and behavioral factors may increase the risk of not adhering to lung cancer treatment. Patients with lung cancer often have poor Eastern Cooperative Oncology Group performance status (PS) [4] at the time of diagnosis resulting in a high burden of side effects, treatment delays, dose-reductions and treatment failure [5]. Chemotherapy is primarily offered to patients with a PS of 0-2. Yet, this measure is not an ideal parameter, and in particularly in older patients with cancer, determination of PS is often inaccurate [6]. The dose of chemotherapy is routinely calculated based on patient's body surface area. This method might be problematic i.e. in patients with sarcopenic obesity, as the combination of a large body surface area and low muscle mass may lead to a lower tolerance for chemotherapy and a worse prognosis [7,8]. Further, initial dose downregulation is based on the patient's age, comorbidity and/or PS. Taken together, it appears that the tools available for physicians to precisely judge if downregulation is appropriate may be insufficient. Even patients with a good PS at time of diagnosis are at risk of developing sarcopenia or cachexia through the course of systemic treatment [9]. This receives little focus in the clinic, although it could provide a potential patient benefit in terms of intervening prior to a loss in physical function and reduced Quality of Life (QoL) [10,11]. If an intervention could be successful in preventing or reversing sarcopenia or cachexia, it can potentially increase patients' chance of completing the scheduled treatment regime. Emerging evidence suggests that resistance training and protein rich diet may have this effect [12], but studies in patients with lung cancer during systemic treatment are lacking [13].

There is marked diversity in current clinical practice in assessing the degree of muscle loss in patients with cancer and in quantifying its functional implications [14]. If the loss of muscle mass and strength have significant clinical implications for patients with cancer, then standardized, validated diagnostic

thresholds are clearly needed [14]. Furthermore, while the effects of sarcopenia have been extensively studied in the elderly patients, factors associated with loss of muscle mass and strength in cancer remain unclear [14].

The prevalence of sarcopenia in lung cancer is higher than in other cancers, ranging from 22-71% depending on the population and definition of sarcopenia [8,15-18], however, no studies have described the prevalence in a Danish lung cancer population. Among associated clinical factors identified in previous studies are older age, smoking, comorbidity, low BMI, low caloric intake, physical inactivity, cancer treatment and progression [19,20]. The knowledge about underlying mechanisms of sarcopenia in cancer is, however, fragmented, and it remains to be uncovered what happens in real life patients and if it can be influenced by an intervention. Further, with the relatively poor prognosis in lung cancer, it is important not only to explore if survival time may be improved, but also if QoL during treatment and survival time can be improved.

Taken together, with the lack of knowledge about patient-related factors and sarcopenia and cachexia prevalence and development, there is a need to explore what influences the individual patient's treatment tolerance, QoL and prognosis. Further, this may provide an opportunity to explore if clinical tools covering social vulnerability, as well as muscle mass and physical function tests, can add valuable and precise information that may be used to better judge the optimal systemic treatment dose and to better identify patients in need of support and symptom management during treatment. Finally, due to the high risk of losing physical function and developing sarcopenia and cachexia in patients with lung cancer, there is a serious need for developing effective interventions that can prevent or restore physical function and muscle mass throughout treatment and into survivorship.

4.0 Aims

The overall aims of the PHILUCA study are in a longitudinal study to examine sarcopenia and cachexia risk factors, the development over time, and the associations with lung cancer treatment tolerance, QoL and prognosis. In addition, the aim is to test whether a vulnerability screening tool can identify patients at high risk of not completing the planned treatment.

4.1 Research Question and hypothesis

What is the prevalence and pattern of development of sarcopenia and cachexia and what are the associated factors, prognosis, treatment tolerance and QoL throughout treatment?

We hypothesize that if the Danish stage distribution of sarcopenia and cachexia is worse than that of other countries - and health is worse than that of other countries, then the risk of sarcopenia and cachexia might also be higher and could explain why we have a relatively larger subgroup of patients with lung cancer who have low 1-year survival rates.

Which patient-related and disease-related factors from can best predict treatment adherence as part of a vulnerability screening instrument?

We hypothesize that selected patient-related and disease-related factors can contribute to a vulnerability scale and that this scale is able to predict treatment adherence.

5.0 Methods

5.1 Patient and public involvement

The design of PHILUCA has been developed and refined by the patient panel of Zealand University Hospital, consisting of former or current cancer patients and their relatives. The patient panel has by the 13th of May 2024 recognized the project's relevance and approved the quantity and type of data collection methods.

5.2 Study design and setting

The PHILUCA study will be a prospective cohort involving 180 participants and will be conducted at the Department of Oncology and Palliative Care at Zealand University Hospital (ZUH) in Næstved. This allows us to investigate the prevalence, patterns of development, and impact of sarcopenia and cachexia throughout the patient's treatment as well as patient and disease-related factors associated with treatment adherence. This approach allows for the identification of associated factors and provides real-time data, ensuring accuracy and reliability.

5.3 Population

5.3.1 Inclusion criteria

- Patients newly diagnosed with histologically verified lung cancer and scheduled for oncological treatment
- Age > 18 years
- Expected survival > 3 months

5.3.2 Exclusion criteria

- Competing cancer
- Pregnancy
- Physical or cognitive disabilities preventing participation
- Not able to understand written and verbal Danish

5.4 Study Procedure

5.4.1 Recruitment procedure

Patients with suspected lung cancer will be recruited from the Department of Pulmonary Medicine, Zealand University Hospital (ZUH), Næstved. According to reports from the Department of Pulmonary Medicine, > 70% of cases patients will be diagnosed with lung cancer, but in the approximately 30% of patients where a lung cancer diagnosis is not confirmed we omit follow-up assessments. This will thoroughly be explained to the patient verbally and in the written information leaflet during invitation.

Moreover, eligible candidates not already identified from Department of Pulmonary Medicine, will be identified during the multidisciplinary team (MDT) lung cancer conference within the Department of Clinical Oncology and Palliative Care. Subsequently, following a comprehensive medical examination during their initial outpatient visit, patients meeting the specified inclusion criteria will be approached by the attending physician regarding potential participation in the study.

It is important to emphasize that patient recruitment may occur at two distinct time points: first, during the diagnostic phase when suspicion of lung cancer arises, and second, during the initial outpatient visit at the Department of Clinical Oncology and Palliative Care after further evaluation and confirmation of eligibility criteria. This dual approach ensures a comprehensive recruitment strategy,

capturing patients at various stages of the diagnostic phase thus facilitating robust data collection for the study.

5.4.2 Participants' information and written informed consent

The treating physician, nurse or investigator will inform eligible patients about the option to bring relatives to be informed and invited into the study by one of the investigators, which will take place in a private room within the Department of Clinical Oncology and Palliative Care, ZUH, Næstved. All patients eligible for participation will receive a verbal explanation in clear Danish regarding the study's purpose and procedures, the voluntary nature of participation, the guarantee of anonymity, the confidential handling of data, and the implications of their involvement, as detailed in Appendix 4c (*Retningslinjer for afgivelse af mundtlig deltagerinformation*). Patients will be assured that participating in the study will not affect their standard medical treatment and that they can withdraw their consent at any time without any impact on their future care. The following written materials about the PHILUCA study will be distributed: the 1) participant information sheet, 2) the written consent form, 3) the latest version of the brochure *"Before You Make Up Your Mind: The Rights of a Trial Subject in a Clinical Research Project,"* and 4) a document outlining our management of personal data according to Region Zealand guidelines (Appendiks 6 *Oplysningspligt).*

Patients will be offered a minimum of 24-hour for consideration, with the opportunity to discuss participation with relatives. After mutual agreement about a contact timepoint, an investigator will contact the patient to determine participation. If participation is agreed and the consent form is signed, the patient will receive a copy, and the baseline test will be scheduled and performed. Patients who decline to participate in the full PHILUCA study will be asked if they would be willing to participate in a minor part of the study by completing the baseline questionnaire and allow that clinical and treatment data is obtained from their medical journal (see Appendix 5, Samtykkeerklæring). This aims to examine the characteristics of these partial decliners and determine if they differ from full participants. Informed consent will be obtained for this purpose before any data about them is collected and stored. The same data from medical records and the baseline questionnaire will be collected from partial participants as from full participants (see part 7.1).

5.4.3 Adherence, retention and dropouts

Physical testing days will be scheduled in coordination with participants' individual hospital schedules to the best extent possible. However, attending physical testing sessions may pose challenges for some patients, particularly those experiencing chemotherapy-related side effects, live alone, have scarce resources, or have functional limitations. Thus, some flexibility in the scheduling of physical testing sessions may be necessary. Any deviations from the testing manual will be communicated with an investigator for discussion and consideration of pragmatic solutions with regards to timing. Adherence to the physical testing protocol, adherence to prescribed intensity, modifications made during testing, interruptions, and reasons for dropouts, will be meticulously recorded throughout the study period. Additionally, any adverse events will be documented electronically by investigators following thorough instruction.

5.4.4 Withdrawal of study participants

Participants will be withdrawn from the study if the participant withdraws consent or if the investigators deem that it is in the best interest of the patient due to e.g. unexpected sudden events such as bone fractures, psychological distress or newly diagnosed severe comorbidities during the study period.

5.5 Study measurements

Participation in the study involves measurements of muscle mass (body composition), muscle strength, muscle function, and patient-reported outcomes on lifestyle and social vulnerability factors (only at time of diagnosis) and QoL and frailty. All physical measurements are performed while the patient is at the hospital for treatment or examination. For patients undergoing chemotherapy, physical tests are - in addition to the planned assessments at the time of diagnosis, after 3 months, and after 6 months - also performed before each treatment cycle, but no later than 6 months after the diagnosis. A timeline of data collection is presented in part 5.6.

Sarcopenia

A critical challenge for using sarcopenia as a risk factor based on current evidence is the differences in the assessment methods applied in different research fields and clinical settings [21]. In aging and

clinical populations outside the oncological field, the sarcopenia diagnosis is based on an assessment of appendicular lean soft tissue by dual-energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA) and rarely magnetic resonance [22,23]. In contrast, sarcopenia is commonly assessed by computed tomography (CT) scans in patients with cancer. CT scans are readily available for many patients with cancer, given their role in diagnosing and monitoring the disease [14,24]. To account for diverging muscle mass measurements within current literature, muscle mass will be measured by both BIA and CT scans.

The European Working Group on Sarcopenia in Older People (EWGSOP2) updated their 2010 sarcopenia definition in 2018, emphasizing muscle strength as a primary indicator, streamlining diagnosis methods, and advocating for early detection, treatment and increased research [23].
Muscle strength will be measured by maximal isometric handgrip strength. The cut-off points for handgrip strength (HGS) will be < 27 kg for males and < 16 kg for females.
Muscle mass measured by BIA will be expressed as appendicular lean mass (ALM) with cut-off points for males < 20 kg and females < 15 kg, and ALM/height^2 with cut-off points for males < 7.0 kg/m^2 and females < 5.5 kg/m^2.
Muscle mass measured by CT scans by the third lumbar vertebra (L3), since muscle mass and adipose tissue at the L3 are highly correlated with the whole-body measurements [25,26], and are a common muscle mass measurement within the context of lung cancer [14]. This cross-sectional area contains visceral and subcutaneous adipose tissue, psoas, and posterior paravertebral muscles, as well as abdominal wall muscles. These images will be analyzed by using the Slice-O-Matic (Tomovision, Montreal, Canada) software which will allow the specification and segmentation of specific tissue. Segmentation describes the process of separating pixels based on their attenuation in Hounsfield units (HU). Structures are labeled on an image by combining attenuation (often using a range of Hus) and anatomic information. When a range of HU values is used, the process is called threshold-based segmentation. The specific HU range selected varies depending on the tissue of interest[27]. By using the HU limits of 29 to þ150 for skeletal muscles (psoas, erector spinae, quadratus lumborum, transversus abdominis, obliquus externus, obliquus internus, and rectus abdominis), 150 to 50 for visceral adipose tissue, and 190 to 30 for subcutaneous and intramuscular adipose tissue[27,28]. The cross-sectional areas (cm^2) will be calculated for each tissue by the sum of pixels multiplied by the surface

area. Lumbar Vertebrae 3 Skeletal Muscle Index (L3SMI) will be calculated by dividing muscle mass in cm^2 by the patient's height in m^2 (cm^2/m^2)[27]. Low muscle mass by L3SMI determined by CT imaging will be defined by (men <55 cm^2/m^2; women <39 cm^2/m^2)[29].

Sarcopenia will be present if both HGS and muscle mass are below the cut-off points[23]. Gait speed will be used to distinguish between sarcopenia and severe sarcopenia. Figure 1 presents the algorithm of diagnosing sarcopenia by the EWGOSP2:

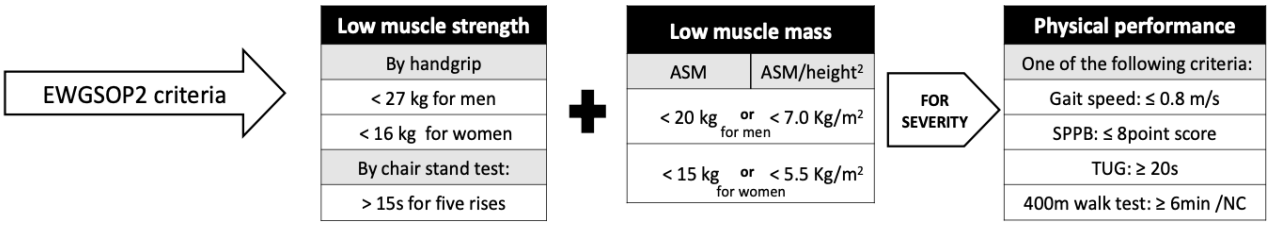

Figure 1: As presented in Meza-Valderrama et. al. (2021) [30].

In addition, through L3 cross-sectional area, a quantification of body composition; muscle mass area, adipose tissue area (visceral, subcutaneous and intramuscular), and muscle attenuation will be obtained. This method presents high sensitivity and specificity for the detection of changes in body composition [28]. Segmentation will be performed by trained researchers; with further evaluation and approval by a board-certified clinical radiologist [31].

Cachexia

Cachexia is a multifactorial syndrome with involuntary progressive weight loss as a result of reduction of skeletal muscle mass with or without depletion of adipose tissue. Cancer cachexia is characterized by systemic inflammation and metabolic changes leading to progressive functional impairment. Sarcopenia as an index for cancer cachexia is a matter of debate. There is a lack of consensus on a definition, diagnostic criteria and classification of cancer cachexia [32]. Therefore, two separate definitions will be accounted for in the PHILUCA study, to ensure possible comparison with existing literature:

The International consensus of the definition of cancer cachexia from Fearon et. al. from 2011 will be used in defining cancer cachexia as >5% self-reported unintended weight loss within the past six months, or a 2–5 % weight loss with either a BMI <20 kg/m^2, or reduced muscle mass (males, <7.3 kg/ m^2; females, <5.5 kg/m^2) [29,33]. Further, cachexia can be stratified into following stages.

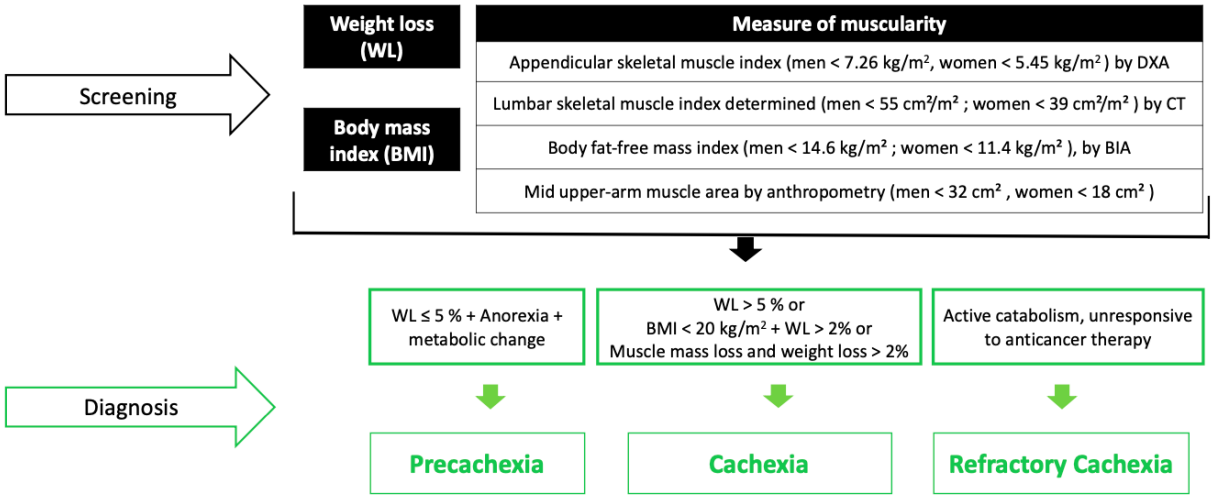

Figure 2: Fearon (2011) [29] definition as presented in Meza-Valderrama et. al. (2021)[30].

To supplement abovementioned, the definition by Evans et. al. from 2008 will be used (Figure 3). Routine blood samples collected during each hospital visit will provide insight into any abnormal biochemistry. Plasma C-reactive protein and serum albumin levels will be used to calculate the modified Glasgow Prognostic Score (mGPS) [34].

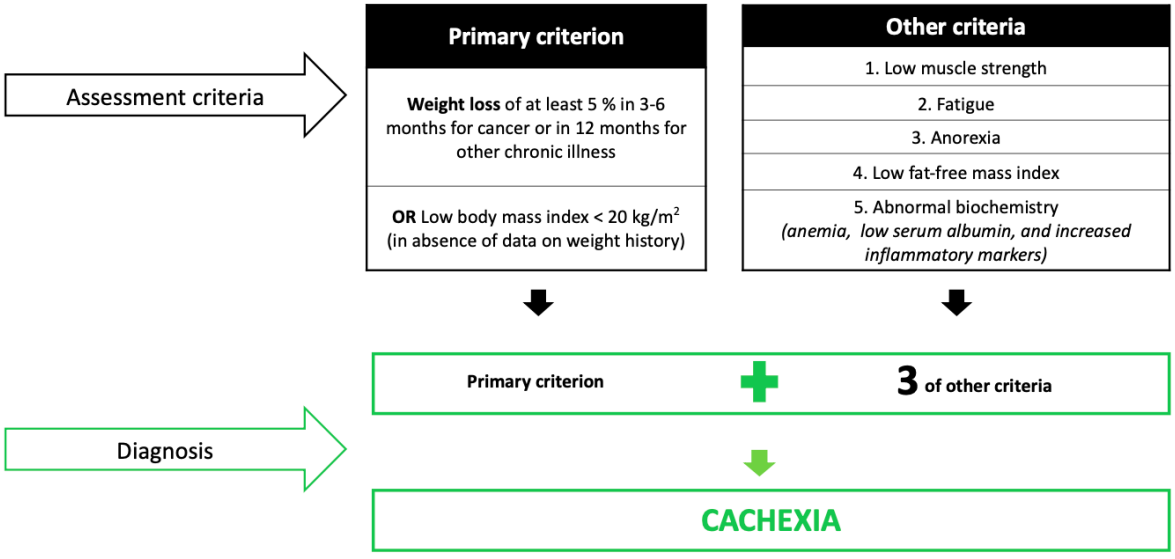

Figure 3: Evans (2008) [35] definition as presented in Meza-Valderrama et. al. (2021)[30].

Frailty

Frailty is a multidimensional clinical condition characterized by a decrease in biological reserve capacity leading to increased vulnerability and reduced ability to resist stressors such as illness, falls, or any circumstances that affect mental and physical well-being[36-40]. Frailty will be assessed by an investigator using the 9-point Clinical Frailty Scale (CFS), according to the definition by Rockwood[41]. A frailty score ≥ 5 indicated the presence of frailty.

5.5.1 Measurements and clinical data

Table 1 shows the outcomes, measurements and sources that will be used in the study period.

Endpoints	Description	Test/sample/source
Primary outcome		
Survival	○ 1-year overall survival ○ 5-year overall survival	Medical records Medical records
Exploratory outcomes		
Sarcopenia	○ Muscle strength and mass and change over time	Routine CT-scan (baseline CT to last performed CT within 12-months after diagnosis) & bioimpedance analysis
Cachexia	○ Stages of cachexia and change over time	Muscle mass (by routine CT-scan and bioimpedance analysis), abnormal biochemistry by routine blood samples and weight loss
Chemotherapy completion rate	○ Mean RDI in % ○ Number of patients with an RDI < and ≥ 85 % ○ Dose-limiting toxicity (DLT) DLT defined as 'switching treatment', 'treatment delay' (≥3 days from initially planned), 'treatment de-escalation' (dose reduction ≥15% of platinum agent), early treatment termination, and hospitalization ≥1 day, all due to chemotherapy-induced side effects.	Medical records
Treatment complications	○ Complications related to surgery, radiotherapy, immunotherapy and targeted therapy.	Medical records
Biomarkers	○ Routine blood tests of plasma CRP and serum-albumin to diagnose cachexia and haematological toxicities	Medical records
Changes in body composition	○ Total muscle and fat mass	Routine CT-scans Bioimpedance analysis

Changes in muscle strength	○ Isometric muscle strength	Dynamometry for handgrip strength (HGS)
Changes in muscle function	○ Muscle power ○ Gait speed	30sSTS 5 x STS 10 m. walking test (maximal and habitual)
Geriatric treatment-related vulnerability	○ Geriatric-8 screening tool	Filling in of the G8 will be partly self-reported by the patient and from medical records.
Frailty	○ Clinical Frailty Scale (CFS)	Assessed at visit at hospital by physician or investigator
Vulnerability index	○ Items for new scale to predict treatment adherence	Self-reported items on social vulnerability and obtained from medical records

A comprehensive health/capacity assessment will be completed by an investigator (physiotherapist or exercise physiologist) before every test session and include the following: (a) exercise preparticipation health screening, and pre-exercise evaluation; (b) measurement of body composition by bioimpedance analysis; (c) measurement of maximal muscle strength by HGS [42] using a hand dynamometer (Jamar); (d) muscular function; firstly, lower-extremity muscular function by 30-second sit to stand test (30sSTS). Concurrently, five times stand up within the 30sSTS test will be measured using an additional stopwatch. Secondly, maximal and habitual gait speed will be measured over a 10-meter straight walking course. In-depth descriptions of the testing procedures can be found in (Appendiks 2a testmanual på dansk).

5.5.2 Questionaries

Treatment-related vulnerability

A tool commonly used to identify prognostic vulnerability among older patients with cancer is the Geriatric-8 screening tool (G8) [43] originally developed from the Mini Nutritional Assessment questionnaire[44]. The G8 is recommended by the International Society of Geriatric Oncology (SIOG) [45] and was originally designed to identify older patients who would benefit from geriatric assessment and intervention in the trajectory of cancer treatment. Studies have found that the G8 has high sensitivity and negative predictive value in identifying older patients at risk of negative outcomes when undergoing surgery for cancer[33,43,46,47]. Patients with a score of ≤ 14 will be regarded vulnerable regarding treatment, while patients with a score of ≥15 will be regarded “fit”. Filling in of the G8 will be partly self-reported by patient and from medical records.

Self-reported physical activity levels

Participants will be asked about their self-reported weekly physical activity, moderate-to-vigorous physical activity and daily sedentary time using single-item questions.

Health-Related Quality of Life

HRQOL, evaluated by self-reported questionnaires, is a valid and strong measure. It correlates with various crucial aspects such as longevity, health habits, mental and physical well-being, social connections, and productivity among cancer patients[48]. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is an integrated system for assessing the HRQoL of cancer patients participating in clinical studies and other types of research in which patient-reported outcomes are collected[49]. The EORTC QLQ-C30 is designed for use in a wide range of cancer populations and is intended to be supplemented by tumour-specific questionnaire modules such as those for lung cancer (QLQ-LC13)[49].

HRQoL will be evaluated by EORTC QLQ-C30 and EORTC QLQ LC13[49]. Items from EORTC-QLQ-C30 contain a global scale covering global Quality of Life (QoL), five functioning scales and 9 symptoms scales. Items from the EORTC QLQ LC13 contain ten disease-specific symptom scales.

All the scales and single-item measures range in score from 0 to 100. Thus, a high score for the global health status / QoL represents a high QoL, a high score for a functional scale represents a high / healthy level of functioning, but a high score for a symptom scale / item represents a high level of symptomatology / problems[49].

Social vulnerability index

We have based on knowledge from previous studies and feedback from clinical experts and patients on factors impacting treatment adherence among lung cancer patients, developed and pilot tested a vulnerability instrument to predict adherence to treatment [50]. The instrument include nine clinical and patient-reported vulnerability criteria: (1) stage (from medical journal), (2) comorbidity (somatic or psychiatric) (from medical journal), (3) age (from medical journal), (4) performance status (from medical journal), (5) activities of daily living (three patient-reported items regarding difficulties with personal hygiene, taking a walk and climbing stairs), (6) social support (three patient-reported items

regarding emotional support as well as support with practicalities at home and transportation), (7) health literacy (three patient-reported items regarding difficulties in understanding healthcare information, instructions from healthcare professionals and filling in forms), (8) transportation related barriers for treatment (three patient-reported items regarding difficulties in reaching the hospital due to lack of transportation, long distance to the hospital or limited energy) or (9) alcohol abuse (three patient-reported items regarding alcohol consumption) [50]

Table 2 – Self-reported questionaries

Patient characteristics and Exploratory outcomes	Scale, Reference	Abbreviation	Details
Sociodemographic factors	Education, work market affiliation, civil status, cohabitation status	Self-constructed	Items: 4 (only at baseline)
Weight, clinical characteristics and smoking	Current weight and 12+6 month(s) ago	Self-constructed and 3 self-reported G8 items	Items: 9 (only at baseline)
Vulnerability index	Items for new scale to predict treatment adherence	New scale that will be validated in this study	Items: 15 (only at baseline)
Physical activity levels	Physical activity levels	Self-constructed	Items: 3 (only at baseline)
Health-Related Quality of Life (Functioning and symptoms)	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire	EORTC QLQ-C30	Items: 30 Domains: 15
Health-Related Quality of Life (Disease-specific symptoms)	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung cancer module: QLQ-LC13	EORTC QLQ-LC13	Items: 13 Domains: 10

Participants will be asked to fill out a questionnaire comprising different scales and self-constructed questions addressing exploratory outcomes and additional information, possible mediators and confounders (Table 2) at diagnosis, after 3 months and after 6 months. The questions will be gathered to comprise one extended questionnaire. Weight and clinical characteristics and sociodemographic factors will only be collected at baseline.

Patients can complete the questionnaire on paper on the first test day if there is enough time and a quiet space available. Further, patients can complete it at home, where they will receive the

questionnaire electronically. If the patient prefers to fill out the questionnaire at home, and lack necessary electronic skills, it can be done over a phone call, where a project staff member assists the patient through the questions verbally. It will be agreed with the patient when and how it would be most convenient for them, but the first questionnaire must be completed before the treatment initiation or as soon as possible thereafter (at the latest, one week after the start of treatment). Data collections will be managed through REDCap.

5.6 Data collection timeline

Table 3

Months (number)	1	2	3	4	5	6	12
Test/Examination							
Muscle mass by routine CT-scans*	•		•			•	•
Muscle mass by bioimpedance analysis	•		•			•	
Muscle strength tests	•	•	•	•	•	•	
Muscle function tests**	•	•	•	•	•	•	
Frailty	•		•			•	
Questionnaires							
Self-constructed G8 items	•						
Social vulnerability instrument	•						
Lifestyle	•						
EORTC-QLQC30, EORTC-QLQLC13	•		•			•	

*Up to 12-months.
Routine CT scans are generally performed at defined intervals during the diagnostic and treatment course, typically at diagnosis, around 3 months, and at 6 months. For our analysis, we aim to utilize the most recent CT scan conducted within 12 months as the post-treatment measure to evaluate changes in muscle mass before and after treatment. If the final CT scan post-treatment occurs earlier, for instance, at 4.5 or 9 months, this scan will be used as the endpoint measure. It is important to note that no additional CT scans beyond routine scans and the established 12-month timeline will be scheduled.
**3 muscle function tests as presented in Table 1
Abbreviations; Computed Tomography (CT); The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30), and lung cancer module (EORTC-QLQLC13).

6.0 Statistics

6.1 Power considerations and statistical analysis

The population size (n=180) is calculated based on a pooled estimate from prospective cohorts, including patients with advanced stage lung cancer, with a hazard ratio for mortality risk of 2.38 and a prevalence of sarcopenia for the population of 50% [8]. With power set to 90% and alpha=0,05, we

have to include 130 patients with advanced stage lung cancer. To account for an expected study withdrawal rate of approximately 28%, we need to ensure that we have 130 patients remaining by the end of the study. To find the initial number of participants required, we divide the final required sample size (n=130) by the retention rate (0.72). Rounded up to the nearest whole number, we need to include 180 patients with advanced stage lung cancer. Our recruitment method (at time of referral for suspicion of lung cancer) will include non-cancer patients, patients at low stage who undergo surgery, which means the total cohort will include n=500 participants, to ensure 180 patients with advanced stage lung cancer. This total cohort will enable subgroup analyses comparing cancer and non-cancer participants, as well as analyses within different treatment subgroups.

We will stratify analyses according to relevant categories in uni- and multivariate regression analyses examine associations between exposures and outcomes, presenting estimates of regression coefficients and odds ratios with 95% confidence intervals and p-values and use mixed effect models for repeated measurements.

For the social vulnerability screening instrument, we will describe the distribution of each factor included in the vulnerability screening tool. Next, we will use statistical analysis ('prediction models') to select the vulnerability factor that best predicts treatment adherence (measured in Relative Dose Intensity). Furthermore, we will examine the sensitivity and specificity of the screening tool using different cut-off scores to assess the optimal cut-off for identifying patients who did not completed treatment optimally.

7.0 Data management and storage

7.1 Data from medical records

Before the study recruitment, relevant clinical information will be passed to the investigators in order to identify potential patients for inclusion at the Department of Pulmonary Medicine, ZUH. Based on patient lists these will include: personal and contact information (name, address, phone number, email), date of next visit to clinic, and sensitive personal information (CPR number, suspected cancer type). During the invitation session, the exclusion criteria of severe physical or cognitive comorbidities will be assessed by asking the patient. We expect up to 10 % of approached patients will decline participation. We therefore need to screen approximately 1550 patients within the period of

01.09.2024 to 01.09.2027. If patients decline participation, all information stored will be deleted immediately.

After written informed consent has been obtained from participants at baseline the medical records will be reviewed by an investigator at regular intervals during lung cancer treatment to collect data on sociodemographic characteristics, anthropometrics, health status, functional status, and clinical information on cancer type and cancer treatment. These include:

- Ordinary personal information; name, address, phone number, email, cohabitation status, employment status, age and sex.
- Sensitive personal information; CPR number, cancer type, cancer treatment, body mass index, body surface area, information on the degree of treatment completion and complications, physical or cognitive comorbidities, CT scan images, PS, time since cancer diagnosis, results from standard blood tests.

The patient's consent gives the investigator and their representative direct access to this information to conduct, monitor, and audit the study. The information from medical records is collected with the aim of investigating whether muscle mass, strength, and function are related to treatment tolerance. The medical records will be reviewed at the end of the study by one of the investigators to extract data on recurrence and survival for a period of up to 1 year and 5-years after lung cancer diagnosis. The data will be handled with confidentiality according to Part 7.2 and used for descriptive statistics of participants and in multivariate analyses of outcomes in a pseudonymised form. Participants who initially provided informed consent and had performed baseline measurements, but were later found not to have lung cancer will contribute with data for comparison analysis between people with and without lung cancer on variables such as sociodemographics, clinical characteristics, baseline physical function and body composition, and survival. No additional measurements beyond baseline testing will be conducted for this cohort. All data will be securely handled in compliance with ethical and confidentiality standards.

7.2 Data storage and safety

We will notify and obtain permission from Region Zealand and Research Ethics Committee Region Zealand before study initiation. Handling of all personal data will comply with the General Data

Protection Regulation and the Data Protection Act. Data will be stored electronically according to Region Zealand's guidelines on data safety. The Clinical Study Management software, Research Electronic Data Capture (REDCap) with off-site backup systems will be used for data management and storage until the end of the study period (and 5 years after the end of the study). REDCap automatically pseudonymises data by giving a unique study number to participants by inclusion. Data in paper form may be stored temporarily behind three locks in a locked cabin at a locked office at a locked hallway in the office located at the Department of Clinical Oncology and Palliative Care, Zealand University Hospital, Rådmandsengen 5, DK-4700 Næstved, room number 50.02.15 before being scanned and uploaded electronically and afterwards destroyed. In addition, pseudonymised documents that may not be suitable for storage in REDCap will be stored in a secured project folder at the O-drive *(ONK_DATA (\\regsj.intern\files) (0:)*, which is protected by passwords. Only the investigators will have data access. For statistical analyses data will be transferred to the Danish Cancer Society (see Appendix 6, Oplysningspligt).

8.0 Ethical considerations

This study is conducted based on the Danish Code of Integrity in Research complying with the principles of integrity and responsibility in research. Participants in the studies will be included upon informed written consent, allowing withdrawal of consent without any consequences for their treatment and without explanation.

The study will be conducted in accordance with the Declaration of Helsinki, and the study procedure will comply with the ethical standards of the participating clinical department. Investigators will be trained in (online course) and comply with guidelines from the Good Clinical Practice unit throughout the study period.

Informed consent will be obtained from all participants prior to initiation of any study procedures. Informed consent will only be obtained after thorough verbal information, discussions, and answers to any questions the patients may have about the written information or other thoughts during the process of deciding to participate or not. Patients will be informed that they may withdraw their consent at any time. We ensure that all obtained data during the study period will be treated

confidentially. All statistical analyses will be conducted on grouped data only, and no results are disclosed revealing individual patient data.

The considerations for the safety, and well-being of research participants, as well as the rights, integrity, and privacy of research participants, take precedence over scientific and societal interests. Since the risk of patients experiencing side effects or harms does not exceed the risks in everyday life, and the societal benefit of the project is significant and beneficial for the treatment of future patients, this is considered fulfilled. In addition to receiving information about muscle mass, muscle strength, and muscle function, no therapeutic benefit is considered for the participants. However, the study participants will contribute to research that may have a significant impact on the development of future treatments for patients with lung cancer.

9.0 Organization

The study will take place in the Department of Pulmonary Medicine and Department of Clinical Oncology and Palliative Care, ZUH. We have formed a unique collaboration between clinical experts in lung cancer treatment, physiotherapists and nutritional specialists, ensuring clinical and scientific relevance and full translational potential to clinical practice. The project will be conducted as a PhD project by Lukas Svendsen who will ensure high quality data collection and the appropriate conduction and scientific documentation. The translational potential of the project will be maximized by the involvement of clinicians and pragmatic solutions in all elements of the study.

PI and primary supervisor is Professor, Director of Danish Research Center for Equality in Cancer (COMPAS), Department of Clinical Oncology and Palliative Care, ZUH, Susanne Dalton and the study will be included as one of the research activities in COMPAS aiming to reduce inequality in outcomes after cancer through targeted interventions to vulnerable/high-risk patients. Primary co-supervisor is Clinical Professor Charlotte Suetta, Department of Clinical Medicine, University of Copenhagen. Co-supervisors will be physiotherapist, postdoc, Gunn Ammitzbøll and Morten Quist, Associate Professor, Department of Clinical Medicine, University of Copenhagen.

The project team further include highly experienced clinicians and researchers; Consultant, Malene Støckel Frank and Professor, Consultant in Pulmonary Medicine Uffe Bødtger, and project nurse Gitte Alstrup all affiliated at ZUH, and Casper Simonsen, PhD, group leader at Centre for Physical Activity Research (CFAS). The work regarding statistical validation of the vulnerability screening instrument

is done in collaboration with Pernille Bidstrup and Rikke Langballe at the Danish Cancer Institute at the Danish Cancer Society.

10.0 Dissemination

Results will be published as at least 2 peer-reviewed papers, presented at national/international conferences, press releases and homepage news (compas.dk, cancer.dk, dccc.dk, dlcg.dk), as well as social media (linkedin and X) and popular science talks to i.e., patient and professional organizations.

11.0 Finances

There is no financial compensation for participation in the project. Participation will not entail additional hospital visits or financial expenses from the participants' side. The initiative of conducting the study was taken by the Clinical Professors Susanne Oksbjerg Dalton and Gunn Ammitzbøll from Department of Clinical Oncology and Palliative Care, Zealand University Hospital. The study is financed through funding from the Danish Cancer Society (A20717, 1.250.000 DKK); the Department of Clinical Oncology and Palliative Care, Zealand University Hospital (342.001 DKK); The Danish Research Center for Inequality in Cancer (COMPAS) (223-A13094-18-S68, 102.500 DKK); Region Zealand's Health Science Research Fund (150.000 DKK). The majority of expenses will be for salary of the PhD student. External funds, such as software, will be applied through independent foundations and government grants during the study period. The financial support and study expenses will be administered from accounts in Region Zealand. None of the investigators or collaborators have financial interests in the study or other conflicts of interest.

12.0 Insurance

Participants will be covered by the regular insurance for patients treated at hospitals in Region Zealand under current legislation as the principal investigator Susanne Oksbjerg Dalton is employed as a Professor at the Department of Clinical Oncology and Palliative Care. In case of severe injuries, compensation for injury will be provided through *Patienterstatningsordningen* for patients included in the study. If any requests occur, the investigators and clinical staff will be obligated to guide the participants in the application process.

13.0 Publication of results

The study will be conducted as part of Lukas Svendsen's PhD project. The study will be registered at www.clinicaltrials.gov. The reporting will follow *"The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies."* The Vancouver criteria will be met for all authors. Positive, negative and inconclusive study findings will be reported to the public. Furthermore, results will be disseminated to the staff of the involved clinical department and presented at both national scientific meetings such as the Danish Cancer Days held by the Danish Comprehensive Cancer Center and at international conferences.

14.0 Perspectives

Results from this study may potentially inform clinical practice and indicate the potential for improving physical function, quality of life and prognosis through treatment. The findings from this prospective cohort study will elucidate which patients are at risk for sarcopenia and cachexia, thereby informing the development of a forthcoming RCT feasibility study incorporating a combined exercise and nutritional intervention.

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