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From pretreatment assessment to (p)rehabilitation for improving treatment tolerance

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Contents

'It is positive to include all patients in a prehabilitation program, but especially patients with a poor preoperative physical condition and/or nutritional status.'

-Healthcare professional-

Chapter 1

General introduction and outline

General introduction and outline

Epidemiology and trends in the occurrence of non-small cell lung cancer

Lung cancer is the fourth most common diagnosed cancer and the most common cause of cancer-related deaths in the United States and Europe (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers (2). The incidence of lung cancer in men peaked in the 1980s, followed by a subsequent decline, with similar patterns in women following 20 years later (3). Although the incidence of lung cancer among men has been decreasing since the early 1990s, it is still the fourth commonly diagnosed cancer among men and the most common cause of cancer death (4). In the past 40 years, women's risk has risen markedly, becoming nearly identical to that of men (4). Lung cancer deaths in men are now declining at an average of 2.9% annually with a percent decrease roughly double that of women (3). In 2019, 14,300 patients were diagnosed with NSCLC in the Netherlands (5) and a total of 10,233 patients had died from NSCLC that year (6). It is predominantly a disease of the elderly, with half of all newly diagnosed patients being ≥70 years(7). Tobacco use or being exposed to second-hand smoke is the most important risk factor for the disease; other behavior-related or lifestyle-related diseases that are important risk factors for NSCLC are emphysema and chronic obstructive pulmonary disease (8).

Treatment

Before treatment decision-making is performed, it is important to evaluate to which extent the cancer has spread at the time of diagnosis. Therefore, detailed staging of the tumor according to the tumor, nodes, and metastases (TNM) guidelines is necessary, as well as pretreatment risk assessment to discuss optimal treatment options with the patients together with prediction of posttreatment status (9). According to Dutch guidelines, it is also mandatory to discuss all newly diagnosed patients with NSCLC in a multidisciplinary tumor board for staging and treatment recommendations.

Early-stage non-small cell lung cancer

Stages IA to IIB NSCLC include tumors that have not invaded clinically significant anatomical structures, such as the heart or great vessels (10). There is also no spread or limited spread to regional lymph nodes and there is no metastasis to distant sites. Therefore, these stages are generally referred to as early-stage NSCLC. This stage group comprises approximately 19% of patients worldwide with NSCLC (10), and 32% of patients in the Netherlands (11).

Case 1
A 58-year-old woman was hospitalized for COVID-19. She had a smoking history of more than 20 years and smoked one pack a day. A lesion on the lung was discovered by chance with an X-ray for COVID-19 diagnostics. Closer examination with a computed tomography (CT) scan also revealed an inflammatory lesion and an obstructive lesion in the left lower lobe. The masses had an increased metabolism and were considered malignant lesions. Furthermore, no distant metastatic signs were shown on positron emission tomography-CT (PET-CT). No abnormal signs were seen on the brain magnetic resonance imaging (MRI) examination either. Pathology results of a needle biopsy showed poorly differentiated squamous cell carcinoma located in the right upper quadrant close by the hilar.

According to European guidelines, lung resection is recommended as primary treatment option for physically fit patients with early-stage I and II NSCLC. One-year and 5-year survival of patients who underwent surgery ranges from 41-67% for stage I and 22-55% for stage II, respectively (12). Stereotactic ablative radiotherapy (SABR) is the advised curative treatment for patients with early-stage NSCLC who are inoperable because of a low physical fitness and/or high comorbidity burden. The use of SABR has increased over time (26% in the period 2004-2008 versus 33% in 2009-2013) (13, 14) and has shown similar survival rates as surgery. SABR makes use of high doses of radiation in a limited number of fractions, thereby avoiding damage to organs close to the tumor. Conventional radiotherapy with a longer schedule is a third treatment option and is offered when resection or SABR are not possible due to the location of the tumor. SABR generally results in better 5-year survival rates than conventional curative radiotherapy and ranges from 27-40% for stage I and from 7-27% for stage II, respectively (15, 16). Despite the fact that physically fit patients are generally advised to undergo surgery, almost 40% of these surgical patients developed postoperative complications, such as prolonged air leakage, bronchopneumonia, or bleeding (17, 18). In patients undergoing SABR, 5-10% of patients suffer from toxicity such as dyspnea, pneumonitis, and lung fibrosis (19). Furthermore, there are developments in neodjuvant treatment for surgery where patients receive immunotherapy (20). However, there is still uncertainty about the long-term effects, but the first results are hopeful.

Case 1
The multidisciplinary team concluded that the clinical staging for this patient with early-stage non-small cell lung cancer (NSCLC) was cT2aN1M0, stage IIB. Because of the enlarged lymph node proximal to the hilum, the curative treatment plan was surgery (lobectomy).

Locally advanced non-small cell lung cancer
Stages IIIA and IIIB NSCLC represent a clinically diverse group of patients. The tumor may or may not have spread to major anatomical structures and spread to regional lymph nodes may be limited or more extensive. However, these stages do not show metastases to distant sites. Stages IIIA and IIIB NSCLC are commonly referred to as locally advanced NSCLC. This stage group comprises approximately 24% of patients worldwide (10), and 20% of patients in the Netherlands (11).

Case 2
A 70-year-old man consulted the general practitioner with coughing and was referred to the nearest general hospital for an X-ray. He was diagnosed with pneumonia; his cough persisted, despite treatment. After two weeks, the man was referred for a chest CT-scan. The CT-scan showed a probable carcinoma in the lungs with metastases to the lymph nodes. In addition, an endobronchial ultrasound and magnetic resonance imaging (MRI) was performed. Thereafter, the patient was diagnosed with stage IIIB adenocarcinoma, centrally in de lungs.

Stage III NSCLC is a heterogeneous patient group with a 5-year survival rate of 30% in patients who underwent treatment (12). Treatment choice depends on resectability of the tumor and operability of the patient. Most patients are inoperable or have unresectable disease. The combination of chemotherapy and radiotherapy is the standard of care for locally advanced NSCLC (21), and has increased from 35% in 2008 to 39%. In international guidelines (22), the recommended curative treatment for relatively physically fit patients with stage III NSCLC is concurrent chemoradiation (cCHRT: chemotherapy and radiotherapy at the same time) over sequential CHRT (sCHRT: chemotherapy followed by radiotherapy), as cCHRT results in a 3-year survival rate of 25% compared to 19% in patients receiving sCHRT (23). A third curative treatment option is radical radiotherapy alone (8), which is applied in 12% of the patients with stage III NSCLC and results in a 3-year survival rate of 15% (24).

Case 2
During the multidisciplinary team meeting with the pulmonologist, radiologist, oncologist, pathologist, and clinical nurse specialist, results of the diagnostics tests (e.g., CT-scan, endoscopy, and pathology) and the treatment options for the patient were discussed. The multidisciplinary team concluded that the diagnosis was NSCLC (stage IIIB: cT2aN3M0; histology: squamous cell carcinoma) and advised the patient to opt for sequential chemoradiotherapy (sCHRT), due to the comorbid conditions hypertension, cognitive impairment, and severe rheumatoid arthritis.

Resilience

The process and result of successful adaptation to difficult or challenging life experiences, especially through mental, emotional and behavioral flexibility and adaptation to external and internal demands is also mentioned as resilience (25). As previously described, NSCLC is predominantly a disease of the elderly, with half of all newly diagnosed patients being ≥70 years of age (7). As can be easily observed, old age is just a number. However, the elderly phenotype is characterized by a loss of quality and decline of function of several organ systems. Although we often do not die solemnly of old age, the effects of the wear and tear of life make bodies more at risk to experience adverse health outcomes when faced with a stressor. Age-related decline has also been defined as frailty (26). Frailty is a loss of resources in several geriatric and physical domains of functioning, which leads to a declining reserve capacity for dealing with psychophysiological stressors (27). Geriatric parameters appraise the health status of elderly people, focusing on somatic, functional, and psychosocial domains (28) in order to determine the presence of frailty in elderly and its associated risk for treatment complications. In addition to geriatric characteristics, physical fitness is also an important characteristic for resilience to treatment in patients with NSCLC. Physical fitness represents the physical capacity that is needed to undertake normal everyday activities, independently and without the early onset of fatigue (29). Physical fitness is a set of attributes that are either health-related or skill-related. The health-related components of physical fitness are aerobic fitness, muscular endurance, muscular strength, body composition, and flexibility (30). The skill-related components of physical fitness focus on agility, balance, coordination, power, speed, and reaction time (30). The aging process tends to reduce physical fitness and results in difficulties in daily life physical activities and normal functioning of the elderly (31, 32). The level of daily physical activities of the elderly also decreases with aging, although it is well known that physical fitness

(e.g., aerobic fitness) is important for independent living (33), prevention of chronic health problems, and health-related quality of life (HRQoL) (34). Furthermore, aerobic fitness is directly related to the integrated function of numerous systems, and it is thus considered a reflection of total body health (35). Therefore, patients with a low resilience have a higher risk for treatment intolerance [8,9].

Pretreatment risk assessment

Pretreatment screening and assessment of risk factors can help to timely identify patients who are at increased or high risk for treatment complications and functional decline. Pretreatment risk assessment is essential for clinical reasoning and shared decision-making for the choice of treatment interventions. By doing so, treatment could potentially be effectively targeted and tailored to patients with, when applicable, attention for individual modifiable risk factors, to reduce their risk of treatment intolerance. Timely identifying high-risk patients before the start of treatment is important to be able to initiate preventive interventions to improve resilience. This thesis focused on three pretreatment risk assessment areas: physical fitness, nutritional status, and geriatric status.

Physical fitness

It is important to gain insight into pretreatment patient characteristics and physical parameters that might be prognostic for physical functioning, treatment tolerance, and survival. As described in the European guideline for operable patients with NSCLC (36), standard pulmonary function tests must be performed to verify surgical operability. When the forced expiratory volume in one second (FEV_1) and/or the carbon monoxide lung diffusion capacity (DLCO) fall below 80% of predicted, a cardiopulmonary exercise test (CPET) should be performed for surgical decision-making (36). These tests can also be used to identify patients at high-risk for postoperative complications (37). The gold standard to evaluate aerobic fitness is assessing the oxygen uptake at maximal exercise (VO_{2peak}) during a progressive CPET until volitional exhaustion (38). VO_{2peak} is determined by the integrative capacity of the pulmonary, cardiovascular, and muscular system to take in, transport, and utilize oxygen during maximal exercise (39). VO_{2peak} as measured during a CPET has been used most widely for preoperative risk stratification in lung surgery (40, 41). Although the CPET is the gold standard to evaluate a patient's aerobic fitness, a CPET is relatively expensive, time-consuming, and requires trained personnel (42, 43). As an alternative for the CPET (42, 43), practical, easy to administer,

and time efficient physical performance tests might be less complicated and cheaper to estimate a patient's preoperative physical fitness (42, 44). The use of field exercise tests such as the incremental shuttle walk test, stair-climb test, 6-minute walk test, and the steep ramp test for estimating aerobic fitness has previously been investigated in patients with cardiac and pulmonary disease (45). Results demonstrated a moderate-to-strong correlation between CPET-derived variables of aerobic fitness and field exercise test outcomes (46). Nevertheless, systematic evidence on the association between pretreatment field exercise tests and treatment complications in patients with NSCLC is lacking, especially in patients undergoing treatment for locally advanced NSCLC. Prognostic parameters are preferably easily measurable and cost-effective with minimal burden on the patient. Such information can be used by medical specialists to identify patients who are expected to tolerate treatment, which is important for shared decision-making.

Case 2
Pretreatment risk assessment supported the clinical impression that this patient had several risk factors that might be associated with intolerance to sCHRT. His advanced age, comorbidity burden (hypertension and rheumatoid arthritis), low handgrip strength (26 kg, 57% of predicted) and his impaired nutritional intake before treatment (60% of recommended) are all independently associated with a high risk for treatment complications such as unplanned hospitalizations, dose reduction, functional decline, and premature discontinuation of CHRT.

Case 1
Due to a poor lung function (forced expiratory volume in one second 72% of predicted and carbon monoxide lung diffusion capacity 54% of predicted), the patient should undergo a preoperative cardiopulmonary exercise test to assess whether she is fit for surgery.

Nutritional status

It has been reported that malnutrition may decrease the response to cancer treatment (47), as well as that malnutrition is associated with poorer HRQoL and higher rates of treatment intolerance in patients with lung cancer (48, 49). Knowing that patients with NSCLC are often nutritionally depleted and therefore at high risk for treatment complications (50), pretreatment nutritional

screening and/or assessment is important. Identification of malnutrition as soon as possible after diagnosis is recommended to identify patients who are at high risk for treatment complications and who therefore might benefit from pretreatment nutritional interventions. Nutritional screening and/or assessment is the process of evaluating characteristics and risk factors that predispose a patient to malnourishment (51). Body mass index (BMI) and body fat percentage seem easily and promising physical and nutritional parameters that already have shown to be associated with treatment tolerance and survival in patients with NSCLC (52). Despite this, the large heterogeneity of included studies with respect to various types and stages of cancer, differences in anticancer therapy, and differences in outcome measurements should be noticed (53). Systematic evidence for the associations between outcomes of various nutritional assessments and treatment complications in patients with NSCLC is lacking.

Geriatric status

A previous study showed that geriatric problems existed in half of the patients with breast, colorectal, ovarian, lung, and prostate cancer ≥70 years, in whom a change in therapeutic strategy was considered. This was revealed by an extensive geriatric assessment after which treatment was adjusted in 25% of the patients (54). A pretreatment geriatric assessment has potential in detecting frailty and unidentified but possible manageable problems (55). Therefore, a geriatric assessment might lead to better outcomes, through the targeted use of an intervention to improve treatment tolerance and by adjusting oncologic treatment plans in the elderly cancer population (55, 56). Geriatric factors such as poor cognitive status, vulnerability, reduced mobility, and having a small social network have a negative influence on treatment tolerance and survival in older patients with cancer (54, 57). While it is still unclear to what extent these geriatric assessments are associated with treatment tolerance and survival in patients with NSCLC (56), it is important to predict treatment intolerance with easy-to-use, cheap, and less time-consuming geriatric assessments as it can be used in treatment decision-making.

Multimodal lifestyle optimization before, during, and after treatment

Evidence about the optimal pretreatment risk assessment can be used to identify high-risk patients who may benefit from lifestyle interventions before and during cancer treatment (prehabilitation and rehabilitation during treatment, respectively). Prehabilitation aims to improve a patient's physical fitness and psychological capacity in the period between diagnosis and the

start of treatment (e.g., lung resection, CHRT) in order to improve resilience and reduce the risk for complications and accelerate recovery of physical functioning (58). Especially patients with a low physical fitness might benefit from prehabilitation as their a priori risk for poorer outcomes is increased as a consequence of their lower psychophysiological reserve capacity (59, 60). Recent systematic reviews in patients with early-stage NSCLC have shown that exercise prehabilitation reduces postoperative complications with almost 50% and length of hospital stay with a mean difference of more than two days; however, individual studies demonstrate inconsistent results (61, 62).

Case 1
The predicted postoperative VO_{2peak} was above 10 mL/kg/min, which means that the patient is considered sufficiently fit for surgery. Due to a poor lung function, low handgrip strength, and low BMI, the patient was advised to preoperatively improve her aerobic fitness and nutritional status with the help of a physical therapist and dietician. The specialized physical therapist in this area was able to coach this patient in a partly supervised prehabilitation program in primary care and at home and improve her aerobic and nutritional fitness in the four weeks before surgery.

Regarding the above mentioned inconsistent results, heterogeneity of patient populations, interventions, and outcome measures, and relatively small sample sizes and inclusion of low-risk populations might contribute to bias (63). Furthermore, a better assessment of the quality of prehabilitation programs could potentially contribute to the certainty of evidence regarding the merit of prehabilitation to reduce postoperative complications, postoperative mortality, length of hospital stay, and to improve HRQoL (64, 65).

Multimodal rehabilitation (e.g., improving physical fitness using physical exercise training, nutritional support, smoking-cessation) during CHRT might also be of added value in patients with locally advanced NSCLC to improve treatment tolerance, to maintain or improve physical fitness, and to improve HRQoL. A feasibility study in patients with rectal cancer shows that rehabilitation during CHRT was feasible for a large part of the patients, safe and seemed able to prevent an often-seen decline in physical fitness (66), which may also be promising for patients being treated for lung cancer. In patients with lung cancer, challenges to physical exercise training due to bouts of fatigue

and decreased mood, decreased motivation, unplanned hospitalizations, and demanding treatment schedules should be considered (32). Unfortunately, evidence on the feasibility of multimodal rehabilitation during CHRT among patients with stage III NSCLC is lacking.

Case 2
The pretreatment examination supported the clinical impression that the patient had several risk factors that might be associated with complications during and after treatment with sequential chemoradiotherapy.
Rehabilitation during CHRT was discussed with the patient to maintain or even improve his physical fitness and prevent loss of muscle mass, as well as to increase his treatment tolerance. The patient performed partially supervised and personalized physical exercise training during CHRT in the home environment and received tailor-made nutritional advice during his cancer treatment. His wife was also involved in the rehabilitation program to support and motivate her husband. The physical exercise training could be performed by adjusting training intensity and the way in which the physical exercise training was delivered and the patient completed CHRT treatment without adverse events.

The development of a feasible lifestyle intervention before, during, and after treatment

Although patients with NSCLC perceive physical activity as being important for recovery during and after treatment, most patients are insufficiently physically active (67). Previous studies in patients with NSCLC show that the willingness and ability to participate in a lifestyle program is low (between 28% and 56% (68, 69)) and that program adherence is only moderate (between 53% and 73% (68, 70)). Among dropout reasons, cancer-related side effects and, mostly, lack of interest and motivation represent key contributors (67). Regarding prehabilitation in patients with early-stage NSCLC, surgeons acknowledge the benefits to decrease the risk of postoperative complications, but it is unclear for surgeons when and where to refer to for prehabilitation (71). Research in patients with colorectal cancer has shown that, next to ensuring a therapeutically valid program content, it is important to identify barriers and preferences of patients in order to develop a feasible and (cost-)effective prehabilitation program in the right context (72, 73). To set up a feasible (p)rehabilitation program in patients with NSCLC before, during, and after

treatment, it is important to provide valuable information on the content and context as indicated by patients and informal caregivers. Social support seems to have a positive influence on participation, compliance, and successfully completing a physical exercise training program for patients with cancer (74, 75). Furthermore, high adherence of patients to rehabilitation during CHRT is crucial to reduce treatment complications (76). Understanding what amount of training volume is feasible, thereby including patient preferences, is important to ensure that patients and their informal caregivers are both able and willing to participate and adhere to the program.

The overall aim of this thesis is to optimize the pretreatment risk assessment for patients requiring treatment for NSCLC and to gather information that can be used to develop an effective and feasible (p)rehabilitation program before and after surgery and during other curative treatment of NSCLC to improve treatment tolerance, in which the patient's view plays an important role. This knowledge contributes to identifying patients with an increased risk of treatment complications, delayed recovery, and worse survival which can contribute to an optimal treatment choice, appropriate to the patient and to possibly select patients to offer a feasible (p)rehabilitation program, thereby reducing treatment risks.

This thesis consists of two parts. The first part focuses on prognostic pretreatment parameters for treatment tolerance and survival in patients with NSCLC. The second part addresses the content and context of lifestyle interventions during treatment for NSCLC.

In **part one** of this thesis, prognostic pretreatment parameters for treatment tolerance and survival are described. To improve pretreatment risk assessment, associations between physical performance tests and nutritional screening before treatment and treatment complications in patients with stage I-III NSCLC from existing evidence are systematically reviewed and described in **chapter 2** and **chapter 3**. The value of using pretreatment physical and geriatric status parameters to predict treatment tolerance and survival in elderly patients with stage I-II NSCLC is described in **chapter 4** using real world data. In **chapter 5**, the associations between pretreatment physical status parameters and tolerance of cCHRT and survival among patients with stage III NSCLC are investigated.

In **part two** of this thesis, attention is focused on the content and context of lifestyle interventions before, during, and after treatment. **Chapter 6** describes systematic evidence on whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality, and length of hospital stay in patients undergoing surgery for NSCLC, thereby accounting for the therapeutic quality of the physical exercise program. In **chapter 7** the effect of prehabilitation and rehabilitation on HRQoL and fatigue in patients with NSCLC undergoing surgery is described by performing a systematic review of the literature. To develop an effective and feasible pretreatment program, it is important to gain insight into beliefs, facilitators, and barriers of patients, informal caregivers and healthcare professionals. To this end, the expectations, preferences, barriers, and facilitators for prehabilitation before lung cancer surgery are described in **chapter 8** by means of a qualitative stakeholder analysis. In **chapter 9**, a proof-of-concept study concerning the feasibility of early rehabilitation during CHRT among patients with stage III NSCLC is presented. Considering the importance of rehabilitation during CHRT in relation to treatment tolerance, a case-study in **chapter 10** demonstrates the clinical decision-making process of healthcare professionals in prescribing and administering a rehabilitation program during CHRT in a high-risk patient diagnosed with stage III NSCLC.

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Part I

Prognostic pretreatment parameters for treatment tolerance and survival

'My condition was sufficient because I cycled to work every day before the diagnosis. In addition, during the test (cardiopulmonary exercise test) before surgery, I did not have to make an effort to reach the level required to be operated on.'
-Patient who underwent surgery for NSCLC-

Chapter 2

Associations between pretreatment physical performance tests and treatment complications in patients with non-small cell lung cancer: a systematic review

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Abstract

This systematic review evaluated which outcome variables and cut-off values of pretreatment exercise tests are associated with treatment complications in patients with stage I-III non-small cell lung cancer (NSCLC).PRISMA and Cochrane guidelines were followed. A total of 38 studies with adult patients undergoing treatment for stage I-III NSCLC who completed pretreatment exercise tests, and of whom treatment-related complications were recorded were included. A lower oxygen uptake at peak exercise amongst several other variables on the cardiopulmonary exercise test and a lower performance on field tests, such as the incremental shuttle walk test, stair-climb test, and 6-minute walk test, were associated with a higher risk for postoperative complications and/or postoperative mortality. Cut-off values were reported in a limited number of studies and were inconsistent. Due to the variety in outcomes, further research is needed to evaluate which outcomes and cut-off values of physical exercise tests are most clinically relevant.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, in which non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers (1).For fit patients with early stage I, II, and – in some cases – IIIa NSCLC, lung resection is recommended according to European guidelines (2). For patients with early stage disease who are considered inoperable, stereotactic radiotherapy is the preferred treatment (3). For fit patients with stage III disease, chemoradiotherapy is the standard treatment with the option of adjuvant immunotherapy after non-progression (4). Clinical trials have shown that intensive treatment results in considerably longer disease-free and overall survival in relatively fit patients (5),but is often accompanied with a high incidence of treatment complications (6). Patients with a higher risk for treatment complications are often characterized as aged ≥70 years, having tobacco-related comorbidity and/or cognitive impairment, being physically inactive and/or malnourished, and especially as having a low physiological reserve capacity (low aerobic fitness) (7, 8).

When standard pulmonary function tests to verify resectability, such as the forced expiratory volume in 1 second (FEV_1) and carbon monoxide lung diffusion capacity (DLCO), fall below 80% of predicted, a cardiopulmonary

exercise test (CPET) is performed for surgical decision-making (9). Oxygen uptake at peak exercise (VO_{2peak}) as measured during a CPET has been used most widely for preoperative risk stratification in lung surgery; however, current cut-off values are not based on solid evidence (10, 11). Although the CPET is the gold standard to evaluate a patient's aerobic fitness, it is relatively expensive, time-consuming, and requires trained personnel (12, 13). Hence, practical, cheap, easy to administer, and time efficient field exercise tests such as the incremental shuttle walk test (iSWT), stair-climb test (SCT), 6-minute walk test (6MWT), 12-minute walk test (12MWT), and steep ramp test might be less complicated tests to estimate a patient's preoperative aerobic fitness (12, 14).The use of field exercise tests for estimating aerobic fitness has previously been investigated in patients with cardiac and pulmonary disease (15). Results demonstrated a moderate-to-strong correlation between CPET-derived variables of aerobic fitness and field exercise test outcomes (16).Nevertheless, systematic evidence on the association between pretreatment field exercise tests and treatment complications in patients with NSCLC is lacking, especially in patients who undergo chemoradiotherapy.

Due to the predictive value of pretreatment exercise tests for treatment complications, outcome variables of the CPET and field exercise tests might be used to identify high-risk patients who might benefit from lifestyle interventions before and during cancer treatment (prehabilitation and early rehabilitation, respectively). Lifestyle interventions might improve a patient's aerobic fitness, which in turn can improve treatment tolerance and effectiveness (17, 18). The aim of this systematic review was to evaluate which outcome variables of pretreatment exercise tests are associated with treatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values for clinical risk stratification.

Methods

A systematic review was performed with respect to outcome variables of pretreatment exercise tests and their association with treatment complications in patients with stage I-III NSCLC. The Cochrane guidelines for systematic reviews (19) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20) were followed.

Literature search

PubMed, Embase, and Cinahl databases were searched for eligible studies published up to December 2019. In addition, references from retrieved studies were screened. The search strategy contained a combination of controlled vocabulary (e.g., MeSH or EMTREE) and key word terms and phrases searched in titles, abstracts, and key word fields, as appropriate. Key terms included in the search strategy included non-small cell lung cancer and lung surgery, exercise test, walk test (6-minute walk test and incremental shuttle walk test), cardiopulmonary exercise test or CPET, anaerobic threshold, aerobic fitness, postoperative complications, overall treatment time and postoperative mortality. Combinations of text words of the literature search are shown in Table 1.

Study selection

Prospective and retrospective cohort studies with adult patients undergoing treatment for stage I-III NSCLC who completed pretreatment exercise tests, and of whom treatment-related complications were recorded were included. Studies primarily investigating the impact of prehabilitation or any structured exercise program on physical fitness before treatment, and studies that primarily described survival as outcome measure were excluded. Conference papers, case series, case reports, opinion studies (non-original research), systematic reviews, randomized clinical trials, and studies not published in English were also excluded. Two reviewers (M.V. and R.F.) independently screened titles and abstracts of studies obtained by the literature search. Assessment of full texts according to eligibility criteria was performed independently by these two reviewers. Any disagreements between reviewers were resolved through discussion and consensus. When no consensus was reached, a third party acted as an adjudicator (J.V.).

Data extraction

Two authors (M.V. and R.F.) independently extracted data from each of the included studies by using a standardized extraction form. Information collected included the name of the first author, year of publication, type of cohort, sample size, age and sex of participants, used pretreatment exercise test, used test protocol with steps, preselection method, follow-up period, type of cancer treatment, outcome variables of treatment complications, measures for associations between outcomes of pretreatment tests and treatment complications, and cut-off values of pretreatment exercise tests. Complications of treatment were reported as cardiac complications and pulmonary complications or as mortality when mortality was separately identified as a complication.

Table 1. Combinations of text words of the literature search according to the PECO-structure.

Databases [a]	Population	Exposure/comparator	Outcome
Embase, PubMed, Cinahl,	("lung neoplasms"[MeSH Terms:NoExp] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR lung-neoplasm*[tiab] OR lung-cancer*[tiab] OR pulmonary-cancer*[tiab] OR pulmonary-neoplasm*[tiab] OR cancer-of-the-lung*[tiab] OR cancers-of-the-lung*[tiab] OR non-small-cell-lung-carcinoma*[tiab] OR NSCLC[tiab] OR non-small-cell-lung-cancer*[tiab]) AND ("Chemoradiotherapy"[Mesh] OR "Radiotherapy"[MeSH] OR "Pulmonary Surgical Procedures"[MeSH] OR "Pneumonectomy"[Mesh] OR "Thoracic Surgical Procedures"[MeSH] OR radiation[tiab] OR radiotherap*[tiab] OR chemotherap*[tiab] OR radiochemotherapy[tiab] OR radiochemotherapies[tiab] OR radio-chemotherapy[tiab] OR radio-chemotherapies[tiab] OR CHRT[tiab] OR chemoradiation[tiab] OR chemo-radiation[tiab] OR pulmonary-surgical-procedure*[tiab] OR lung-operation*[tiab] OR lung-resection*[tiab] OR ((lobectomy[tiab] OR lobectomies[tiab] OR segmentectomy[tiab] OR segmentectomies[tiab] OR resection*[tiab] OR surgery[tiab] OR surgic*[tiab]) AND (pulmonary*[tiab] OR lung[tiab] OR pneumon*[tiab])) OR pneumonectomy[tiab] OR thoracic-surgical-procedure*[tiab] OR "Therapeutics"[Mesh] OR therapeutic*[tiab] OR treatment*[tiab]) OR operable[tiab]	"Walk Test"[MeSH] OR "Walking"[MeSH] OR field-test*[tiab] OR walk-test*[tiab] OR walking-test*[tiab] OR "exercise test"[MeSH] OR exercise-test*[tiab] OR 6-minute-walk-test*[tiab] OR 6-minute-walking-test*[tiab] OR 6MWT[tiab] OR 6MWD[tiab] OR 6-minute-walk-distance*[tiab] OR 6-minute-walking-distance*[tiab] OR six-minute-walk-test*[tiab] OR six-minute-walk[tiab] OR 6-minute-walk[tiab] OR six-minute-walking-test*[tiab] OR six-minute-walk-distance*[tiab] OR six-minute-walking-distance*[tiab] OR "stair climbing"[MeSH Terms] OR stair-climbing-test*[tiab] OR SCT[tiab] OR steep-ramp-test*[tiab] OR shuttle-walk-test*[tiab] OR shuttle-walk-distance[tiab] OR shuttle-walking-test*[tiab] OR ESWT[tiab] OR ISWT[tiab] OR ESWD[tiab] OR ISWD[tiab] OR SWT[tiab] OR SWD[tiab] OR "exercise test"[MeSH] OR "Ergometry"[Mesh] OR exercise-test*[tiab] OR cardiopulmonary-exercise-test*[tiab] OR VO_{2peak}-test*[tiab] OR VO2-max-test*[tiab] OR physical-fitness-test*[tiab] OR ergometry-test*[tiab] OR cycle-ergometr*[tiab] OR cardiopulmonary-exercise*[tiab] OR CPX[tiab] OR (CPET[tiab] NOT clostridium[tiab]) OR exercise-tolerance[tiab] OR Peak-oxygen-consumption[tiab] OR Peak-oxygen[tiab]	"postoperative complications"[MeSH] OR postoperative-complication*[tiab] OR associated-conditions[tiab] OR coexistent-disease[tiab] OR complication*[tiab] OR toxicity-of-side-effects[tiab] OR toxicit*[tiab] OR adverse-effects[tiab] OR side-effects[tiab] OR adverse-reaction*[tiab] OR adverse-events[tiab] OR "mortality"[MeSH] OR mortality[tiab] OR Mortalities[tiab] OR death[tiab] OR fatality[tiab] OR fatal*[tiab] OR "hospitalization"[MeSH] OR hospitalisation[tiab] OR hospitalization[tiab] OR length-of-stay[tiab] OR length-of-hospital-stay[tiab] OR patient-discharge[tiab] OR reduce-treatment-dose[tiab] OR overall-treatment-time[tiab] OR time-to-treatment[tiab] OR delay*[tiab] OR dose-modification*[tiab] OR completion-of-planned-treatment[tiab] OR toxicity-of-systematic-treatment[tiab] OR withdrawal[tiab] OR chemotherapy-toxicity[tiab] OR toxicity-systematic-treatment[tiab] OR postoperative-decrease[tiab] OR pulmonary function[tiab] OR health-outcomes[tiab] OR postoperative[tiab] OR post-operative[tiab] OR operative-risk[tiab] OR risk-stratification[tiab]

[a]: search presented for PubMed only: the search strategy has been adjusted for searching in the other databases.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (20). Studies scoring 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain were defined as good-quality studies. Studies scoring 2 stars in the selection domain, 1or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain were defined as fair-quality studies, and a score of 0-1 star in selection domain were classified as fair-quality studies. Studies scoring 0 stars in the comparability domain, or 0 or 1 stars in the outcome/exposure domain, were defined as low-quality studies (21). Two investigators (M.V. and R.F.) independently assessed the quality of included studies. Discrepancies were resolved by consensus. When consensus was not reached, a third person acted as an adjudicator (J.V.).

Data analyses

Associations between pretreatment exercise tests and treatment complications were interpreted as statistically significant when p-values were <0.05. Cut-off values for outcomes of exercise tests for an increased risk of treatment complications were presented when receiver operating characteristic (ROC) curves, including area under the curve (AUC), sensitivity and specificity, and/or odds ratios were determined in the included studies.

Results

Study characteristics

Study selection

Initially, the literature search identified 684 studies, of which 38 were eventually included. A flow diagram for the selection of studies is shown in Figure 1. An overview of the characteristics of the 38 studies is shown in Table 2. Twenty-three studies were prospective observational, eleven studies were retrospective observational, and four studies had an unclear observational design. The oldest publications dated from 1984 (22, 23)and the most recent from 2018 (24-27). Median sample size was 110 patients (ranging from 12 to 287, with a total of 4191) and the mean age of the included patients ranged between 56 and 72 years. In nine studies (24%), it was indicated which stages of NSCLC had been included (24, 25, 28-34), of which five studies (14%) also

reported stage distribution among patients (35-39). No study was found in which patients underwent any other NSCLC treatment than surgery, such as chemoradiotherapy. One or more of the following surgical techniques were used in the included studies: pneumonectomy, lobectomy, segmentectomy, bilobectomy, wedge resection, and thoracotomy. Although the initial search strategy captured CPET as well as field exercise tests, the resultant outcomes of the CPET and field exercise tests are presented separately. Preselection of participants by means of FEV_1 or DLCO was used in 22 studies (58%).

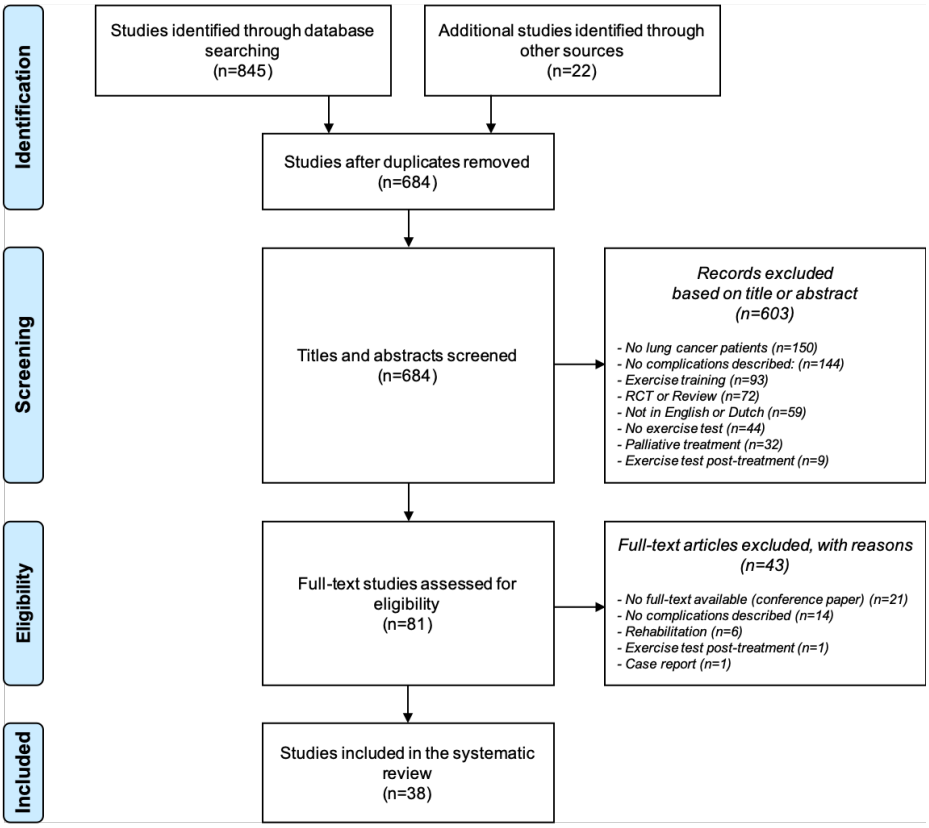

Figure 1. PRISMA flow diagram displaying the selection of studies and reasons for exclusion.

Table 2. Study and characteristics of included studies that evaluated the association of preoperative exercise tests and postoperative complications.

First author	Year of publication	Type of cohort [a]	Sample size (n)	Age (years) mean ± SD (range)	Male (%)
Miyazaki(26)	2018	Retrospective	209	72.4 ± 8.3	58
Rodrigues(40)	2016	NR	54	64.7 ± 7.9 (46-80)	92
Shafiek(37)	2016	Retrospective	51	65.4 ± 9.1	82
Vargas(41)	2014	Prospective	83	64.6 ± 9.5 (38-80)	82
Fang(29)	2013	Prospective	107	65.3 ± 7.0	97
Licker(42)	2011	Retrospective	243	NR	58
Campione(35)	2010	Retrospective	99	67.4 ± 8.1 (41-83)	81
Varela(43)	2010	Prospective	103	62.6 ± 13.5 (20-85)	NR
Brunelli(44)	2009	Prospective	204	66.5 ± 9.6	NR
Nagamatsu(30)	2004	NR	211	65.9 ± 8.4	62
Villani(45)	2004	NR	150	57.1 ± 0.7	94
Villani(46)	2003	NR	150	57.1 ± 0.7 (33-79)	94
Brutsche(28)	2000	Prospective	125	63 ± 11 (20-80)	81
Bechard(47)	1987	Prospective	50	63.8 (47-76)	100
Bolliger(48)	1995	Prospective	25	62.8 ± 8.2 (47-77)	68
Richter Larsen(31)	1997	Prospective	97	64.3 ± 8.9 (38-80)	69
Epstein(49)	1993	Prospective	42	62.7 ± 2.2	98
Smith(22)	1984	Prospective	22	55.7 ± 2.0	86
Pate(36)	1996	Prospective	12	63.6 ± 4.9	NR
Holden(50)	1992	Prospective	23	NR	NR
Kasikcioglu(24)	2018	Prospective	49	61 ± 9 (35-78)	90
Yakal(25)	2018	Prospective	123	63 ± 8 (44-85)	85
Torchio(51)	2010	Retrospective	145	64.2 ± 7.9 (41-82)	88
Win(52)	2005	Prospective	99	68.4 ± 8.0 (42-85)	60
Dales(53)	1993	Retrospective	117	NR	62
Fennelly(54)	2016	Retrospective	101	65.5 ± 11.6 (19-85)	32

Preselection	Preoperative exercise test	Protocol	Follow-up period (days)	Type of surgery
NR	CPET (cycle ergometer)	Ramp, 1 Watt/6 seconds	30, 90	L, S
NR	CPET (cycle ergometer)	Ramp, NR	30	L
FEV_1 <30% [b] and DLCO <40% [b]	CPET (cycle ergometer)	Incremental, NR	30, 365	P, L, S
FEV_1 and DLCO <40% [b]	CPET (cycle ergometer)	Ramp, Wasserman	NR	P, L, S, B
FEV_1 <60% [b]	CPET (cycle ergometer)	Ramp, 10-20 Watt/min	30	P
FEV_1 <80% [b]	CPET (cycle ergometer)	Ramp, 20 Watt/min	30	R
FEV_1 ≤70% [b]	CPET (cycle ergometer)	Ramp, 10 Watt/min	30	P, L, S
NR	CPET (cycle ergometer)	Incremental, 30 Watt/2 min	NR	P, L
FEV_1 <30% [b]	CPET (cycle ergometer)	Ramp, NR	30	P, L, S, WR
No preselection	CPET (cycle ergometer)	Ramp, 20 Watt/2 min	30	P, L, B
No preselection	CPET (cycle ergometer)	Incremental, 25 Watt/3 min	30	P
No preselection	CPET (cycle ergometer)	Incremental, 25 Watt/3 min	30	P
FEV_1 <1.6 L	CPET (cycle ergometer)	Ramp, 20 Watt/min	30	R
FEV_1 >0.9 L, FEV_1 WR >1.2 L, $FEV_{1,}$ P >1.7 L	CPET (cycle ergometer)	Incremental, 12.5 Watt/min	30	P, L, T
FEV_1 <2 L and DLCO <50% [b]	CPET (cycle ergometer)	Ramp, 20 Watt/min	30	NR
FEV_1 >2.0 L	CPET (cycle ergometer)	Ramp, 10-15 Watt/min	30	P, L, S
FEV_1 <70% [b]	CPET (cycle ergometer)	Ramp, Wasserman	30	P, WR
No preselection	CPET (cycle ergometer)	Incremental, 10 Watt/min	30	L, B, T
FEV_1 <35% [b]	CPET (cycle ergometer), SCT, 12MWT	Incremental, 10 Watt/min	NR	T
FEV_1 >2.0 L	CPET (cycle ergometer), SCT, 6MWT	Incremental, 15 Watt/min	30	P, L, T, WR
NR	CPET (treadmill)	Naughton	NR	P, L, T, WR
No preselection	CPET (treadmill)	Bruce	NR	P, L, WR
No preselection	CPET (cycle ergometer)	Balke	30	P, L, S, B
No preselection	CPET (treadmill)	Steep	30	P, L
NR	CPET (treadmill)	Multistage incremental	30	P, L, T, WR
FEV_1 and DLCO <80% [b]	iSWT	Singh	30	T

Table 2. Continued

First author	Year of publication	Type of cohort [a]	Sample size (n)	Age (years) mean ± SD (range)	Male (%)
Erdogan(38)	2013	Prospective	24	61.5 ± 8.6	96
Win(39)	2004	Prospective	111	69 (42-85)	36
Dong(55)	2017	Retrospective	171	65 ± 9	76
Refai(56)	2014	Prospective	287	66.5 ± 8.9	79
Nikolic(57)	2007	Prospective	101	61.1 ± 8.4	81
Toker(58)	2007	Prospective	150	60.4 ± 10.6	85
Brunelli(59)	2001	Prospective	115	66.5 ± 9.5	77
Nakagawa(27)	2018	Retrospective	121	71.4 ± 7.0	89
Irie(33)	2015	Prospective	188	71 (64-77) [c]	62
Marjanski(34)	2015	Retrospective	253	63	59
Ha(32)	2013	Retrospective	96	65.6 ± 9.6	52
Bagg(23)	1984	Prospective	30	NR	NR

Abbreviations: B=bilobectomy resection; CPET=cardiopulmonary exercise test; iSWT=incremental shuttle walk test; L=lobectomy; NR=not reported; P=pneumonectomy; SCT=stair-climb test; S=segmentectomy, T=thoracotomy; WR=wedge resection; 12MWT=12-minute walk test; 6MWT=6-minute walk test.[a]: all studies were observational. [b]: values are expressed as a percentage of predicted. [c]: median (interquartile range).

	Preselection	Preoperative exercise test	Protocol	Follow-up period (days)	Type of surgery
	NR	iSWT	Singh	30	P, L, B WR
	NR	iSWT	Singh	NR	P, L, B, WR
	NR	SCT	Symptom-limited: as fast as they could without stopping to rest until they reached the highest floor possible	30	T
	No preselection	SCT	Climb at a pace of their own choice, the maximum number of steps	30	P, L
	FEV_1 <2.0 L	SCT	Climb the maximum number of steps, at a pace of their own choice	NR	P, K, T, B
	NR	SCT	Do their best during 2-flat climbing exercises	NR	P, L
	No preselection	SCT	Symptom-limited: as fast as they could until they reached the highest floor possible	30	P, L
	FEV_1 and DLCO <60%[b]	6MWT	Walking as rapidly as possible	90	L, WR
	Tumor ≤6 cm and FEV_1 >600 mL	6MWT	ATS statement	NR	L
	FEV_1 and DLCO <80%[b]	6MWT	ATS statement	30, 90	L
	NR	6MWT	ATS statement	30	P, S, WR
	NR	12MWT	Cooper	28	T

Treatment complications

In all included studies, surgical resection for NSCLC was performed. Neoadjuvant chemotherapy and/or adjuvant chemotherapy were included in five studies (13%) (40, 44-46, 58). An association between outcome variables of pretreatment exercise tests and postoperative cardiac and pulmonary complications and/or postoperative mortality was found in 33 of the 38 studies (87%). The included studies do not provide information about which complications occur most frequently stratified by type of surgery. The most frequently reported complications were pneumonia (in 88% of the studies), lobar atelectasis (bronchoscopy required) (78%), symptomatic cardiac arrhythmias requiring treatment (61%), myocardial infarction (60%), mortality (65%), pulmonary embolism (57%), long-term mechanical ventilation (>48 hours) (51%), infiltration on chest radiography (27%), and purulent sputum (19%). In two studies (5%), complications were not categorized, and in 15 studies (39%), postoperative mortality was reported separately.

Quality assessment

The results of the quality assessment are depicted in Table 3. In seven studies there was no consensus, because one of the domains was interpreted differently between the reviewers. These discrepancies were resolved by discussion between the two reviewers. In 26 studies (68%), there was a poor methodological quality, five studies (13%) were ranked with a fair quality, and seven studies (19%) had a good quality. A poor score on the Newcastle-Ottawa quality assessment scale was often the result of the lack of: 1) an accurate description of the representativeness of the exposed cohort (23/38, 61%), 2) a clear description of the outcome of interest at start of the study (34/38, 89%), 3) a clear description on the comparability of cases in the cohorts (21/38, 55%), and 4) complete description of complications and/or mortality (24/38, 63%). In addition, length of follow-up and adequacy of follow-up of the missing cases were poorly or not described (15/38, 39%).

Pretreatment exercise tests

Associations between pretreatment exercise tests and postoperative complications are presented in Table 4.

Cardiopulmonary exercise test

In 20 (80%) of the 25 studies where the CPET was used preoperatively, one or more outcomes were statistically significant associated with postoperative complications. Cycle ergometry was used in 20 studies (80%) (22, 26, 28-

31, 35-37, 40-50), of which 16 (80%) reported that preoperative CPET variables were associated with postoperative complications. Different CPET protocols were used, with ten different workload increment protocols. A total of 24 different CPET variables were associated with one or more types of complications after surgery. Fifteen studies (22, 26, 28, 30, 31, 36, 37, 40, 42, 44-47, 49) reported that VO_{2peak} (both absolute values and values normalized for body mass) was associated with cardiac and pulmonary complications or mortality after surgery, whereas two studies merely reported an association with postoperative pulmonary complications (29, 46). Predicted VO_{2peak} was associated with postoperative cardiac and pulmonary complications (22, 28, 29, 40, 42, 45, 46), pulmonary complications (44), and postoperative mortality (31, 44). Oxygen pulse at peak exercise was found to be associated with postoperative cardiac and pulmonary complications (29, 35, 49), as well as with postoperative mortality (29). Oxygen uptake at the ventilatory anaerobic threshold normalized for body mass was associated with cardiac and pulmonary complications (47, 60) and postoperative mortality (29). The slope describing the relation between minute ventilation and carbon dioxide production (VE/VCO_2-slope) was also associated with cardiac and pulmonary complications (26, 37) and postoperative mortality (26). For all associations, a better preoperative score on the respective CPET variable with cycle ergometry was associated with a lower risk of postoperative complications, with the exception of four studies in which no association was reported (20%) (41, 43, 48, 50). In five studies (20%) (24, 25, 51-53) treadmill ergometry was performed. In these studies, a total of seven different CPET outcomes were associated with one or more types of postoperative complications and/or postoperative mortality. AbsoluteVO_{2peak} was associated with postoperative cardiac and pulmonary complications (24, 25, 51) with pulmonary complications (53), and postoperative mortality (25, 51). Predicted VO_{2peak} was associated with postoperative complications (52). The oxygen uptake efficiency slope (24, 25) and the VE/VCO_2-slope were associated with cardiac and pulmonary complications after surgery (51).

Table 3. Quality assessment based on the Newcastle-Ottawa Scale for cohort studies.[a]

First author	Selection			
	Representativeness exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest present at start of the study
Miyazaki(26)	-	A☆	A☆	B
Rodrigues(40)	D	A☆	A☆	B
Shafiek(37)	B☆	A☆	A☆	B
Vargas(41)	D	A☆	A☆	B
Fang(29)	B☆	A☆	A☆	B
Licker(42)	D	A☆	A☆	B
Campione(35)	A☆	A☆	A☆	B
Varela(43)	D	A☆	A☆	B
Brunelli(44)	D	A☆	A☆	B
Nagamatsu(30)	A☆	A☆	A☆	B
Villani(45)	D	A☆	A☆	A☆
Villani(46)	D	A☆	A☆	B
Brutsche(28)	B☆	A☆	A☆	B
Bechard(47)	D	A☆	A☆	B
Bolliger(48)	D	A☆	A☆	B
Richter Larsen(31)	B☆	A☆	A☆	B
Epstein(49)	D	A☆	A☆	B
Smith(22)	D	A☆	A☆	B
Pate(36)	B☆	A☆	A☆	B
Holden(50)	D	A☆	A☆	B
Kasikcioglu(24)	A☆	A☆	A☆	B
Yakal(25)	A☆	A☆	A☆	B
Torchio(51)	D	A☆	A☆	B
Win(52)	A☆	A☆	A☆	B
Dales(53)	D	A☆	A☆	B
Fennelly(54)	D	A☆	A☆	A☆
Erdogan(38)	A☆	A☆	A☆	B
Win(39)	B	A☆	A☆	B
Dong(55)	D	A☆	A☆	B
Refai(56)	D	A☆	A☆	B
Nikolic(57)	D	A☆	A☆	B
Toker(58)	D	A☆	A☆	B
Brunelli(59)	D	A☆	A☆	B
Nakagawa(27)	D	A☆	A☆	A☆
Irie(33)	A☆	A☆	A☆	A☆
Marjanski(34)	A☆	A☆	A☆	B
Ha(32)	A☆	A☆	A☆	B
Bagg(23)	D	A☆	A☆	B

[a]: stars (☆) are awarded on the basis of answers (A, B, C, or D) provided for each item.[b]: thresholds for converting the Newcastle-Ottawa scale scores to AHRQ standards (good, fair, and poor): good quality= 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; fair quality=2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; poor quality=0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

Comparability	Outcome			
Comparability of cohorts on the basis of the design of analysis	Assessment of outcome	Follow-up time	Adequacy of follow-up of cohort	Quality [b]
A☆	B☆	A☆	D	Fair
-	B☆	A☆	A☆	Poor
A☆	D	A☆	D	Poor
-	B☆	B	A☆	Poor
A☆	D	A☆	A☆	Good
A☆	B☆	A☆	A☆	Fair
A☆	D	A☆	A☆	Good
A☆	D	B	D	Poor
A☆, B	D	A☆	D	Poor
A☆	D	A☆	A☆	Good
-	D	A☆	A☆	Poor
-	D	A☆	D	Poor
-	D	A☆	A☆	Poor
-	D	A☆	A☆	Poor
-	D	A☆	B	Poor
-	D	A☆	A☆	Poor
A☆	B☆	A☆	A☆	Fair
-	D	A☆	A☆	Poor
-	A☆	A☆	A☆	Poor
-	D	A☆	A☆	Poor
-	D	B	A☆	Poor
-	D	B	A☆	Poor
A☆	D	A☆	A☆	Fair
A☆	B☆	A☆	A☆	Good
-	B☆	A☆	A☆	Poor
A☆	B☆	A☆	A☆	Good
-	D	A☆	A☆	Poor
-	D	B	D	Poor
A☆	D	A☆	B	Poor
-	D	A☆	A☆	Poor
A☆	B☆	A☆	A☆	Poor
A☆	D	B	D	Poor
A☆, B	D	A☆	A☆	Fair
-	B☆	A☆	B	Poor
-	B☆	B	A☆	Good
A☆	B☆	A☆	A☆	Good
-	B☆	A☆	A☆	Poor
-	D	A☆	D	Poor

Incremental shuttle walk test

Three studies (38, 39, 54) investigated the association between preoperative iSWT performance and postoperative complications. One study reported that oxygen desaturation ≥4% during the iSWT, and distance walked <400 m were associated with a higher risk of postoperative complications (54). In two studies, no associations were found between outcomes of the preoperative iSWT and postoperative complications (38, 39).

Stair-climb test

A preoperative SCT was performed in seven studies (36, 50, 55-59), in which different SCT protocols were used. Patients were asked 1) to climb the maximum number of steps at a pace of their own choice (36, 50, 56, 57, 59), 2) to climb five stairs with 20 steps as fast as they could without stopping to rest (55), or 3) to do their best during 2 stair-climbing exercises in which each flight of stairs was composed of 20 steps and climbing time was recorded (58). There were also differences between studies concerning test duration, step height, and number of steps. The total number of steps that were taken was associated with postoperative complications (36, 44, 50, 57) and postoperative mortality (57). There was an association between the height of climbing in meters, exercise oxygen desaturation, and the change in heart rate from start to finish on the one hand and cardiac and pulmonary complications after surgery on the other hand (55).Test duration, speed, heart rate, and oxygen saturation during exercise were associated with postoperative complications and postoperative mortality (57). Oxygen saturation at the end of the SCT, and the change in oxygen saturation during the SCT were associated with postoperative complications (58). In all studies where the preoperative SCT was used, better scores on the test variables were associated with a lower risk of postoperative complications, with the exception of one study that reported no association (36).

Six- and twelve-minute test

Five studies (27, 32-34, 50) assessed the ability of the preoperative 6MWT to predict the risk of postoperative complications and postoperative mortality. Distance walked as a percentage of predicted was associated with cardiac and pulmonary complications (32). Other studies reported an association between shorter walked distances and a higher risk of postoperative complications (33, 34, 36, 50), and postoperative mortality (50). All studies using the preoperative 6MWT showed that a poor performance was associated with a higher risk for postoperative complications. Two studies (23, 36) used the 12MWT during

the preoperative assessment. Both studies reported no association between the distance walked and postoperative complications. One small study (36) described a relation between the walked distance in meters and complications, in which a better performance on the 12MWT was associated with a lower risk on postoperative complications.

Table 4. Association between preoperative exercise tests and postoperative complications.

First author	Mean age of patients without /with complications (years)	Variables associated with cardiac and/or pulmonary complications		
CPET, cycle ergometer		**VO_{2peak}**	**VE/VCO_2-slope**	**VO_{2peak} (% of predicted)**
Miyazaki(26)	NR	Y	Y	-
Rodrigues(40)	65.0/64.1	Y	-	Y
Shafiek(37)	64.0/67.1	Y	Y	
Vargas(41)	63.8/69.0	N	-	N
Fang(29)	64.7/66.9	Y	-	Y
Licker(42)	62/66	Y	-	Y
Campione(35)	67.2/68.3	N	-	-
Varela(43)	NR	-	-	-
Brunelli(44)	66.3/67.6	Y	-	Y [b]
Nagamatsu(30)	NR	Y	-	-
Villani(45)	57.2/57.1	Y	-	Y
Villani(46)	57.2/57.1	Y	-	Y
Brutsche(28)	63/64	Y	-	Y
Bechard(47)	63.6/66.6	Y	-	-
Bolliger(48)	NR	N	-	N
Richter Larsen(31)	NR	Y	-	-
Epstein(49)	63/62	Y	-	-
Smith(22)	51.8/59.6	Y	-	Y
Pate(36)	64.2/63.1	Y	-	-
Holden(50)	67.0/70.1	N	-	-
CPET, treadmill		**VO_{2peak}**	**VE/VCO_2-slope**	**VO_{2peak} (% of predicted)**
Kasikcioglu(24)	NR	Y	-	-
Yakal(25)	NR	Y	-	-
Torchio(51)	63.7/67.1	Y	Y	N
Win(52)	NR	N	-	Y
Dales(53)	NR	Y [b]	-	N
Incremental shuttle walk test		**Distance**		
Fennelly(54)	64.0/70.7	Y	-	-
Erdogan(38)	NR	N	-	**-**
Win(39)	NR	N	-	**-**
Stair-climb test		**Height of climbing**	**Steps**	

		Variables associated with postoperative mortality			
	Other	**VO_{2peak}**	**VE/VCO_2-slope**	**VO_{2peak} (% of predicted)**	**Other**
	-	-	Y	-	-
	-	N	-	-	-
	WR_{peak}	-	-	-	-
	-	-	-		-
	O_2 $pulse_{peak}$ ΔSpO_2 VAT	-	-	-	-
	-	-	-	-	-
	O_2 $pulse_{peak}$	-	-	-	-
	-	-	-	-	-
	-	Y	-	Y	O_2 $pulse_{peak}$
	VAT	-	-	-	-
	WR_{peak}	-	-	-	-
	WR_{peak}	-	-	-	-
	-	-	-	-	-
	VAT	-	-	-	-
	-	-	-	-	-
	WR_{peak} VE_{peak}	-	-	Y	WR_{peak}
	O_2 $pulse_{peak}$	Y	-	-	-
	-	-	-	-	-
	-	-	-	-	-
	-	N	-	-	-
	Other	**VO_{2peak}**	**VE/VCO_2-slope**	**VO_{2peak} (% of predicted)**	**Other**
	OUES	-	-	-	-
	OUES VE_{peak} HR at the VAT	Y	-	-	$OUESVE_{peak}$
	-	Y	Y	N	-
	-	N	-	N	-
	VE_{peak} [b]	-	-	-	-
	-	-	-	-	-
	-	**-**	**-**	**-**	**-**
	-	**-**	**-**		**-**
	Other	**Height of climbing**	**Steps**		**Other**

Table 4. Continued

First author	Mean age of patients without /with complications (years)	Variables associated with cardiac and/or pulmonary complications		
Dong(55)	NR	Y	-	-
Refai(56)	65.5/69.7	N	-	-
Nikolic(57)	58.2/67.1	-	Y	-
Toker(58)	60.7/59.3	-	-	-
Brunelli(59)	NR	-	Y	-
Pate(36)	64.2/63.1	Y	Y	-
Holden(50)	67.0/70.1	-	Y	-
6-minute walk test/12-minute walk test		**Distance**	**ΔSpO_2**	
Nakagawa(27)	65.3/69.2	-	Y	-
Irie(33)	NR	Y	-	
Marjanski(34)	NR	Y	-	-
Ha(32)	64.8/66.7	N	N	-
Holden(50)	67.0/70.1	Y	-	-
Pate(36)	64.2/63.1	Y	-	-
Bagg(23)	NR	N	-	

Abbreviations: ATS=American Thoracic Society; CPET=cardiopulmonary exercise test; DLCO=carbon monoxide lung diffusion capacity; FEV_1=forced expiratory volume in 1 second; HR=heart rate; HRR=heart rate reserve; iSWT=incremental shuttle walk test; N=no, not statistically significant; NR=not reported; OUES=oxygen uptake efficiency slope; O_2 $pulse_{peak}$=oxygen pulse (VO_2/HR) at peak exercise; P=pneumonectomy; SCT= stair-climb test; SpO_2 = transcutaneous pulse oxygen; VAT=ventilatory anaerobic threshold; VE_{peak}=minute ventilation at peak exercise; VE/VCO_2-slope=slope describing the relationship between the minute ventilation and carbon dioxide production; VO_{2peak}=oxygen uptake at peak exercise; WR=wedge resection; WR_{peak}=work rate at peak exercise; Y= yes, statistically significant; 12MWT=12-minute walk test; 6MWT=6-minute walk test; ΔHR=difference between heart rate at start and end of exercise; ΔSpO_2=transcutaneous pulse oxygen saturation difference during load exercise.
[a]: % of predicted
[b]: Only pulmonary complications.

		Variables associated with postoperative mortality			
	Predicted exercise SpO_2ΔHR	-	-	-	-
	-	-	-	-	-
	SpO_2 during exerciseHR$_{max}$	-	Y	-	SpO_2 during exercise HR$_{max}$
	SpO_2 at startSpO_2 at the end SpO_2 change during exercise	-	-	-	
	VO_{2peak}	-	-	-	-
	Number of flights	-	-	-	-
	VO_{2peak}	-	Y	-	VO_{2peak}
	Other	**Distance**	**ΔSpO_2**		**Other**
	SpO_2	-	Y	-	SpO_2
	-	-	-	-	-
	-	N	-	-	-
	Heart rate reserveDistance % of predicted	-	-	-	Heart rate reserve
	-	Y	-	-	-
	-	-	-	-	-
	-	-	-	-	-

Cut-off values

Cut-off values of outcomes of pretreatment exercise tests associated with an increased risk of postoperative complications and postoperative mortality are presented in Table 5. A limited number of studies reported a cut-off value of outcomes of pretreatment exercise tests for a higher risk for postoperative complications; however, the accuracy of these cut-off values was usually moderate. A study using the CPET on a cycle ergometer reported VO_{2peak} cut-off values of <12.8 mL/kg/min and <58% of predicted to be optimal cut-off values for a higher risk for postoperative cardiac complications (42). In the same study, optimal cut-off values indicating a higher risk for postoperative pulmonary complications were a VO_{2peak} <13.6 mL/kg/min or a predicted VO_{2peak} <53% of predicted, whereas a VO_{2peak} <12.3 mL/kg/min and a predicted VO_{2peak} <37% were optimal cut-off values for postoperative mortality (42). In another study, a VO_{2peak} cut-off value of ≤500 mL/min was reported to indicate a higher risk for postoperative cardiac and pulmonary complications (49).In another study, most optimal VE/VCO_2-slope cut-off values for an increased risk for postoperative complications were >35 (37), while a VE/VCO_2-slope >40 was reported as a cut-off value for an increased risk for postoperative mortality (26). A VO_{2peak} <19.1 mL/kg/min, measured by means of a CPET on a treadmill, was a cut-off value for an increased risk for postoperative complications (24), whereas a VE/VCO_2-slope ≥34 reflected an increased risk for postoperative mortality (51). Participants who walked a distance <500 meter at the iSWT had an increased risk for cardiac and pulmonary postoperative complications (54). When using the preoperative 6MWT, a distance walked <400 meters (33) and <500 meters (34) were cut-off values for an increased risk for postoperative complications.

Table 5. Cut-off values at pretreatment exercise tests for an increased risk for postoperative complications and postoperative mortality.

First author, year	Variable	Cut-off value for an increased risk for postoperative complications	
CPET, cycle ergometer			
Licker(42)	**VO_{2peak}**	<12.8 mL/kg/min [a]<13.6 mL/kg/min [b]<12.3 mL/kg/min [c]	AUC 0.717 (95% CI of 0.651-0.777), sensitivity 51%, specificity 85%AUC 0.708 (95% CI of 0.640-0.771), sensitivity 63%, specificity 72%AUC 0.723 (95% CI of 0.654-0.784), sensitivity 51%, specificity 85%
Epstein(49)	**VO_{2peak}**	>500 mL/min≤500 mL/min [a, b]≥500 mL/min<500 mL/min [a]	1.0 (reference category)OR 6.0 (95% CI of 1.4-26.0)1.0 (reference category) OR 6.2 (95% CI of 1.36-28.5
Rodrigues(40)	**VO_{2peak} % of predicted**	>61%≤61% [a, b]	1.0 (reference category)OR 5.1 (95% CI of 1.5-17.8)
Licker(42)	**VO_{2peak} % of predicted**	<58% [a]<53% [b]<37% [c]	AUC 0.657 (95% CI of 0.589-0.722), sensitivity 75%, specificity 48%AUC 0.633 (95% CI of 0.562-0.700), sensitivity 64%, specificity 61%AUC 0.616 (95% CI of 0.544-0.684), sensitivity 30%, specificity 95%
Miyazaki(26)	**VE/VCO_2-slope**	<40≥40 [c]	1.0 (reference category)OR 1.05 (95% CI of 1.0-1.1)
Shafiek(37)	**VE/VCO_2-slope**	≤35>35 [a, b, c]	1.0 (reference category)OR 5.3 (95% CI of 1.3-20.8)
Richter Larsen(31)	**WR_{peak}**	<70 Watt [a, b]	Sensitivity 39%, specificity 83%
CPET, treadmill			
Kasikcioglu(24)	**VO_{2peak}**	19.1 mL/kg/min	AUC 0.81
Torchio(51)	**VE/VCO_2-slope**	≥34 [c]	AUC 0.871 (95% CI 0.70-1.01)
iSWT			
Fennelly(54)	**Distance**	≥400 meter<400 meter [a, b]	1.0 (reference category)OR 4.3 (95% CI of 1.4-15.9)
6MWT			
Irie(33)	**Distance**	≥400 meter<400 meter [a, b]	1.0 (reference category) OR 4.0 (95% CI of 1.6-10.2)
Marjanski(34)	**Distance**	≥500 meter<500 meter [a, b]	1.0 (reference category)OR 2.6 (95% CI of 1.4-4.9), sensitivity 36%, specificity 81.9%

Abbreviations: VE/VCO_2-slope=slope describing the relationship between the minute ventilation and carbon dioxide production; VO_{2peak}=oxygen uptake at peak exercise; AUC=area under the curve; CI=confidence interval; WR_{peak}=work rate at peak exercise; ROC=receiver operating characteristic.[a]:cardiac complications.[b]: pulmonary complications.[c]: postoperative mortality.

Discussion

This systematic review aimed to evaluate which outcome variables of pretreatment exercise tests are associated with treatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values that can be used for clinical risk stratification. Results demonstrate that a wide variety of outcome variables of different preoperative exercise tests seem to be associated with postoperative complications and/or postoperative mortality. However, used exercise protocols varied widely between the studies. In addition, only a limited number of cut-off values with a moderate accuracy were provided. Publications on other treatment strategies than surgery were lacking.

The CPET is the most frequently used preoperative exercise test and mandatory in guidelines as a risk assessment tool when lung function tests values are <80% of predicted. VO_{2peak} was associated with postoperative complications and/or postoperative mortality in 18 of the 25 studies (72%), in which a higher aerobic fitness reflected a reduced risk. Lower preoperative aerobic fitness has been shown to be associated with an increased risk for short-term and long-term postoperative complications in several other surgical populations as well (61-64). Although the CPET seems to be a valuable test that is associated with postoperative complications in patients with NSCLC, accurate and consistent cut-off values to identify patients with a higher risk for complications are lacking. This means that the best method for pretreatment risk assessment based on CPET is still unclear, given the wide variety of associated outcomes and study characteristics. In the current systematic review, VO_{2peak} cut-off values for an increased risk for postoperative complications ranged between <12.8 mL/kg/min and <19.1 mL/kg/min (24, 42). One study (42) reported a VO_{2peak} cut-off value of <58% of predicted to reflect a higher risk for cardiac complications. A VO_{2peak} cut-off value of <53% of predicted was reported in the same study for a higher risk for postoperative pulmonary complications, and <37% of predicted for a higher risk for postoperative mortality (42). Interpretation of these cut-off values is debatable, because of uncertainty concerning the used VO_{2peak} references values and the poor methodological quality of studies. Several international guidelines have described a large range of VO_{2peak} cut-off values between <16 mL/kg/min and <20 mL/kg/min, and a VO_{2peak} between <35% and <40% of predicted to identify patients undergoing lung resection for cancer with an increased risk for postoperative complications (65, 66). A broad range in used cut-off values was also seen in the current review, possibly as a result of poor methodological quality and inadequate

sample size of studies. VO_{2peak} is a measure of aerobic fitness that requires a maximal effort of the patient, whereas the oxygen uptake at the ventilatory anaerobic threshold is a submaximal indicator of aerobic fitness that has been consistently reported to be an independent predictor of morbidity, mortality, and length of stay following major abdominal surgery (61). Nevertheless, only a limited number of studies (29, 30, 47) addressed the prognostic value of the preoperative oxygen uptake at the ventilatory anaerobic threshold for postoperative outcomes in patients undergoing lung surgery. Therefore, more research is needed.

Field tests require little equipment and training prior to use (67). In comparison, the CPET requires well-trained staff and relatively expensive equipment. The CPET provides a more in-depth assessment of cardiopulmonary function and gas exchange and, as described above, has been reported to predict outcome following lung cancer surgery. Unfortunately, the CPET may not always be available; making field tests an attractive alternative. However, there is only limited evidence to justify their use in the preoperative setting. Intuitively, the preoperative iSWT is more demanding than submaximal field tests and may therefore be a superior method of estimating aerobic fitness when the CPET is unavailable. Nevertheless, associations between the iSWT and postoperative complications are not covered sufficiently by study results; in only one of three studies a statistically significant association was found. Therefore, currently using the iSWT for risk-stratification seems not to be recommended. Similar to a study in abdominal surgery (68), this systematic review demonstrated that a better performance on the preoperative SCT was associated with a lower risk for postoperative complications following lung surgery. This is in line with a previous publication, in which stair-climbing seemed to be predictive for postoperative outcomes after abdominal surgery (68). In the current systematic review, also an association between a lower distance walked on the preoperative 6MWT and a higher risk for postoperative complications was shown. In two studies (33, 34), 6MWT distance cut-off values of respectively <400 m and <500 m were associated with postoperative complications. A difference of 100 m in cut-off values is rather large. This is possibly a reflection of the small number of included patients. In addition, the 6MWT is susceptible to biased results, as patients can regulate their physical effort during the test which may underestimate or overestimate the results (69). No study was found that investigated the association between the preoperative steep ramp test and postoperative complications or postoperative mortality. A previous study in adult cancer survivors demonstrated a strong correlation between steep ramp

test performance and aerobic fitness (VO_{2peak}) as objectively measured during the CPET (70). Furthermore, another study in hepatic surgery demonstrated that a lower aerobic fitness, as estimated with the steep ramp test, was associated with postoperative complications (71). This easy-to-use short-time maximal exercise test (72) might therefore also be used for preoperative risk assessment in patients with lung cancer; however, evidence is currently lacking.

To correctly interpret the results, it is essential to know that there are limitations in the included studies. A poor score on the Newcastle-Ottawa Scale was particularly found in articles older than ten years. This is mainly due to the non-description or incomplete description of the population, as well as the representativeness of the exposed cohort, the assessment of the outcome, and the follow-up time. There was considerable variation between the studies in the type of surgery, the used outcome variables of exercise tests, and the incomplete description of postoperative complications. This variation could have influenced the associations between the outcome of the exercise test, and postoperative complications or mortality. The physiological impact and risks of a segmentectomy are expected to be less than those of a pneumonectomy; therefore, in different surgical procedures it would intuitively be expected to use different relative VO_{2peak} thresholds for preoperative risk stratification, depending on the extent of the surgical trauma (42).

Although studies have shown that preoperative exercise tests are associated with postoperative complications, more attention needs to be paid to which outcome variables and cut-off values of the CPET are clinically relevant, as well as to the possibility of supplementing the CPET with field tests. In an optimal situation there is a possibility of identifying high-risk patients before the start of the treatment, after which the physical performance status might be improved by prehabilitation in order to reduce a patient's risk for complications during and/or after treatment (73, 74).

Only surgical patients were included in this systematic review. More attention should be paid to the potential of exercise tests to predict treatment complications in patients with NSCLC who undergo other intensive treatments, such as chemoradiotherapy. Efforts should be made internationally to reach consensus on standardizing pretreatment exercise tests for accurate cut-off values in pretreatment risk stratification. In future studies, the description of postoperative complications and postoperative mortality should be used according to a standardized protocol, and consensus should be reached to

use the same follow-up time regarding complications and mortality to enable pooling of study results. Currently, the evidence of field tests to predict treatment complications is weaker than for the CPET. In addition, research regarding the prognostic values of pretreatment field tests for treatment complications is of poor quality, which underlines the need for high-quality research using standardized field exercise test protocols.

Conclusion

A better performance of patients on preoperative exercise tests, especially a higher aerobic fitness as measured by the CPET, is associated with a lower risk for postoperative complications in patients with NSCLC. However, it is difficult to provide recommendations for pretreatment exercise tests to predict the risk of treatment complications due to a lack of accurate test-specific cut-off values. Additionally, recommendations for the use of field tests are difficult due to heterogeneity in tests, protocols, and used outcome measures in the current literature. Therefore, standardizing pretreatment exercise test protocols is eminent and more attention needs to be paid to which outcome variables and cut-off values of pretreatment exercise tests are clinically relevant. In addition, further research is needed concerning the ability of pretreatment exercise tests to accurately identify patients who have an increased risk for treatment complications across all curative NSCLC treatment options. This is important, as especially these high-risk patients might benefit from interventions to improve their physical performance status before treatment initiation.

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'I think prehabilitation is important for patients with lung cancer who have a poor nutritional status, so if they have lost a lot of weight or have a high body mass index (BMI).'

-Healthcare professional-

Chapter 3

Associations between pretreatment nutrition screening tests and treatment complications in patients with non-small cell lung cancer: a systematic review

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Abstract

Background Patients with stage I-III non-small cell lung cancer (NSCLC) are often nutritionally depleted and therefore at high-risk for treatment complications. Identifying these patients before the start of treatment is important to initiate preventive interventions for better treatment outcomes. This study aimed to evaluate which outcome variables of pretreatment nutritional assessments are associated with posttreatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values for clinical risk stratification.

Methods In this systematic review, PubMed, Embase, and Cinahl databases were searched for eligible studies published up to March 2021. Studies describing the association between pretreatment nutritional assessment and treatment complications in patients with NSCLC were included. Methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale for cohort studies.

Results A total of 23 studies were included, which merely focused on surgical treatment for NSCLC. Methodological quality was poor in thirteen studies (57%). Poor outcomes of body mass index, sarcopenia, serum albumin, controlling nutritional status, prognostic nutrition index, nutrition risk score, and (geriatric) nutrition risk index were associated with a higher risk for treatment complications. Cut-off values for pretreatment nutritional assessment were reported in a limited number of studies and were inconsistent.

Conclusion Poor outcomes of pretreatment nutritional assessments are associated with a higher risk for posttreatment complications. Further research is needed on the ability of easy-to-use pretreatment nutritional assessments to accurately identify patients who are at high risk for treatment complications, as high-risk patients may benefit from pretreatment interventions to improve their nutritional status.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) constitutes the majority (85%) of lung cancers (1).Surgery remains the best (curative) option for patients with stage I and II NSCLC and for selected patients with locally-advanced disease (stage IIIA). For inoperable patients with early-stage disease, stereotactic body radiation therapy (SBRT) is the advised treatment (2). For patients with locally advanced stage NSCLC (40%), chemoradiotherapy is the standard treatment (2). Despite the fact that generally the physically fit patients with a good performance status are advised for surgery, almost 40% of these surgical patients develop postoperative complications (3, 4). Patients with a higher risk for treatment-related complications are often characterized as aged ≥70 years, having tobacco-related comorbidity and/or cognitive impairment, being physically inactive and/or malnourished, and especially as having a low physiological reserve capacity (low aerobic fitness) (5, 6).

The importance of an adequate nutritional status has been established in patients with cancer. It has been reported that malnutrition may decrease the response to cancer treatment (7), as well as that malnutrition is associated with poor quality of life and higher rates of treatment intolerance in patients with lung, esophagus, colon, liver, or pancreas cancer (8-11). Patients with NSCLC are often nutritionally depleted and therefore at high risk for treatment complications (12). Identification of malnutrition as soon as possible after diagnosis is recommended to identify patients who are at high risk for treatment complications and who therefore might benefit from pretreatment nutrition interventions. Nutritional screening is the process of assessing characteristics and risk factors that predispose a patient to malnourishment (13). Many tools can be used to evaluate nutritional status. For example, a recent systematic review showed that the prognostic significance of nutritional status, measured with the mini nutritional assessment, was associated with treatment complications in patients with various types of cancer (14). However, the large heterogeneity of included studies with respect to various types and stages of cancer, differences in anticancer therapy (chemotherapy and/or surgery), and differences in outcome measurements should be noticed when interpreting results (14). Systematic evidence for the associations between outcomes of various nutritional assessments and treatment complications in patients with NSCLC is lacking. The aim of this systematic review was therefore to evaluate which outcome variables of pretreatment nutritional screening

or nutritional assessments are associated with treatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values for clinical risk stratification.

Methods

The Cochrane guidelines for systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15) were followed. The study protocol was registered at PROSPERO (CRD42020220639).

Literature search

PubMed, Embase, and Cinahl databases were searched for eligible studies published up to March 2021. In addition, references from retrieved studies were screened. The search strategy contained a combination of controlled vocabulary (e.g., MeSH, EMTREE) and key word terms and phrases searched in titles, abstracts, and key word fields, as appropriate. Key terms included in the search strategy are non-small cell lung cancer combined with the various treatment options, pretreatment nutritional assessment, treatment complications, overall treatment time, and treatment mortality. Combinations of text words of the literature search are shown in Table 1.

Table 1. Combinations of text words of the literature search according to the PECO-structure.

Databases [a]	Population	Exposure/comparator	Outcome
Embase, PubMed, Cinahl,	"Chemoradiotherapy"[Mesh] OR "Radiotherapy"[MeSH] OR radiation[tiab] OR radiotherap*[tiab] OR chemotherap*[tiab] OR radiochemotherap*[tiab] OR radio-chemotherap*[tiab] OR CHRT[tiab] OR chemoradiation[tiab] OR chemo-radiation[tiab] chemoradiotherapy[tiab] OR radiochemotherapy[tiab] OR radiochemotherapies[tiab] OR CHRT[tiab] OR "Pulmonary Surgical Procedures"[MeSH] OR "Pneumonectomy"[Mesh] OR "Thoracic Surgical Procedures"[MeSH] OR pulmonary-surgical-procedure*[tiab] OR lung-operation*[tiab] OR lung-resection*[tiab] OR lobectomy[tiab] OR lobectomies[tiab] OR segmentectomy[tiab] OR segmentectomies[tiab] OR resection*[tiab] OR surgery[tiab] OR surgic*[tiab] OR pneumonectomy[tiab] OR thoracic-surgical-procedure*[tiab] OR operable[tiab] AND "lung neoplasms"[MeSH Terms:NoExp] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR lung-neoplasm*[tiab] OR lung-cancer*[tiab] OR pulmonary-cancer*[tiab] OR pulmonary-neoplasm*[tiab] OR cancer-of-the-lung*[tiab] OR cancers-of-the-lung*[tiab] OR non-small-cell-lung-carcinoma*[tiab] OR NSCLC[tiab] OR non-small-cell-lung-cancer*[tiab] OR lung-tum*[tiab] OR lung-malignanc*[tiab] OR lung-tumor[tiab] OR lung-tumour[tiab]	"Nutrition Assessment"[Mesh] OR nutrition-assessment*[tiab] OR nutritional-screening[tiab] OR nutritional-status[tiab] OR nutrition-disorders[tiab] OR PG-SGA[tiab] OR Patient-Generated-Subjective-Global-Assessment-Short-Form[tiab] OR nutriscore[tiab] OR malnutrition-screening-tool[tiab] OR nutritional-risk-screening[tiab] OR NRS-2002[tiab] OR nutritional-risk-index[tiab] OR prognostic-inflammatory-and-nutritional-index[tiab] OR prognostic-nutritional-ind*[tiab] OR PNI[tiab] OR short-nutritional-assessment-questionnaire[tiab] OR SNAQ[tiab] OR general-nutritional-status-score[tiab] OR malnutritional-universal-screening-tool[tiab] OR MUST[tiab] OR Nottingham-screening-tool[tiab] OR malnutrition-screening-tool*[tiab] OR nutritional-screening-questionnaire[tiab] OR subjective-global-assessment[tiab] OR SGA[tiab] OR Nutritional-Appetite-Questionnaire[tiab] OR mini-nutritional-assessment[tiab] OR MNA[tiab] OR albumin[tiab] OR CRP-albumin-ratio[tiab] OR C-reactive-protein-albumin-ratio[tiab] OR CRP/ALB[tiab] OR CRP/ALB-ratio[tiab] OR serum-albumin[tiab] OR sarcopenia[tiab] OR CT-defined-sarcopenia[tiab] OR Nutrition*-Ind*[tiab] OR malnutrition-screening[tiab] OR "nutrition surveys"[MeSH Terms] OR ("nutrition"[tiab] OR "surveys"[tiab]) OR ("nutrition"[tiab] OR "survey"[tiab]) OR Nutrition-survey[tiab] OR nutrition-survey*[tiab]	"complications"[MeSH Subheading] OR complication*[tiab] OR associated-conditions[tiab] OR coexistent-disease[tiab] OR toxicit*[tiab] OR adverse-effects[tiab] OR side-effects[tiab] OR "mortality"[MeSH Terms] OR mortality[tiab] OR mortalities[tiab] OR "mortality"[MeSH Subheading] OR "death"[MeSH Terms] OR death*[tiab] OR fatal*[tiab] OR "hospitalization"[MeSH Terms] OR hospitalization[tiab] OR hospitalisation[tiab] OR "length of stay"[MeSH Terms] OR length-of-stay[tiab] OR length-of-hospital-stay[tiab] OR "patient discharge"[MeSH Terms] OR patient-discharge[tiab] OR dose-reduction[tiab] OR dose-modification*[tiab] OR "time to treatment"[MeSH Terms] OR time-to-treatment[tiab] OR treatment-delay[tiab] OR completion-of-treatment[tiab] OR early-termination[tiab] OR withdraw*[tiab] OR health-outcomes[tiab] OR risk-stratification[tiab] OR stratifications[tiab] OR risk-stratification[tiab] OR pulmonary-function[tiab]

[a]: search presented for PubMed only: the search strategy has been adjusted for searching in the other databases.

Study selection

Prospective and retrospective cohort studies with adult patients undergoing treatment for stage I-III NSCLC who completed a pretreatment nutritional assessment and of whom treatment-related complications were recorded were included. All types of assessment methods for nutritional status (e.g., functional or biochemical tests, anthropometric measurements, questionnaires) were included. Studies primarily investigating the impact of prehabilitation or any structured exercise program on physical fitness before treatment, and studies describing long-term survival as outcome measure were excluded. Postoperative mortality (within 90 days) was included as an outcome measure. Conference papers, case series, case reports, opinion studies (non-original research), systematic reviews, and studies not published in English were also excluded. Two reviewers (M.V. and K.B.) independently screened titles and abstracts of studies obtained by the literature search. Assessment of full texts according to eligibility criteria was performed independently by these two reviewers. Any disagreements between reviewers were resolved through discussion and consensus. When no consensus was reached, a third party acted as an adjudicator (M.J).

Data extraction

Two authors (M.V. and K.B.) independently extracted data from each of the included studies by using a standardized extraction form. Information collected included the name of the first author, year of publication, type of cohort, sample size, age and sex of participants, used pretreatment nutritional screening and/or assessment, preselection method, follow-up period, outcome variables of treatment complications, measures for associations between outcomes of pretreatment nutritional screening and/or assessments and treatment complications, and cut-off values of pretreatment nutritional assessments. Outcome variables of treatment complications were categorized as overall complications of treatment, cardiac complications and pulmonary complications, length of hospital stay and unplanned hospital stay, or as mortality when mortality was separately identified as a complication. The classification used for treatment complications was reported when described in the included studies.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS) (15). Studies scoring 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure

domain were defined as good-quality studies. Studies scoring 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain were defined as fair-quality studies. Studies scoring 0 or 1 stars in the selection domain, or scoring 0 stars in the comparability domain, or 0 or 1 stars in the outcome/exposure domain, were defined as low-quality studies (16). Two investigators (M.V. and K.B.) independently assessed the quality of included studies. Discrepancies were resolved by consensus. When consensus was not reached, a third person acted as an adjudicator (M.J).

Data-analyses

Associations between pretreatment nutritional assessment and treatment complications were interpreted as statistically significant when p-values were <0.05. Cut-off values for outcomes of pretreatment nutritional assessments for an increased risk for treatment complications were presented. Receiver operating characteristic (ROC) curves, including area under the curve (AUC), sensitivity and specificity, and/or odds ratios were also determined in the included studies.

Results

Study characteristics

Study selection

Initially, the literature search identified 1485 studies, of which 23 were eventually included. A flow diagram for the selection of studies is shown in Figure 1. An overview of the characteristics of the 23 studies is shown in Table 2. Seventeen (73%) were retrospective observational studies (17-33) and six (26%) had a prospective observational design (34-39). The oldest publication dated from 2001 (36) and the most recent publications from 2020 (21, 22, 26, 29). Median sample size was 228 patients (ranging from 52 to 1011, with a total of 7522) and the mean age of the included patients ranged between 56 and 79 years. In all studies, the intention was to include only curative patients. Ultimately, ten studies (43%) included patients with stage I-IV NSCLC (17-21, 34-38), nine studies (39%) stage I-III NSCLC (22-28, 32, 33), two studies (9%) stage I-II NSCLC (29, 30), one study (4%) stage I NSCLC (31), and in one study (4%) the included NSCLC stage was unclear (39). With the exception of one study (30), cancer treatment consisted at least of surgery (96%). In one of these studies (35), adjuvant chemotherapy and

chemoradiotherapy was applied, and in one study (24) patients also underwent adjuvant chemotherapy. In one study (30), cancer treatment consisted of SBRT. One or more of the following surgical techniques were used in 22 of the included studies (17-29, 31-39): pneumonectomy, lobectomy, segmentectomy, bilobectomy, wedge resection, and thoracotomy. Preselection of participants by means of forced expiratory volume in one second, carbon monoxide lung diffusion capacity, or oxygen uptake at peak exercise was used in two studies (21, 37) (9%) and preselection of participants by means of age in three studies (17, 32, 33) (13%).

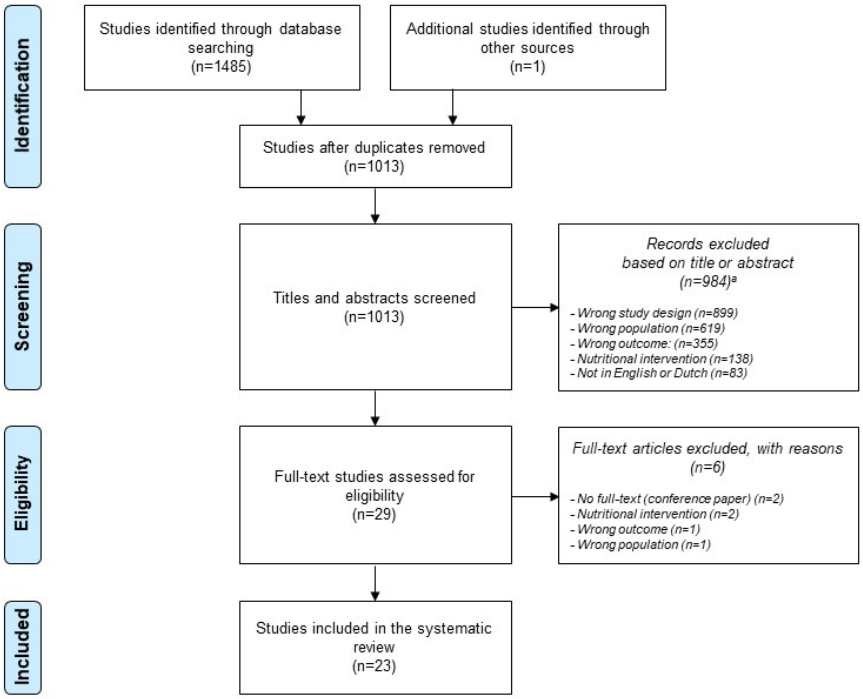

Figure 1. PRISMA flow diagram displaying the selection of studies and reasons for exclusion.
[a]: multiple reasons are possible.

Classification of treatment complications

An association between poorer outcomes of pretreatment nutrition tests and a higher risk for treatment complications and/or treatment mortality was found in all studies. The included studies did not provide information about which complications occurred most frequently stratified by type of surgery. The most frequently reported overall complications were pneumonia (in 65% of the studies), lobar atelectasis (bronchoscopy required) (57%), myocardial infarction (57%), wound infection (52%), air leak (52%, bronchopleural fistula (52%), acute respiratory distress syndrome (43%), acute renal failure (43%), and mortality (26%). In three studies (13%), treatment complications were graded on severity using the Clavien-Dindo classification system (40). In the other studies, no classification of complications was described, and in three studies (17, 34, 36) (13%), treatment mortality was reported separately.

Quality assessment

The results of the quality assessment are depicted in Table 3. In two studies there was no consensus, because the assessment of outcome domain was interpreted differently between the reviewers. These discrepancies were resolved by discussion with the adjudicator. In thirteen studies (57%), there was a poor methodological quality, whereas ten studies (43%) were ranked as having a good methodological quality. A poor score on the NOS was often the result of the lack of a clear description of the outcome of interest at the start of the study (13/23, 57%) and an unclear description on the comparability of cases in the cohorts (12/23, 52%).

Table 2. Characteristics of included studies that evaluated the association between pretreatment nutritional assessments and posttreatment complications and posttreatment mortality.

First author	Year of publication	Country	Type of observational cohort	Stage of disease	Sample size (n)
Bagan (34)	2013	France	Prospective	I-IV	86
Bianchi (39)	2006	Brazil	Prospective	NR	71
Fiorelli (17)	2014	Italy	Retrospective	I-IV	117
Illa (35)	2015	Czech	Prospective	I-IV	188
Jagoe (36)	2001	UK	Prospective	I-IV	52
Kawaguchi (32)	2019	Japan	Retrospective	I-III	173
Kim (18)	2018	Korea	Retrospective	I-IV	272
Lee (22)	2019	Korea	Retrospective	I- II	236
Lee (29)	2020	Korea	Retrospective	I-III	922
Li (19)	2018	China	Retrospective	I-IV	533
Madariaga (21)	2020	USA	Retrospective	I-IV	130
Nakada (31)	2019	Japan	Retrospective	I	173
Nakamura (23)	2018	Japan	Retrospective	I-III	228
Okada (24)	2017	Japan	Retrospective	I-III	248
Okada (20)	2018	Japan	Retrospective	I-IV	515
Park (25)	2019	Korea	Retrospective	I-III	1011
Ramos (37)	2018	Spain	Prospective	I-IV	219
Shaverdian (30)	2016	USA	Retrospective	I-II	118
Shoji (33)	2017	Japan	Retrospective	I-III	272
Takahashi (26)	2020	Japan	Retrospective	I-III	475
Tewari (38)	2007	UK	Prospective	I-IV	642
Tsukioka (27)	2017	Japan	Retrospective	I-III	215
Zhang (28)	2019	Germany	Retrospective	I-III	626

Abbreviations: B=bilobectomy resection; BMI=body mass index (kg/m^2); CHRT=chemoradiotherapy; CONUT; controlling nutritional status; CT=chemotherapy; FFMI=fat free mass index; GNRI=geriatric nutritional risk index; L=lobectomy; nCT=neoadjuvant chemotherapy; NR=not reported; NRI=nutritional risk index; nRT=neoadjuvant radiotherapy; P=pneumonectomy; PNI=prognostic nutritional index; RT=radiotherapy; S=segmentectomy; SBRT=stereotactic body radiation therapy; T=thoracotomy; WR=wedge resection.

[a]: protocols used for nutritional assessments are shown in supplementary file 1.

[b]: median (interquartile range).

Age (years) mean (range)	Male %	Pretreatment nutritionalassessments [a]	Type of treatment
62	86	BMI, serum albumin, transthyretin	P
56 (19-77)	70	BMI, serum albumin	B, L, P, S, WR
75	80	BMI, serum albumin, serum transferrin	P
65	70	NRS 2002	S, aCT, aRT, CT, CHRT
64	67	BMI, FFMI, sarcopenia, serum albumin	B, L, P, S
79	70	PNI	L
63 (33–81)	60	Sarcopenia	B, L, P, T
66	42	Sarcopenia, Sarcopenia	L, S
64	57	CONUT	L, S, WR, B, P
62	58	Serum albumin	L, S
61	57	BMI, sarcopenia	P
68	57	Sarcopenia, PNI, serum albumin	L
70	86	Sarcopenia	L
67	64	PNI	L, aCT
71	63	BMI, PNI	L
NR	91	PNI	T
62	81	BMI, NRI	L, P
NR	NR	Serum albumin	SBRT
70 [b] (75-91)	57	BMI, PNI, CONUT, GNRI	P, L
70 [b] (64-75)	62	PNI, CONUT, GNRI	L
66 [b] (32-89)	62	BMI, weight loss, serum albumin	T, L
68 (46-93)	100	Sarcopenia	L, S
67 [b]	54	Serum albumin, C-reactive protein	L, S

Table 3. Quality assessment based on the Newcastle-Ottawa scale for cohort studies.

First author	Representativeness exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest present at start of the study
Bagan (34)	B☆	A☆	A☆	A☆
Bianchi (39)	D	A☆	A☆	A☆
Fiorelli (17)	B☆	A☆	A☆	B
Illa (35)	A☆	A☆	A☆	B
Jagoe (36)	B☆	A☆	A☆	B
Kawaguchi (32)	B☆	A☆	A☆	B
Kim (18)	B☆	A☆	A☆	A☆
Lee (22)	B☆	A☆	A☆	A☆
Lee (29)	B☆	A☆	A☆	A☆
Li (19)	B☆	A☆	A☆	A☆
Madariaga (21)	B☆	A☆	A☆	B
Nakada (31)	B☆	A☆	A☆	B
Nakamura (23)	B☆	A☆	A☆	B
Okada (24)	B☆	A☆	A☆	B
Okada (20)	B☆	A☆	A☆	A☆
Park (25)	B☆	A☆	A☆	A☆
Ramos (37)	B☆	A☆	A☆	A☆
Shaverdian (30)	C	A☆	A☆	B
Shoji (33)	B☆	A☆	A☆	B
Takahashi (26)	B☆	A☆	A☆	B
Tewari (38)	D	A☆	A☆	B
Tsukioka (27)	B☆	A☆	A☆	B
Zhang (28)	B☆	A☆	A☆	A☆

Abbreviations: NR=not reported

[a]: stars (☆) are awarded on the basis of answers (A, B, C, or D) provided for each item.

[b]: thresholds for converting the Newcastle-Ottawa scale scores to the Agency for Healthcare Research and Quality standards (good, fair, and poor): good quality=3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; fair quality=2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; poor quality=0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

	Comparability of cohorts on the basis of the design of analysis	Assessment of outcome	Follow-up time	Adequacy of follow-up of cohort	Quality
	A☆	A☆	A☆	A☆	Good
	A☆	A☆	B	D	Poor
	A☆	A☆	B	A☆	Good
	NR	A☆	B	A☆	Poor
	A☆	A☆	A☆	A☆	Poor
	A☆	A☆	A☆	A☆	Good
	B☆	A☆	A☆	A☆	Good
	A☆	A☆	A☆	A☆	Good
	A☆	A☆	B	A☆	Poor
	A☆	A☆	A☆	A☆	Good
	A☆	A☆	A☆	A☆	Good
	A☆	A☆	B	A☆	Poor
	A☆	A☆	B	A☆	Poor
	A☆	A☆	A	A☆	Good
	A☆	A☆	B	A☆	Poor
	A☆	A☆	B	A☆	Poor
	A☆	A☆	A☆	A☆	Good
	A☆	A☆	A☆	C	Poor
	B☆	A☆	B	A☆	Poor
	A☆	A☆	A☆	A☆	Good
	NR	A☆	B	A☆	Poor
	NR	A☆	B	A☆	Poor
	A☆	A☆	B	A☆	Poor

Associations between pretreatment nutritional assessments and treatment complications

Associations between pretreatment nutritional assessments and treatment complications and treatment mortality are presented in Table 4. When comparing results from univariable analyses and multivariable analyses: although some effect sizes were somewhat larger in univariable analyses compared to multivariable analyses, no clear differences in effect sizes or significance were seen.

Pretreatment assessment of anthropometry and body composition tests

Seven studies (17, 20, 21, 26, 33, 36, 37) (30%) assessed the ability of pretreatment anthropometry and body composition to predict the risk for treatment complications, and in two studies (17, 36) the risk for treatment mortality was evaluated as well. A body mass index (BMI) <18.5 kg/m^2 was associated with a higher risk for treatment complications in two of seven studies (17, 26) and a lower BMI in another two studies (33, 36) (25%) and with a higher risk for pretreatment mortality in two of two studies (17, 36) (100%). In the only study that looked at fat free mass index (FFMI), a lower FFMI was associated with a higher risk for treatment complications (36).

Pretreatment assessment of sarcopenia

Pretreatment assessment of sarcopenia was performed in seven studies (18, 21, 23, 27, 31, 32, 36) (30%), in which different protocols were used. The third lumbar vertebra muscle mass index, psoas muscle mass index, thoracic skeletal muscle area, bone-free midarm muscle area, subscapular skinfold thickness, and triceps skinfold thickness were used to assess the presence of sarcopenia. A low psoas muscle mass index (males: <3.70 cm^2/m^2, females: <2.50 cm^2/m^2 (32) and males: <6.36 cm^2/m^2, females: <3.92 cm^2/m^2 (23)) in two of three studies (66.7%), a lower thoracic skeletal muscle area and a lower bone-free midarm muscle area in one study (21) (100%), and a lower subscapular skinfold thickness and a lower triceps skinfold thickness in one study (36) (100%) were associated with a higher risk of treatment complications.

Pretreatment assessment of a combination of multiple nutritional parameters

All five studies (26, 34, 35, 37, 38) (22%) reported an association between the ability of a combination of multiple nutritional parameters and the risk for treatment complications, whereas the risk for treatment mortality was also evaluated in one study (34). The nutrition risk screening (NRS) 2002 is a malnutrition risk assessment tool that evaluates common signs of nutritional

status (weight loss, body mass index, and dietary intake) and a score >2 was found to be associated with treatment complications in the only study that looked at the NRS (35). In the only study that looked a combination of BMI, serum albumin, and transthyretin; a low BMI, high serum albumin, and high transthyretin was associated with a higher risk for treatment complications and treatment mortality (34). In another study (38), the combination of low BMI, high serum albumin, and weight loss was associated with a high risk for treatment complications. In the only study that looked at the geriatric nutritional risk index, a score ≤101 was associated with a higher risk of treatment complications (26). In the only study that looked at the nutritional risk index, a score <100 and a higher score on the NRI were associated with a higher risk for treatment complications (37).

Pretreatment assessment of nutritional biomarkers

In 13 of the 23 studies (57%) in which pretreatment outcomes of biomarkers were collected, one or more biomarkers were significantly associated with treatment complications or treatment mortality. Biomarker serum albumin was used in eight studies (17, 19, 22, 26, 28, 30, 36, 39) (35%), of which in three of eight studies (37%) a pretreatment high serum albumin (>15.86 ml/dl (39), ≥35 g/L (17), ≥14.97% (19)) and in two studies (22, 30) (25%) higher pretreatment serum albumin was associated with a higher risk for treatment complications. In the only study (13%) that looked at serum albumin, a score of ≥35 g/L was associated (17) with treatment mortality. In the only study (17) were the biomarker transferrin was appraised, and in the two studies (22, 28) were the biomarker C-reactive protein was evaluated, there was no association with treatment complications or treatment mortality. In four of five studies (80%), a low score on the prognostic nutritional index (<48 (24), <45 (20), <50 (25), and ≤47 (26)) and a lower score on the prognostic nutritional index in one of five studies (24) (20%) were associated with a higher risk for treatment complications. A high score (>1(29) and ≥2 (26)) (9%) on the controlling nutritional status in both studies in which was looked at de controlling nutritional status was associated with a higher risk for treatment complications.

Table 4. Association between pretreatment nutritional assessments and posttreatment complications and posttreatment mortality

Author	Pretreatment nutritional assessments	Posttreatment complications/mortality
Pretreatment assessment of anthropometry and body composition		
Fiorelli (17)	BMI <18.5 kg/m^2	90-day postoperative complications
		90-day postoperative mortality
	BMI ≥18.5 km/m^2	
Takahashi (26)	BMI <18.5 kg/m^2	Postoperative complications [a]
	BMI ≥18.5 km/m^2	
Okada (20)	BMI (kg/m^2) *median IQR*	30-day postoperative complications
Shoji (33)	BMI (kg/m^2) *median IQR*	Postoperative complications [a]
Jagoe (36)	BMI (kg/m^2) *continuous*	30-day postoperative pulmonary complications
		30-day postoperative mortality
Madariaga (21)	BMI (kg/m^2) *continuous*	90-day postoperative complications
		90-day postoperative cardiopulmonary complications
		Length of hospital stay
Ramos (37)	BMI (kg/m^2) *continuous*	Postoperative complications
Fiorelli (17)	Weight loss ≥5% *continuous*	90-day postoperative complications
Jagoe (36)	FFMI (kg/m^2) *continuous*	30-day postoperative complications
Pretreatment assessment of sarcopenia		
Kim (18)	L3 muscle mass index <55 cm^2/m^2 [c], <39 cm^2/m^2 [d]	30-day postoperative complications
	L3 muscle mass index ≥55 cm^2/m^2 [c], ≥39 cm^2/m^2 [d]	
Tsukioka (27)	L3 muscle mass index <49 cm^2/m^2	Postoperative complications [a]
	L3 muscle mass index ≥49 cm^2/m^2	
Kawaguchi (32)	Psoas muscle mass index <3.70 cm^2/m^2 [d], <2.50 cm^2/m^2 [e]	30-day postoperative complications Clavien-Dindo classification grade ≥2
Nakada (31)	Psoas muscle mass index cm^2/m^2 <4.61 cm^2/m^2 [c], <3.26 cm^2/m^2 [d]	Postoperative complications [a]
Nakamura (23)	Psoas muscle mass index <6.36 cm^2/m^2 [c], <3.92 cm^2/m^2 [d]	Postoperative complications Clavien-Dindo classification grade ≥3 [a]
Madariaga (21)	Thoracic skeletal muscle area cm^2/m^2 *continuous*	90-day postoperative complications
		90-day postoperative cardiopulmonary complications
	Thoracic skeletal muscle area cm^2/m^2 *continuous*	Length of hospital stay
Jagoe (36)	Bone-free midarm muscle area (%) *continuous*	30-day postoperative pulmonary complications
	Subscapular skinfold thickness (%) *continuous*	30-day postoperative pulmonary complications

	P-value	**OR**	**95% CI**	
	<**0.01**	**5.4**	**5.78-6.23**	Univariable
	0.02	**3.8**	**1.72-6.53**	Multivariable
		Reference		
	0.06	**1.84**	**0.98-3.46**	Univariable
		Reference		
	0.47	1.02	0.97-1.08	Univariable
	0.02			Univariable
	<**0.01**			Univariable
	0.02			Univariable
	0.32	1.04	0.97-1.11	Multivariable
	0.09[b]	**1.07**	**0.99-1.16**	Multivariable
	0.10	0.97	0.93-1.01	Multivariable
	0.85			Univariable
	0.80	0.80	0.09-6.86	Univariable
	0.02			Univariable
	P-value	**OR**	**95% CI**	
	0.16	1.59	0.84-3.02	Univariable
		Reference		
	0.34			Univariable
		Reference		
	<**0.01**			Univariable
	0.38	1.50	0.69-3.70	Multivariable
	<**0.01**			Univariable
	0.04	**0.87**[e]	**0.75-0.99**	Multivariable
	0.04	**0.86**[e]	**0.74-0.99**	Multivariable
	0.18	1.05	0.98-1.12	Multivariable
	0.03			Univariable
	<**0.01**			Univariable

Table 4. Continued

Author	Pretreatment nutritional assessments	Posttreatment complications/mortality
	Triceps skinfold thickness (%) *continuous*	30-day postoperative pulmonary complications
Pretreatment assessment of a combination of multiple nutritional parameters		
Illa (35)	NRS 2002 >2	Postoperative complications [a]
	NRS 2002 ≤2	
Bagan (34)	BMI <18.5 kg/m^2, serum albumin <35 g/dL, transthyretin <0.16 g/L	30-day postoperative complications
		90-day operative mortality
	BMI ≥18.5 kg/m^2, serum albumin ≥35 g/dL, transthyretin ≥0.16 g/L	
Tewari (38)	BMI <18.5 kg/m^2, serum albumin <30 g/L, weight loss	Postoperative pulmonary complications [a]
Takahashi (26)	GNRI ≤101	Postoperative complications [a]
		Postoperative complications [a]
		Air leakage
		Pneumonia
		Atrial fibrillation
	GNRI >101	
Ramos (37)	NRI <100	30-day postoperative complications
	NRI ≥100	
	NRI *continuous*	30-day postoperative complications
Pretreatment assessment of nutritional biomarkers		
Bianchi (39)	Serum albumin *IQR >15.86 ml/dl*	Postoperative complications [a]
Fiorelli (17)	Serum albumin (mg/dl) ≥35 g/L	Postoperative complications
		Operative mortality
	Serum albumin (mg/dl) <35 g/L	
Li (19)	Serum albumin≥14.97%	30-day postoperative pulmonary complications
	Serum albumin<14.97%	
Takahashi (26)	Serum albumin>40 g/dl	Postoperative complications [a]
	Serum albumin≤40 g/dl	
Shaverdian (30)	Serum albumin (mg/dl) *median IQR*	Posttreatment complications after SBRT [a]
	Serum albumin (mg/dl) *median IQR*	Posttreatment pulmonary complications after SBRT [a]
Jagoe (36)	Serum albumin (mg/dl) *continuous*	30-day postoperative complications

	<**0.01**			Univariable
	P--value	**OR**	**95% CI**	
	0.04	**2.71**		Univariable
		Reference		
	0.03	**1.76**	**1.1-2.43**	Univariable
	<**0.01**	**6.50**	**9.11-4.14**	Univariable
		Reference		
	0.02			Chi^2
	<**0.01**	**2.41**	**1.52-3.79**	Multivariable
	<**0.01**	**2.58**	**1.70-3.94**	Univariable
	<**0.01**	**3.52**	**1.98-6.44**	Univariable
	<**0.01**	**2.55**	**1.31-5.08**	Univariable
	0.22	1.92	0.65-6.07	Univariable
		Reference		
	0.05	**2.38**	**1.02-5.58**	Multivariable
		Reference		
	<**0.01**	**0.96**[c]	**0.94-0.99**	Univariable
	P-value	**OR**	**95% CI**	
	0.01	**0.80**[c]	**0.68-0.95**	Univariable
		Reference		
	0.02	**2.3**	**1.43-2.01**	Univariable
	0.05	**3.3**	**0.99-1.14**	Univariable
		Reference		
	<**0.01**	**3.13**	**1.75-5.61**	Univariable
	0.02	**2.27**	**1.15-4.46**	Multivariable
		Reference		
	0.61	0.99	0.95-1.04	Univariable
		Reference		
	0.29	3.09		Multivariable
	0.05	**26.87**		Multivariable
	0.91			Univariable

Table 4. Continued

Author	Pretreatment nutritional assessments	Posttreatment complications/mortality
Lee (22)	Serum albumin (mg/dl) *continuous*	90-day postoperative complications
	Serum albumin (mg/dl) *continuous*	90-day postoperative pulmonary complications
Zhang (28)	Serum albumin (mg/dl) *continuous*	90-day postoperative cardiopulmonary complications
Fiorelli (17)	Transferrin >1.7 g/L	90-day postoperative complications
		90-day operative mortality
	Transferrin ≤1.7 g/L	
Zhang (28)	C-reactive protein <35 mg/l	90-day postoperative cardiopulmonary complications
	C-reactive protein ≥35 mg/l	
Lee (22)	C-reactive protein *continuous*	30-day postoperative complications
	C-reactive protein *continuous*	30-day postoperative pulmonary complications
Lee (29)	CONUT >1	Postoperative pulmonary complications [a]
	CONUT 0	
Takahashi (26)	CONUT ≥2	Postoperative pulmonary complications [a]
		Postoperative pulmonary complications [a]
		Air leakage
		Pneumonia
		Atrial fibrillation
	CONUT <1	
Okada (24)	PNI <48	Postoperative complications [a]
		Postoperative pulmonary complications [a]
	PNI ≥48	
Okada (20)	PNI <45	30-day postoperative complications Clavien-Dindo classification grade ≥2
		30-day postoperative complications Clavien-Dindo classification grade ≥3
		Air leak
		Pneumonia
		Atrial fibrillation
		Pulmonary infection
	PNI ≥45	
Park (25)	PNI <50	Postoperative pulmonary complications [a]

	0.03	**0.40**[c]	**0.18-0.91**	Univariable
	0.15	0.53	0.22-1.27	Univariable
	0.61	0.80	0.34-1.88	Univariable
	0.8	0.8	0.10-3.48	Univariable
	0.9	1.1	0.13-6.58	Univariable
		Reference		
	0.78	0.99	0.95-1.04	Univariable
		Reference		
	0.65	1.06	0.82-1.37	Univariable
	0.54	1.09	0.84-1.41	Univariable
	<**0.01**	**1.91**	**1.17-3.10**	Univariable
		Reference		
	0.02	**1.63**	**1.07-2.51**	Multivariable
	<**0.01**	**1.88**	**1.22-2.80**	Univariable
	0.04	**1.01**	**1.73-3.01**	Univariable
	0.44	1.28	0.67-2.46	Univariable
	0.02	**1.63**	**1.07-2.51**	Univariable
		Reference		
	<**0.01**	**1.08**[f]	**1.02-1.14**	Univariable
	0.2	1.11[f]	0.94-1.28	Univariable
		Reference		
	<**0.01**	**2.55**	**1.40-4.57**	Univariable
	<**0.01**	**3.87**	**1.79-8.10**	Univariable
	<**0.01**	**4.38**	**1.18-10.2**	Univariable
	0.04	**6.04**	**1.39-26.2**	Univariable
	0.06	0.62	0.18-1.64	Univariable
	<**0.01**	**8.08**	**1.73-42.0**	Univariable
		Reference		
	<**0.01**	**1.7**	**1.3-2.3**	Multivariable

Table 4. Continued

Author	Pretreatment nutritional assessments	Posttreatment complications/mortality
		Postoperative pulmonary complications [a]
		Atrial fibrillation [a]
		Postoperative complications [a]
	PNI ≥50	
Takahashi (26)	PNI ≤47	Postoperative complications [a]
		Postoperative complications
		Air leakage
		Pneumonia
		Atrial fibrillation
	PNI >47	
Okada (20)	PNI per unit decrease *continuous*	30-day postoperative complications Clavien-Dindo classification grade ≥2
	PNI per unit decrease *continuous*	30-day postoperative complications

Abbreviations: BMI=body mass index; CI=confidence interval; cm=centimeter; CONUT; controlling nutritional status; dl=deciliter; FFMI=fat free mass index; GNRI=geriatric nutritional risk index; kg=kilogram; l=liter; l3=the third lumbar vertebra; m=meter; mg=milligram; NRI= nutritional risk index; NRS 2002=nutrition risk screening 2002; OR=odds ratio; PNI=prognostic nutritional index; SBRT= stereotactic body radiation therapy.
[a] follow-up was not described, [b] due to the small population in this study, a p-value of 0.10 was significant, [c] males, [d] females, [e] Analysis focused on the non-occurrence of postoperative complications, [f] adjusted for smoking status and COPD

	<0.01	**1.7**	**1.1-2.6**	Univariable
	0.05	**1.4**	**1.0-2.1**	Univariable
	0.02	**1.6**	**1.2-2.2**	Univariable
		Reference		
	0.03	**1.64**	**1.05-2.55**	Multivariable
	<0.01	**2.09**	**1.38-3.17**	Univariable
	0.06	1.67	0.96-2.90	
	0.02	**2.13**	**1.11-4.14**	
	0.32	1.67	0.56-5.08	
		Reference		
	<0.01	**1.08**	**1.04-1.12**	Univariable
	0.01	**1.06**[f]	**1.01-1.11**	Multivariable

Cut-off values

Cut-off values of outcomes of pretreatment nutritional assessments associated with an increased risk for treatment complications and treatment mortality are presented in Table 5. A limited number of studies reported a predetermined cut-off value of outcomes of pretreatment nutritional assessment to indicate a higher risk for postoperative complications; however, the accuracy of these cut-off values was usually moderate. One study reported a BMI <18.5 kg/min^2 as optimal cut-off value for a higher risk for treatment complications (37). In the same study, an optimal cut-off value indicating a higher risk for pulmonary complications was a score <100 on the nutritional risk index (37). In another study, a cut-off value for sarcopenia on the psoas muscle mass index of ≤3.70 cm^2/m^2 in male and ≤2.50 cm^2/m^2 in female was reported to indicate a higher risk for treatment complications (32). The most optimal cut-off value for the geriatric nutritional risk index for predicting a higher risk for treatment complications was a score ≤101 (26). A score ≥1 on the controlling nutritional status was used as a cut-off value in two studies (26, 33). In another study, the most optimal prognostic nutritional index cut-off value for an higher risk for treatment complications was ≤49.6 (33), while a prognostic nutritional index score ≤47 was reported as a cut-off value for an higher risk for treatment complications (26).

Table 5. Cut-off values at pretreatment nutritional assessments and posttreatment complications and posttreatment mortality

Author	Pretreatment nutritional assessments	Posttreatment complications/mortality	
Pretreatment assessment of anthropometry and body composition			
Ramos (37)	BMI 18.5 kg/m^2	Postoperative complications	AUC 0.56 (95% CI 0.47-0.65)
Pretreatment assessment of sarcopenia			
Kawaguchi (32)	Psoas muscle index 3.70 cm^2/m^2 [a]	30-day postoperative complications Clavien-Dindo classification grade ≥2	AUC 0.63, Sensitivity 86.4%, specificity 65.0%
	Psoas muscle index 2.50 cm^2/m^2 [b]	30-day postoperative complications Clavien-Dindo classification grade ≥2	AUC 0.59 Sensitivity 97.5%, specificity 58.3%
Pretreatment assessment of a combination of multiple nutritional parameters			
Takahashi (26)	GNRI 101	Postoperative complications [c]	AUC 0.64 (95% CI 0.58-0.69)
Ramos (37)	NRI 100	30-day postoperative complications	AUC 0.64 (95% CI 0.55-0.72)
Pretreatment assessment of serum albumin			
Li (19)	Serum albumin14.97%	30-day postoperative pulmonary complications	AUC 0.66 (95% CI 0.58-0.73), sensitivity 57.7%, specificity 69.6%
Pretreatment assessment of CONUT			
Shoji (33)	CONUT 1	Postoperative complications [c]	AUC 0.56, sensitivity 34.69%, specificity 73.98%
Takahashi (26)	CONUT 1	Postoperative complications [c]	AUC 0.61 (95% CI 0.55-0.67), sensitivity 63.3%, specificity 51.7%
Pretreatment assessment of PNI			
Shoji (33)	PNI 49.6	Postoperative complications [c]	AUC 0.53, sensitivity 50.3%, specificity 58.5%
Takahashi (26)	PNI 47	Postoperative complications [c]	AUC 0.62 (95% CI 0.56-0.68), sensitivity 53.1%, specificity 65.2%

Abbreviations: AUC=area under the curve; BMI=body mass index; CI=confidence interval; cm=centimeter; CONUT; controlling nutritional status; dl=deciliter; FFMI=fat free mass index; GNRI=geriatric nutritional risk index; kg=kilogram; l=liter; m=meter; mg=milligram; NRI= nutritional risk index; NRS 2002=nutrition risk screening 2002; OR=odds ratio; PNI=prognostic nutritional index. [a] males, [b] females, [c] follow-up was not described

Discussion

The aim of this systematic review was to evaluate which outcome variables of pretreatment nutritional assessments are associated with treatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values that can be used for preoperative risk assessment. Results demonstrated that a wide variety of variables of pretreatment nutritional assessments seem to be associated with posttreatment complications and/or posttreatment mortality. A good comparison between studies is hampered due to a large variation in the used outcome criteria between studies. When similar outcomes or criteria were used, studies used a different definition of the outcome or criterion. In addition, only a limited number of cut-off values were provided, all with a poor accuracy. Studies on other treatment strategies than surgery or SBRT were lacking.

Seven included studies investigated the predictive value of BMI in NSCLC, in which two different protocols were used. Being underweight (BMI ≤18.5 kg / m^2) was associated with treatment complications in two studies (17, 26). In addition, three of five studies (21, 33, 36) that examined BMI as a continuous variable, found a significant association between a lower BMI and a higher risk for posttreatment complications. A previous study among patients with bladder cancer (41) has shown that it is difficult to use BMI to predict treatment mortality, probably because it is not an adequate indicator of body composition. Patients with less muscle mass may have the same BMI as patients with higher muscle mass and therefore BMI provides insufficient insight into the patient's fitness (41). When interpreting BMI outcomes, it is important to keep in mind that BMI has its limitations. First, the measurement of BMI includes both fat and fat free mass, both of which are known to be influenced by age and sex (42). Second, many studies used weight loss expressed in percentages and calculated from the previous six months based on memory recall, so the risk of recall bias should be noted (43). It is therefore recommended not to use BMI as the only measurement to assess nutritional status.

Seven included studies investigated the predictive value of sarcopenia in NSCLC, in which six different protocols were used. Four of these seven studies found a significant association between sarcopenia and a higher risk for posttreatment complications and/or treatment mortality. Sarcopenia is a commonly used method to predict postoperative complications in esophagus, bladder, urologic, and head and neck cancer (41, 44-46). It therefore seems

to be an important predictor for cancer treatment complications. Since a computed tomography scan is standard care for diagnosing NSCLC (47), it can be easily applied to measure sarcopenia for predicting treatment complications in this patient group.

In five of the included articles, a combination of assessments was used to evaluate pretreatment nutritional status. In all of these studies (26, 34, 35, 37, 38) a significant association was found between worse nutritional status and the occurrence of posttreatment complications. Furthermore, biomarkers, especially serum albumin, were examined in eight included articles, which found that higher serum albumin was significantly associated with a higher risk for posttreatment complications and/or treatment mortality in five articles (17, 19, 22, 30, 39). Blood tests are usually taken in the diagnostic phase of lung cancer and are easy to acquire in the clinic. In the current review, included articles using a combination of biomarkers such as a low score on the prognostic nutritional index in four studies (20, 24-26) and a high score on the controlling nutritional status in two studies (26, 29) showed an association between pretreatment higher nutritional biomarkers and a higher risk for posttreatment complications and/or treatment mortality. Other biomarkers, such as the modified Glasgow prognostic score, can reflect inflammatory status and are recognized as predictive factors for survival in NSCLC (48) and renal cell cancer (49) but no articles were found in this systematic review that used the modified Glasgow prognostic score as a predictive variable for treatment complications or treatment mortality. Although the measurement of serum albumin is simple and relatively inexpensive, the biochemical relevance of this assessment in patients with cancer is questionable and difficult, because underlying disease may interfere with albumin synthesis (50). Due to high physiological stress with local tissue damage (tumor hypoxia and/or necrosis), a systemic release of pro-inflammatory cytokines and growth factors will occur before hypoalbuminemia. This leads both to the production of C-reactive protein (CRP), as well as to a decrease in the production of albumin (51). Therefore, the use of a combination of different biomarkers such as the prognostic nutritional index might be a better a predictor of malnutrition and ultimately the risk for posttreatment complications.

This review provides a good overview of studies supporting pretreatment risk assessment using nutritional assessments in patients with operable NSCLC, as well as in the single included study in patients undergoing SBRT. These results can be used as a basis for further research to timely identify malnourished

patients who are at high risk for treatment complications and mortality. There are some limitations in this systematic review.

First, when choosing a nutritional assessment tool to identify individuals at risk for malnutrition, it is important to ensure that the nutritional assessment tool accurately identifies individual patients at risk for, or with, malnutrition. However, one of the major limitations is that there is no "gold standard" to diagnose malnutrition, leading to heterogeneity in the included studies. Moreover, it was difficult to evaluate the effect of confounding in multivariable analysis reported in the included studies, due to heterogeneity in the selection of confounders, the definition of outcome of nutritional assessments, and the used posttreatment outcomes. Second, various ways of examining nutritional status are applied in patients with NSCLC. Although this systematic review includes articles that have investigated anthropometry and body composition parameters, sarcopenia, a combination of BMI, serum albumin and weight loss parameters, and biomarkers, no studies have been found that have investigated the association between nutritional assessment questionnaires or surveys and treatment complications in patients with NSCLC. Easy-to-administer nutritional assessments to identify patients with NSCLC who are at high risk for treatment complications are useful in daily practice (52, 53). As a recommendation, tools such as the mini nutritional assessment (54, 55), the malnutrition universal screening tool (56), and the short nutritional assessment questionnaire (57) are practical and inexpensive to apply and can predict clinical outcomes in elderly patients (53). Nutritional assessments such as the patient-generated subjective global assessment (PS-SGA) and the mini nutritional assessment, as well as the assessment of biochemical and laboratory parameters and clinical and dietetically factors (52, 53) allow for a targeted nutritional intervention to replenish nutritional deficits before surgery, eventually as part of a prehabilitation program. Moreover, previous research among patients with cancer has shown that these nutritional assessments best covered the breadth of the definitions of nutritional status (58) and were classified with the highest content validity (59). Third, a poor score on the NOS was particularly found in almost half of the included articles. This is mainly due to the non-description of the outcome of interest present at start of the study or incomplete description of the follow-up. Fourth, there was considerable variation between the studies in type of treatment, used nutritional assessment, definitions and cut-off values of nutritional assessments, and there was incomplete description of posttreatment complications in several studies. This variation could have influenced the associations between the outcome of the pretreatment

nutritional assessment, and posttreatment complications or mortality. Moreover, no information was found about the association between different types of surgery and postoperative complications and mortality, while the physiological impact and risks of a segmentectomy are expected to be less than those of a pneumonectomy. Therefore, in different surgical procedures different outcomes on the nutritional assessment would intuitively be expected (42). Fifth, confounding by smoking and chronic obstructive pulmonary disease may play a role in the association between the outcomes of nutritional assessment and postoperative complications (63). Only two studies (22, 26) adjusted for smoking and COPD; they reported that associations between outcomes of nutritional assessment and postoperative complications were independent of smoking status and COPD.

Although studies have shown that worse outcomes of pretreatment nutritional assessments are associated with a higher risk for posttreatment complications, the nutritional biomarkers and a computed tomography scan may not always be available, making nutritional assessment questionnaires an attractive alternative. However, there is only limited evidence to justify their use in the preoperative setting in patients with cancer and no evidence in patients with NSCLC. Therefore, research on the predictive value of nutritional assessment questionnaires is recommended. Consideration should be given to which outcome variables and cut-off values are easy-to-use to identify patients who are at high-risk for complications so that nutritional interventions can be applied to the individual patient, as well as to the possibility to perform a pretreatment nutritional assessment, after which the nutrition performance status might be improved by prehabilitation to reduce a patient's risk for complications during and/or after treatment (60).

Almost all articles included surgical patients in this systematic review. More attention should be paid to the potential of nutritional assessments to predict treatment complications in patients with NSCLC who undergo other intensive treatments, such as chemoradiotherapy and radical radiotherapy. Efforts should be made to standardize easy-to-administer pretreatment nutritional assessment with accurate cut-off values in pretreatment risk stratification. In future studies, the description of posttreatment complications and posttreatment mortality should be used according to a standardized protocol, and consensus should be reached to use the appropriate follow-up time regarding complications and mortality to enable pooling of study results.

Conclusion

A poor outcome on pretreatment nutritional assessment is associated with a higher risk for posttreatment complications and posttreatment mortality. However, providing specific recommendations for the use of nutritional assessments is difficult due to the heterogeneity in test protocols and used outcome measures in the current literature. Therefore, standardization of the use of pretreatment nutritional assessments is recommended. In addition, more research is needed regarding the ability of easy-to-use pretreatment nutritional assessments, such as nutritional assessment questionnaires, to accurately identify patients who have a high-risk for treatment complications across all curative treatment options for NSCLC. This is important because particularly these high-risk patients may benefit from interventions to improve their physical performance before starting treatment, thereby improving treatment outcomes.

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'I would consider that information about the preparation for surgery in terms of physical exercise training and nutritional support is being of additional value.'

-Patient who underwent surgery for NSCLC-

Chapter 4

Association of pretreatment physical and geriatric parameters with treatment tolerance and survival in elderly patients with stage I–II non-small cell lung cancer: an evaluation of usual care data

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Abstract

In this study, the association of pretreatment physical and geriatric parameters with treatment tolerance and survival in elderly patients with stage I-II NSCLC was evaluated. Retrospective data for patients aged ≥70 years, diagnosed between 2016 and 2020 with stage I-II NSCLC, and who underwent surgery or stereotactic ablative radiotherapy (SABR) in a large Dutch teaching hospital were retrieved from medical records. Associations of pretreatment physical and geriatric parameters with treatment tolerance and survival were analyzed. Of 160 patients, 49 of 104 (47%) patients who underwent surgery and 21 of 56 (38%) patients who received SABR did not tolerate treatment. In univariable analysis, World Health Organization (WHO) performance status ≥2, short nutritional assessment questionnaire score >1, short physical performance battery score ≤9, and geriatric-8 score ≤14 were significantly associated with postoperative complications. Forced expiratory volume of one second <80% of predicted was significantly associated with intolerance of SABR. In multivariable analysis, WHO performance status ≥2 and diffusing capacity for carbon monoxide <80% were significantly associated with decreased overall survival. This is the first study that investigated the association between pretreatment physical and geriatric parameters and treatment outcomes in patients with stage I-II NSCLC. Evaluation of physical and geriatric parameters before treatment initiation seems highly recommended to select patients who might benefit from preventive interventions before and/or during treatment.

Introduction

Lung cancer is the leading cause of cancer mortality worldwide (1). It is predominantly a disease of older people, with half of all newly diagnosed patients being ≥70 years of age (1). According to European guidelines (2), surgery is advised for relatively fit patients with resectable early-stage (stage I–II) non-small cell lung cancer (NSCLC). Stereotactic ablative radiotherapy (SABR) is the advised treatment for inoperable patients (e.g., due to a low physical fitness) and has shown similar survival rates (3). Intensive treatment allows for longer diseasefree and overall survival (3,4), but is often accompanied by treatment intolerance, such as no completion of treatment and/or unplanned hospitalizations (5). In 2018, >35% of all operated patients with NSCLC had a postoperative complication, such as prolonged air leakage, bronchopneumonia, or bleeding. In patients undergoing SABR, 5-10% patients suffered from toxicity, such as dyspnea, pneumonitis, or lung fibrosis (6,7). Patients with a higher risk for treatment complications are often characterized as aged ≥70 years, having tobacco-related comorbidity and/or cognitive impairment, being physically inactive and/or malnourished, and/or especially as having a low physiological reserve capacity (low aerobic fitness) (8,9).

In addition to making well-informed shared decisions concerning treatment options, pretreatment screening and/or assessment might be used to identify patients who are expected to benefit from pretreatment lifestyle interventions. These prehabilitation interventions aim to improve a patient's physical fitness before and during cancer treatment. The comprehensive geriatric assessment (CGA) is a systematic procedure that objectively appraises the health status of elderly people, thereby focusing on somatic, functional, and psychosocial domains (10,11) and aiming to determine the presence of frailty in older people. Frailty is a loss of resources in several domains of functioning, which leads to a declined reserve capacity for dealing with psychophysiological stressors (12). The CGA has historically been adopted to identify elderly patients who are unfit for intense oncologic treatment, but is time-consuming and therefore costly. Next to a geriatric assessment, specific physical function in older adults can be assessed by performance tests (13). Timely identifying high-risk patients before the start of treatment is important to be able to initiate preventive interventions to improve treatment outcomes. It is still unclear to what extent these physical and geriatric tests are associated with treatment tolerance and survival in patients with NSCLC (14). The aim of the present study was to gain

insight into the association of pretreatment physical and geriatric parameters with treatment tolerance and survival in elderly patients with stage I-II NSCLC by evaluating usual care data.

Materials and Methods

Study Design and Patients

In this retrospective cohort study, real world usual care data from the medical records from Zuyderland, a large teaching hospital in the Netherlands, were used. This study started after approval of the Medical Research Ethics Committee Zuyderland (reference number: METCZ20200181). As a pretreatment physical and geriatric assessment is usual care for patients aged ≥70 years in Zuyderland, data of all patients aged ≥70 years who underwent curative intent treatment for stage I-II NSCLC (surgery or SABR) between 2016 and 2020 were included. Patients who underwent surgery or adjuvant chemotherapy for NSCLC in the year before diagnosis of the current tumor, patients who had radiotherapy to the ipsilateral thorax or mediastinum, patients with clinical superior vena cava syndrome, and patients who underwent previous cancer treatment within the last 3 years were excluded, because of the risk of biased outcomes.

Measurements

Pretreatment patient characteristics

The following patient characteristics were obtained from the electronic patient files: age at diagnosis, sex (male, female), smoking status (current, former, never), lung cancer histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma/not otherwise specified), stage of disease (classified according to the clinical classification of the Tumor Node Metastases (cTNM) supplemented with the pathological TNM (8th edition of the TNM classification for non-small lung cancer) (15)), World Health Organization (WHO) performance status, adult comorbidity index-27 (ACE-27), body mass index (BMI), and the short nutritional assessment questionnaire (SNAQ). The WHO performance status was assessed by the case manager or pulmonologist to indicate the level of performance. Patients with a score ≥2 were classified as patients with a poor performance status (16). Comorbidities were obtained using the ACE-27, a validated chart-based instrument. The ACE-27 grades specific conditions into levels of severity, grade 1 (mild), grade 2 (moderate), or grade 3 (severe). Based on the highest ranked single ailment, an overall comorbidity score (none to mild comorbidity (0 to 1) or moderate to severe

comorbidity (≥2)) was assigned (10). BMI was calculated as body mass divided by body height squared. BMI was categorized as underweight (<18.5 kg/m^2) and normal and overweight (>18.5 kg/m^2). Nutritional status was scored according to the SNAQ and subdivided into two categories: normal nutritional status (≤1) or malnourished (>1) (17).

Pretreatment physical performance parameters at baseline

The following baseline physical performance parameters were obtained from the electronic patient files: forced expiratory volume in 1 second (FEV_1), diffusing capacity for carbon monoxide (DLCO), short physical performance battery (SPPB), timed up-and-go (TUG) test, and handgrip strength (HGS). FEV_1 and DLCO were both measured according to the ATS/ERS guideline (18) and expressed as a percentage of predicted based on sex and age (19). Using spirometry, patients were asked to breathe in as deeply as possible, and then exhale as hard, quickly, and long as possible (20,18). DLCO is a medical test that determines how much oxygen travels from the alveoli of the lungs to the blood stream (18). Scores ≤80% of predictive for FEV_1 and DLCO were classified as low (2). The SPPB consists of 1) the ability to stand for up to 10 seconds with feet positioned in three ways (together side-by-side, semi-tandem, and tandem), 2) time to complete a 4-meter walk, and 3) time to rise from a chair five times without the hands resting on the armrests (21). A total score <9 points was indicated as having a lower level of functioning (21). The TUG test measures of the duration required for the patient to rise from a chair, walk over a distance of 3 meters, turn around, walk back, and sit on the chair (22). A score >12 seconds was indicated as having a lower level of functioning (22). HGS is a reliable measure of maximum grip force evaluated using a handheld dynamometer (JAMAR Hydraulic Hand Dynamometer, JA Preston Corporation, Jackson, MI, USA) and was included as a measure of muscle strength. A value below the 10th percentile of the UK Biobank reference values, taking sex, age, and body height into account, in at least one side, was considered as handgrip weakness (23).

Pretreatment geriatric assessment at baseline

Based on the outcomes of a geriatric assessment and predefined cut-off points, patients were classified as fit or (pre)frail. The G8 screening tool consists of an 8-item questionnaire. It places significant weight on nutritional status (46% of the total score), but also focuses on functional mobility, neuropsychological problems, medication use, selfrated health status, and age (24). Geriatric impairment was defined as a score ≤14 on the G8 screening tool (24). The Groningen frailty indicator (GFI) is a short and easy to administer 15-item

screening questionnaire to determine a person's level of frailty (12). The GFI screens for the loss of functions and resources in 4 domains of functioning: physical (functional mobility, multiple health problems, physical fatigue, vision, hearing), cognitive (cognitive functioning), social (emotional isolation), and psychological (depressed mood and feelings of anxiety). Geriatric impairment was defined as a score ≥4 on the GFI (12). The definition of CGA vulnerability was based on previous research and defined as meeting the cut-off scores for impairment in two or more CGA domains (25,26), as an impairment in ≥2 domains has been found to increase the risk for future disability or mortality (27). The following measurements were included in the CGA. Cognitive performance was measured by the Montreal cognitive assessment (MoCa) with a score <26 indicating cognitive impairment (28). Depression was assessed with the hospital anxiety and depression scale (HADS) (>8 demonstrating at risk for depression) was used for psychological distress (29). The instruments of Barthel and Katz were used to quantify the activities of daily living (ADL) (<10 indicating dependency) (30,16), the Lawton and Brody instrument for the instrumental activities of daily living (IADL) (<5 male/<8 female representing dependency) (31), history of falls (≥1), and the mini nutritional assessment (MNA) (<24 indicating at risk for malnutrition score) for nutritional status (32).

Outcomes of Treatment Tolerance and Survival

In case of surgery, treatment intolerance was defined as at least one of the following events occurring during a 30-day postoperative period: complications classified as Clavien-Dindo grade 2 or higher (33), at least one readmission, and/or a postoperative hospital length of stay >5 days. In case of SABR, treatment intolerance was defined as toxicities grade 3 or higher according to the common terminology criteria for adverse events (CTCAE, v6.0) and/or at least one readmission. Overall survival (OS) was calculated as time from diagnosis of lung cancer until death from all causes.

Statistical Analyses

Data was analyzed using IBM SPPS Statistics for Windows version 24 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were used to summarize patient characteristics and crosstabulations were used to analyze associations between pretreatment baseline patient and tumor characteristics, physical performance parameters, geriatric performance parameters, and type of treatment using chi2 tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Associations of pretreatment baseline patient and tumor characteristics, physical performance parameters, and geriatric parameters

with treatment intolerance were analyzed by univariable binary logistic regression analysis, according to treatment type. Because of small numbers, P-values <0.10 were considered statistically significant. The odds ratios (ORs) and corresponding 90% confidence intervals (CIs) were displayed. An OR >1.0 indicated poorer tolerance of treatment. Patients who were alive at the end of the study were censored. Univariable hazard ratios (HRs) and 90% CIs for associations of patient and tumor characteristics, physical parameters, geriatric parameters, and type of treatment with OS were calculated by Cox proportional hazards analyses. Because of small numbers, associations with a P-value <0.10 were considered statistically significant. Parameters with a P-value <0.10 in the univariable analyses were selected for the multivariable regression analyses. Worse survival compared to the reference group was indicated by a HR >1.0.

Results

Pretreatment Patient Characteristics and Physical and Geriatric Parameters

Data of 160 consecutive patients aged ≥70 years who were diagnosed with stage I-II NSCLC were included. An overview of patient and tumor characteristics according to type of treatment is presented in Table 1. Initial treatment consisted of surgery in 104 patients (65.0%) and SABR in 56 patients (35.0%). Stage I NSCLC was more common in patients receiving SABR (89.3%) compared to those undergoing surgery (60.6%). Patients receiving SABR had a statistically significant higher mean age (78.3 years) compared to patients undergoing surgery (75.7 years). Of the patients undergoing surgery, 58.7% had an adenocarcinoma and 41.3% had a squamous cell carcinoma, compared to 21.4% and 8.9% respectively for patients receiving SABR. In addition, stage I disease, WHO performance status ≥2, ACE-27 score ≥2, BMI <18.5 kg/m2, SNAQ score >1, FEV_1 and DLCO <80% of predicted, SPPB score ≤9, TUG test >12 seconds, G8 ≤14, and GFI ≥4 were significantly more present among patients receiving SABR than among those undergoing surgery.

A geriatric assessment was completed in 63.1% of the included patients. Geriatric assessment was omitted more often in patients undergoing SABR than in patients undergoing surgery. Patients who did not undergo a CGA more often had a large cell carcinoma/not otherwise specified and fewer readmissions. An overview of patient, tumor, and treatment characteristics in subgroups of fit patients, frail patients, and patients who did not undergo a CGA is shown in Table 2.

Table 1. Overview of patient and tumor characteristics (including physical performance parameters and geriatric assessment at baseline) of patients with stage I-II NSCLC aged ≥70 years according to treatment modality.

Parameters	**Surgery n=104 n (%)**	**SABR n=56 n (%)**	***P*-value[a]**
Mean ± SD age (years)	75.7 ± 4.3	78.3 ± 5.2	**<0.01**
Sex			
Male	61 (58.7)	32 (57.1)	0.85
Female	43 (41.3)	24 (42.9)	
Lung cancer histology			
Adenocarcinoma	61 (58.7)	12 (21.4)	
Squamous cell carcinoma	43 (41.3)	5 (8.9)	**<0.01**
Large cell carcinoma/not otherwise specified	0 (0.0)	39 (69.6)	
Stage of disease			
Stage I	63 (60.6)	50 (89.3)	**<0.01**
Stage II	41 (39.4)	6 (10.7)	
WHO performance status			
0-1	83 (79.8)	30 (53.6)	
≥2	17 (16.3)	26 (46.4)	**<0.01**
Unknown	4 (3.8)	0 (0.0)	
ACE-27			
0-1	77 (74.8)	32 (58.2)	**0.03**
≥2	26 (25.2)	23 (41.8)	
BMI			
Normal weight (18.5 to 25.0 kg/m^2)	101 (97.1)	50 (89.3)	
Underweight (<18.5 kg/m^2)	3 (2.9)	5 (8.9)	**0.09**
Unknown[a]	0 (0.0)	1 (1.8)	
SNAQ score			
Adequate nutritional status ≤1	87 (83.7)	39 (69.6)	**0.04**
Malnourished >1	16 (15.4)	16 (28.6)	
Pretreatment physical status parameters			
FEV_1			
≥80% of predicted	57 (54.8)	16 (28.6)	
<80% of predicted	47 (45.2)	37 (66.1)	**<0.01**
Unknown[a]	0 (0.0)	3 (5.4)	
DLCO			
≥80% of predicted	36 (34.6)	6 (10.7)	
<80% of predicted	62 (59.6)	46 (82.1)	**<0.01**
Unknown[a]	6 (5.8)	4 (7.1)	

Table 1. Continued

Parameters	Surgery n=104 n (%)	SABR n=56 n (%)	*P*-value[a]
SPPB score			
Higher level of functioning (>9 s)	25 (24.0)	8 (14.3)	
Lower level of functioning (≤9 s)	47 (45.2)	17 (30.4)	**<0.01**
Not assessed[b]	32 (30.8)	31 (55.4)	
TUG test			
Higher level of functioning (≤12 s)	56 (53.8)	16 (28.6)	
Lower level of functioning (>12 s)	5 (4.8)	5 (8.9)	**0.06**
Not assessed[b]	43 (41.3)	35 (62.5)	
Handgrip strength[c]			
Normal	48 (46.2)	17 (30.4)	
Weak	5 (4.8)	2 (3.6)	0.89
Not assessed[b]	51 (49.0)	37 (66.1)	
Pretreatment Geriatric status parameters			
G8			
Fit (>14)	31 (29.8)	6 (10.7)	
Frail (≤14)	37 (35.6)	19 (33.9)	**0.06**
Not assessed[b]	36 (34.6)	31 (55.4)	
GFI			
Fit (<4)	43 (41.3)	9 (16.1)	
Frail (≥4)	29 (27.9)	18 (32.1)	**0.02**
Not assessed[b]	32 (30.8)	29 (51.8)	
Pretreatment comprehensive geriatric assessment			
CGA			
Fit (<2)	24 (23.1)	9 (16.1)	
Frail (≥2)	49 (47.1)	19 (33.9)	0.94
Not assessed[b]	31 (29.8)	28 (50.0)	
MoCa[d]			
Fit (≥26)	27 (26.0)	11 (19.6)	0.83
Frail (<26)	46 (44.2)	17 (30.4)	
HADS depression[d]			
No risk at depression (≤8)	66 (63.5)	25 (44.6)	0.87
Risk at depression (<8)	7 (6.7)	3 (5.4)	
Barthel and Katz ADL[d]			
No restrictions (≥10)	11 (10.6)	4 (7.1)	0.92
Restrictions (<10)	62 (59.6)	24 (42.9)	

Table 1. Continued

Parameters	Surgery n=104 n (%)	SABR n=56 n (%)	*P*-value[a]
Lawton and Brody IADL[d]			
No restrictions (≥5 male, ≥8 female)	54 (51.9)	19 (33.9)	0.54
Restrictions (<5 male, <8 female)	19 (18.3)	9 (16.1)	
History of falls[d]			
<1	65 (62.5)	19 (33.9)	**0.01**
≥1	8 (7.7)	9 (16.1)	
MNA[d]			
Normal nutritional status (≤1)	1 (1.0)	2 (3.6)	0.13
Malnourished (>1)	72 (69.2)	26 (46.4)	

Data are presented as means ± SD or n (%).

Abbreviations: ACE-27= adult comorbidity index-27; ADL=activities of daily living; BMI=body mass index; CGA=comprehensive geriatric assessment; DLCO=diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; GFI=Groningen frailty index; HADS=hospital anxiety and depression scale; IADL=instrumental activities of daily living; MNA=mini nutritional assessment; MoCa=Montreal cognitive assessment; SABR=stereotactic ablative radiotherapy; SD=standard deviation; SNAQ=short nutritional assessment questionnaire; SPPB=short physical performance battery; TUG= timed up-and-go; WHO=World Health Organization.

[a]: unknown was not included in statistical analyses.

[b]: patients that were not assessed were not included in the statistical analyses.

[c]: <10th percentile of norm values (25).

[d]: the number and percentages of 'not assessed' are the same as for 'CGA' and not shown for this geriatric variable.

Treatment Intolerance

A total of 70 patients (43.7%) did not tolerate treatment. Treatment intolerance occurred in 49 of 104 (47.1%) patients undergoing surgery and in 21 of 56 (37.7%) patients receiving SABR. Type of treatment intolerance, stratified for type of treatment, is shown in Table 3. In univariable regression analyses in patients undergoing surgery, stage II disease (OR 2.54), WHO performance status ≥2 (OR 4.46), SNAQ score >1 (OR 2.84), SPPB score ≤9 (OR 4.14), G8 score ≤14 (OR 3.79), or a GFI score ≥4 (OR 3.40) were significantly associated with postoperative complications. An FEV_1 <80% of predicted (OR 5.33) was significantly associated with treatment intolerance in univariable regression analyses in patients receiving SABR. Results of the univariable regression analyses for intolerance of surgery respectively SABR are shown in Table 4.

Table 2. Overview of patient, tumor, and treatment characteristics in relation to comprehensive geriatric assessment.

Parameters	**Fit (n=33) n (%)**	**Frail (n=68) n (%)**	**Not assessed (n=59) n (%)**	***P*-value[a]**
Mean ± SD age (years)	75.2 ± 4.9	77.4 ± 5.1	76.5 ± 4.2	**0.08**
Sex				
Male	21 (63.6)	40 (58.8)	32 (54.2)	0.67
Female	12 (36.4)	28 (41.2)	27 (45.8)	
Lung cancer histology				
Adenocarcinoma	13 (39.4)	31 (45.6)	29 (49.2)	
Squamous cell carcinoma	12 (36.4)	26 (38.2)	10 (16.9)	**0.04**
Large cell carcinoma/not otherwise specified	8 (24.2)	11 (16.2)	20 (33.9)	
Stage of disease				
Stage I	26 (78.8)	37 (54.4)	50 (84.7)	<0.01
Stage II	7 (21.2)	31 (45.6)	9 (15.3)	
Type of treatment				
Surgery	24 (72.7)	49 (72.1)	31 (52.5)	**0.04**
SABR	9 (27.3)	19 (27.9)	28 (47.5)	
Pretreatment comprehensive geriatric assessment				
WHO performance status				
0-1	24 (72.7)	44 (65.7)	45 (80.4)	
≥2	9 (27.3)	23 (34.3)	11 (19.6)	0.19
Unknown	0	1	3	
ACE-27				
0-1	24 (72.7)	49 (72.1)	36 (63.2)	0.49
≥2	9 (27.3)	19 (27.9)	21 (36.8)	
BMI				
Normal weight (18.5 to 25.0 kg/m^2)	33 (100.0)	65 (95.6)	53 (91.4)	
Underweight (<18.5 kg/m^2)	0 (0.0)	3 (4.4)	5 (8.6)	0.19
Unknown	0	0	1	
SNAQ score				
Adequate nutritional status ≤1	23 (71.9)	56 (83.6)	47 (79.7)	
Malnourished >1	9 (28.1)	11 (16.4)	12 (20.3)	0.40
Unknown	1	1	0	

Table 2. Continued

Pretreatment physical status parameters				
FEV_1				
≥80% of predicted	18 (54.5)	28 (41.8)	27 (47.4)	
<80% of predicted	15 (45.5)	39 (58.2)	30 (52.6)	0.48
Unknown	0	1	2	
DLCO				
≥80% of predicted	6 (18.8)	19 (29.7)	17 (31.5)	
<80% of predicted	26 (81.3)	45 (70.3)	37 (68.5)	0.41
Unknown	1	4	5	
Treatment intolerance				
Clavien-Dindo grade ≥2 or CTCAE grade ≥3	11 (33.3)	26 (38.8)	14 (23.7)	0.19
Readmission	11 (33.3)	23 (33.8)	9 (15.5)	**<0.05**
Postoperative hospital length of stay >5 days	13 (54.2)	27 (55.1)	11 (37.9)	0.31
Survival				
1-year	84.8	83.8	89.8	0.60
3-year	69.7	73.5	81.4	0.40

Data are presented as means ± SD or n (%).
Abbreviations: ACE-27= adult comorbidity index-27; BMI=body mass index; CTCAE=Common Terminology Criteria for Adverse Events; DLCO=diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; MoCa=Montreal cognitive assessment; SABR=stereotactic ablative radiotherapy; SD=standard deviation; SNAQ=short nutritional assessment questionnaire; TUG= timed up-and-go; WHO=World Health Organization.
[a]: unknown was not included in statistical analyses.

Table 3. Type of treatment intolerance, stratified for type of treatment.

Clavien-Dindo classification	**Surgery (n=104) n (%)**	**CTCAE grade**	**SABR (n=56) n (%)**
0-I	58 (55.8)	0-II	48 (85.7)
II	28 (26.9)	III	4 (7.1)
III	9 (8.7)	IV	1 (1.8)
IV	4 (3.8)	V	1 (1.8)
V	5 (4.8)		
No readmission	79 (76.0)	No readmission	38 (67.9)
Readmission	25 (24.0)	Readmission	18 (32.1)

Abbreviations: CTCAE=common terminology criteria for adverse events; SABR=stereotactic ablative radiotherapy.

Table 4. Univariable odds ratios for associations of pretreatment patient characteristics, physical status parameters and geriatric status parameters with intolerance of treatment in patients with stage I-II NSCLC, stratified for type of treatment.

	Surgery (n=104) Treatment intolerance n=49 (47%) Univariable		**SABR (n=56) Treatment intolerance n=21 (38%) Univariable**	
	OR (90% CI)	***P*-value**	**OR (90% CI)**	***P*-value**
Age (continuous, in years)	1.01 (0.93-1.11)	0.78	0.96 (0.86-1.07)	0.46
Sex				
Male	Reference		Reference	
Female	1.82 (0.83-4.00)	0.14	1.00 (0.34-2.98)	1.00
Stage of disease				
Stage I	Reference		NI[a]	
Stage II	**2.54 (1.13-5.69)**	**0.02**		
WHO performance status				
0-1	Reference		Reference	
≥2	**4.46 (1.34-14.83)**	**0.02**	1.47 (0.49-4.35)	0.49
ACE-27				
0-1	Reference		Reference	
≥2	1.14 (0.47-2.77)	0.77	1.23 (0.40-3.73)	0.71
BMI				
Normal weight (≥18.5 kg/m^2)	NI[a]		NI[a]	
Underweight (<18.5 kg/m^2)				
SNAQ score				
Adequate nutritional status ≤1	Reference		Reference	
Malnourished >1	**2.84 (0.91-8.86)**	**0.07**	1.56 (0.47-5.12)	0.47
Physical status parameters				
FEV_1				
≥80% of predicted	Reference		Reference	
<80% of predicted	0.84 (0.39-1.82)	0.65	**5.33 (1.06-26.90)**	**0.04**
DLCO				
≥80% of predicted	Reference		NI[a]	
<80% of predicted	1.89 (0.81-4.38)	0.14		
SPPB				
Higher level of functioning (>9 s)	Reference		Reference	
Lower level of functioning (≤9 s)	**4.14 (1.45-11.87)**	**0.01**	2.38 (0.42-13.39)	0.33

Table 4. Continued

	Surgery (n=104) Treatment intolerance n=49 (47%) Univariable		**SABR (n=56) Treatment intolerance n=21 (38%) Univariable**	
	OR (90% CI)	***P*-value**	**OR (90% CI)**	***P*-value**
TUG test				
Higher level of functioning (≤12 s)	NI[a]		Reference	
Lower level of functioning (>12 s)			0.52 (0.07-4.00)	0.52
Handgrip strength				
Normal	NI[a]		NI[a]	
Weak[b]				
Geriatric status parameters				
G8				
Fit (>14)	Reference		Reference	
Frail (≤14)	**3.79 (1.38-10.37)**	**0.01**	0.36 (0.05-2.50)	0.30
GFI				
Fit (<4)	Reference		Reference	
Frail (≥4)	**3.40 (1.26-9.21)**	**0.02**	0.32 (0.06-1.71)	0.18
Comprehensive geriatric assessment				
CGA				
Fit (<2)	Reference		Reference	
Frail (≥2)	1.04 (0.39-2.77)	0.94	0.51 (0.12-2.88)	0.50
MoCa				
Fit (≥26)	Reference		Reference	
Frail (<26)	0.73 (0.28-1.91)	0.52	0.31 (0.06-1.51)	0.15
HADS depression				
No risk for depression (≤8)	NI[a]		NI[a]	
Risk for depression (<8)				
Barthel and Katz ADL				
No restrictions (≥10)	Reference		Reference	
Restrictions <10	0.54 (0.14-2.02)	0.36	0.85 (0.10-7.04)	0.88
Lawton and Brody IADL				
No restrictions (≥5 male, ≥8 female)	Reference		Reference	
Restrictions (<5 male, <8 female)	0.84 (0.29-2.38)	0.74	0.89 (0.18-4.38)	0.89

Table 4. Continued

	Surgery (n=104) Treatment intolerance n=49 (47%) Univariable		SABR (n=56) Treatment intolerance n=21 (38%) Univariable	
	OR (90% CI)	***P*-value**	**OR (90% CI)**	***P*-value**
History of falls				
<1	NI[a]		3.43 (0.65-18.22)	0.15
≥1				
MNA				
Normal nutritional status (≤1)	NI[a]		Reference	
Malnourished (>1)			0.86 (0.05-15.22)	0.92

Data are presented as means ± SD or n (%).

Abbreviations: ACE-27=adult comorbidity index-27; ADL=activities of daily living; BMI=body mass index; CGA=comprehensive geriatric assessment; CI=confidence interval; DLCO=diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; GFI=Groningen frailty index; HADS=hospital anxiety and depression scale; IADL=instrumental activities of daily living; MNA=mini nutritional assessment; MoCa=Montreal cognitive assessment; NI=not included; NSCLC=non-small cell lung cancer; OR=odds ratio; SABR=stereotactic ablative radiotherapy; SD=standard deviation; SNAQ=short nutritional assessment questionnaire; SPPB=short physical performance battery; TUG= timed up-and-go; WHO=World Health Organization.

[a]: the following variables were not included in statistical analyses because numbers in subgroups were too small.

[b]: <10th percentile of norm values (25).

Overall survival

Median follow-up was 49 months. Median overall survival for the total group was 41 months, and at the time of analysis 50 patients (31.3%) had died. In univariable analyses, SABR (HR 2.00), squamous cell carcinoma or large cell carcinoma/not otherwise specified (HR 2.52 and 2.89), a WHO performance status ≥2 (HR 2.25, P<0.01: Figure 1), a BMI <18.5 kg/m2 (HR 2.69), a DLCO <80% of predicted (HR 2.97, P<0.01: Figure 1), a SPPB score ≤9 (HR 2.21), a TUG test >12 seconds (HR 3.42), and treatment intolerance (HR 2.26) were significantly associated with poorer survival. The following factors were analyzed for their association with survival in multivariable analyses: type of treatment, histology, WHO performance status, and DLCO. Squamous cell carcinoma (HR 2.37), WHO performance status ≥2 (HR 2.03), and DLCO <80% of predicted (HR 2.37) remained significantly associated with poorer survival. Geriatric assessment variables were not included due to high proportions of missing values, whereas BMI was not included in multivariate analysis, because of a very low percentage of patients being underweight. Due to the high proportion of missing cases, the SPPB and TUG test were also excluded from multivariable analyses. Results of univariable and multivariable Cox regression analyses for survival are shown in Table 5.

Table 5. Univariable and multivariable hazard ratios and 95% CIs for associations of pretreatment patient, tumor and treatment characteristics with overall survival in patients with stage I-II NSCLC

	1-year survival %	3-year survival %	Univariable		Multivariable	
			HR (90% CI)	*P*-value	HR (90% CI)	*P*-value
Age	-	-	0.97 (0.92-1.03)	0.37	NI[a]	
Type of treatment						
Surgery	88.5	79.8	Reference		Reference	
SABR	82.1	67.9	**2.00 (1.15-3.51)**	**0.01**	1.73 (0.74-4.07)	0.29
Sex						
Male	83.9	72.0	Reference		NI[a]	
Female	89.6	80.6	0.68 (0.38-1.21)	0.19		
Histology						
Adenocarcinoma	95.9	83.6	Reference		Reference	
Squamous cell carcinoma	75.0	70.8	**2.52 (1.25-5.01)**	**0.01**	**2.37 (1.31-4.27)**	**0.02**
Large cell carcinoma/not otherwise specified	82.1	66.7	**2.89 (1.44-5.82)**	**<0.01**	1.53 (0.80-2.92)	0.28
Stage of disease						
Stage I	88.5	77.9	Reference		NI[a]	
Stage II	80.9	70.2	1.36 (0.77-2.41)	0.29		
WHO performance status						
0-1	90.3	79.6	Reference		Reference	
≥2	74.4	62.8	**2.25 (1.24-4.10)**	**<0.01**	**2.03 (1.16-3.53)**	**0.04**
ACE-27						
0-1	87.2	75.2	Reference		NI[a]	
≥2	85.7	77.6	1.08 (0.56-2.09)	0.81		
BMI						
Normal weight (≥18.5 kg/m^2)	87.4	76.8	Reference		NI[b]	
Underweight (<18.5 kg/m^2)	75.0	62.5	**2.69 (0.96-7.59)**	**0.06**		
SNAQ score						
Adequate nutritional status ≤1	85.7	76.2	Reference		NI[a]	
Malnourished >1	87.5	75.0	1.46 (0.76-2.81)	0.262		
Pretreatment physical status parameters						
FEV_1						
≥80% of predicted	87.7	78.1	Reference		NI[a]	
<80% of predicted	85.7	73.8	1.35 (0.769 -2.40)	0.31		
DLCO						
≥80% of predicted	92.9	88.1	Reference		Reference	
<80% of predicted	83.3	69.4	**2.97 (1.33-6.62)**	**<0.01**	**2.37 (1.17-4.77)**	**0.04**
SPPB						
Higher level of functioning (>9 s)	92.7	80.0	Reference		NI[c]	
Lower level of functioning (≤9 s)	73.8	61.9	**2.21 (1.14-4.26)**	**0.02**		
TUG test						
Higher level of functioning (≤12 s)	88.9	75.0	Reference		NI[c]	
Lower level of functioning (>12 s)	50.0	30.0	**3.42 (1.52-7.70)**	**<0.01**		
Handgrip strength						
Normal	84.6	75.4	Reference		NI[a]	
Weak[d]	71.4	57.1	2.30 (0.78-6.77)	0.13		

	1-year survival %	3-year survival %	Univariable		Multivariable	
			HR (90% CI)	*P*-value	HR (90% CI)	*P*-value
Pretreatment geriatric status parameters						
G8						
Fit (>14)	89.2	78.4	Reference		NI[a]	
Frail (≤14)	78.6	67.9	1.60 (0.81-3.16)	0.18		
GFI						
Fit (<4)	86.5	72.1	Reference		NI[a]	
Frail (≥4)	80.9	74.5	1.11 (0.57-2.22)	0.76		
Pretreatment ggeriatric assessment						
CGA						
Fit (<2)	84.8	69.7	Reference		NI[a]	
Frail (≥2)	83.8	73.5	0.77 (0.38-1.53)	0.45		
MoCa						
Fit (≥26)	84.2	71.1	Reference		NI[a]	
Frail (<26)	84.1	73.0	0.72 (0.38-1.39)	0.33		
HADS depression						
No risk at depression (≤8)	84.6	71.4	Reference		NI[a]	
Risk at depression (<8)	80.0	80.0	0.59 (0.14-2.46)	0.47		
Barthel and Katz ADL						
Fit (≥10)	73.3	60.0	Reference		NI[a]	
Frail (<10)	86.0	74.4	0.77 (0.34-1.75)	0.53		
Lawton and Brody IADL						
Fit (≥5 male, ≥8 female)	83.6	72.6	Reference		NI[a]	
Frail (<5 male, <8 female)	85.7	71.4	0.86 (0.43-1.71)	0.67		
History of falls						
<1	86.9	73.8	Reference		NI[a]	
≥1	70.6	64.7	1.67 (0.79-3.54)	0.12		
MNA						
Adequate nutritional status (≤1)	100.0	100.0	Reference		NI[a]	
Malnourished (>1)	83.7	71.4	0.90 (0.12-6.59)	0.92		
Treatment intolerance						
Treatment intolerance						
No	95.5	84.3	Reference		NI	
Yes	74.6	64.8	**2.26 (1.27-4.03)**	**<0.01**		

Abbreviations: ACE-27= adult comorbidity index-27; ADL=activities of daily living; BMI=body mass index; CGA=comprehensive geriatric assessment; CI=confidence interval; DLCO=diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; GFI=Groningen frailty index; HADS=hospital anxiety and depression scale; HR=hazard ratio; IADL=instrumental activities of daily living; MNA=mini nutritional assessment; MoCa=Montreal cognitive assessment; NSCLC=non-small cell lung cancer; SABR=stereotactic ablative radiotherapy; SNAQ=short nutritional assessment questionnaire; SPPB=short physical performance battery; TUG= timed up-and-go; WHO=World Health Organization.

[a]: not included when P-value ≥0.10.

[b]: BMI was not included in multivariate analysis, because of a low percentage of patients with underweight (5%).

[c]: SPPB and TUG were not included in multivariate analysis, because of a high percentage of missing cases (39% and 49%) and because of violating the proportional hazards assumption

[d]: <10th percentile norm values (25).

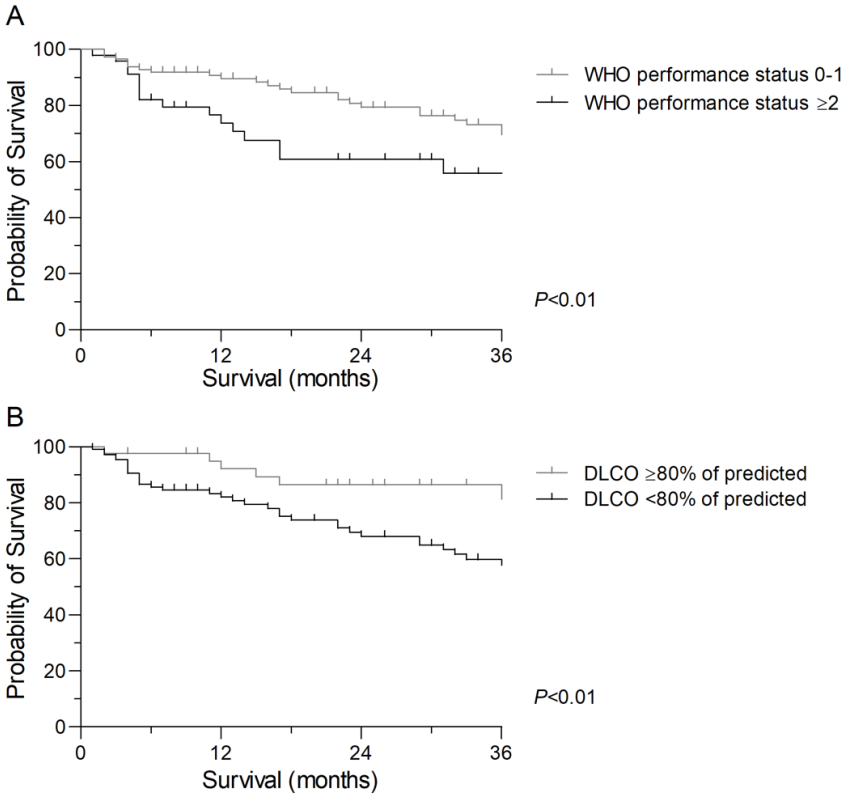

Figure 1. Kaplan-Meier survival curves for patients with non-small cell lung cancer who underwent surgery or stereotactic ablative radiotherapy. **A**. according to world health organization performance status (Log rank: *P*<0.01). **B.** according to diffusing capacity for carbon monoxide (Log rank: *P*<0.01).

Discussion

The aim of this study was to investigate associations of pretreatment physical and geriatric parameters with treatment tolerance and survival in patients aged ≥70 years with stage I-II NSCLC. Results demonstrated that several physical parameters and a limited number of pretreatment geriatric parameters were associated with treatment tolerance, with worse scores indicating a higher risk for adverse treatment outcomes. Moreover, worse performance on pretreatment physical parameters were significantly associated with reduced overall survival, whereas pretreatment geriatric parameters were not associated with survival.

In this study, patients with an FEV_1 <80% of predicted were more often selected for SABR, which is in line with European guidelines (2). According to these guidelines (2), surgical risk is not increased when FEV_1 and the DLCO are both ≥80% of predicted. Almost half (46%) of the patients with a WHO performance status ≥2 underwent SABR. Current study results and results of a previous study (34) therefore suggest that FEV_1, DLCO, and WHO performance status have an added value in identifying patients at high risk for postoperative complications who are therefore advised to undergo SABR. However, even in patients with an adequate WHO performance status (0-1), outcome is heterogeneous (35), because geriatric impairments can still be present in patients with a WHO performance status of 0 or 1 (65.7%). Therefore, a more detailed evaluation of patient's functional status may be of added value in addition to WHO performance status.

Regarding physical parameters, only a SPPB score ≤9 and SNAQ score >1 were associated with a higher risk for postoperative complications in this study, whereas a FEV_1 <80% of predicted was related with a higher risk for intolerance of SABR. In addition to demonstrating that pretreatment screening of physical status is associated with both treatment intolerance and survival, information on the associations between physical status and recovery of physical functioning is also essential to make adequate treatment decisions together with patients. Also, specific pretreatment assessment of aerobic fitness using a cardiopulmonary exercise test (CPET) (36), steep ramp test (a short maximal test on a cycle ergometer that is strongly related to aerobic fitness) (37), or incremental shuttle walk test (iSWT) (38) with adequate cut-off points in patients with NSCLC might improve pretreatment risk assessment. A systematic review reported that a better performance on preoperative exercise

tests, especially a higher aerobic fitness as objectively measured by the CPET, was associated with a lower risk for postoperative complications in patients with NSCLC (39). Moreover, the iSWT and steep ramp test for estimating a patient's preoperative aerobic fitness (38,37) might also be used to timely identify high-risk patients who might benefit from lifestyle interventions (e.g., physical exercise training) before and during cancer treatment (prehabilitation and early rehabilitation, respectively) (40).

In the current univariable analyses, physical parameters were associated with poorer survival in patients undergoing surgery or SABR. This agrees with a previous study in patients with lung cancer (41). The association between physical parameters and survival might partly be explained by the fact that patients with a poor physical status suffered more often from treatment intolerance. This means that especially patients with a poor physical status could benefit from pretreatment preventive lifestyle interventions. Physical exercise training on top of medical treatment could optimize physical status, leading to better tolerance of intensive treatment (42) and preservation of physical functioning. This can be achieved by exercise prehabilitation (physical exercise training before treatment initiation). The physiological reserve capacity can be increased by a combination of aerobic and resistance training (42). Even better outcomes might be achieved when the diet is adapted to the needs of training as well, including healthy and protein-rich products (43). The univariable analysis also showed that patients receiving SABR had a significantly worse survival than patients undergoing surgery. However, this association disappeared after adjusting for differences in baseline characteristics between patients undergoing surgery and patients receiving SABR. This is in line with previous research demonstrating that outcomes between SABR and surgery for operable patients with stage I NSCLC are comparable (5). For shared decision-making, it is therefore important to gain insight into patient characteristics that are associated with the risks and benefits of both treatment options (5).

With respect to pretreatment geriatric parameters, a frailty score determined from the geriatric screening tools G8 or GFI was associated with complications after surgery, but not with intolerance of SABR. The latter is in line with previous research in patients with head and neck cancer undergoing radiotherapy (44). It is likely that the gradual increase in complaints during radiation treatment in vulnerable patients is better tolerated than the major impact of the surgery-induced stress response. As frailty refers to decreases in physiological reserves after a stressful event (45), one can speculate that the duration and intensity of

the stress response are an important aspect. In contrast, when the stress response is prolonged and less intense, which is the case with radiation therapy, the patient can adapt to disrupted homeostasis. Although not supported by the current study findings, a geriatric assessment is able to detect unidentified but manageable problems (46). Therefore, a geriatric screening might lead to better outcomes using targeted prehabilitation interventions to improve treatment tolerance and by adjusting oncologic treatment plans in the elderly cancer population (46).

Despite the novelty of prognostic physical and geriatric parameters in patients with NSCLC aged ≥70 years and undergoing surgery or SABR, results reported in this study need to be interpreted with caution due to some limitations. In the current retrospective observational study, a geriatric assessment was not performed in 36.9% of the patients. To provide a good overview of usual care data, it was decided to present all data and to also provide insight into the group without pretreatment geriatric assessments. Due to the large proportion of missing data, information from detailed geriatric and physical parameters could unfortunately not be included in the multivariable regression analyses. This might have biased the results, since the group of patients in whom no geriatric assessment had been performed more often received SABR, more often had a large cell carcinoma/not otherwise specified, and had fewer readmissions. Failure to refer a patient for a pretreatment geriatric assessment might be explained by the fact that SABR has become the standard of care for medically inoperable early-stage NSCLC (47), regardless of poor WHO performance status or physical status. However, both the International Society for Geriatric Oncology and the National Comprehensive Cancer Network recommend that elderly patients with cancer undergo a geriatric assessment prior to treatment decisions to detect problems which may not promptly be identified by routine physical examinations or medical history. This geriatric assessment can be used to predict treatment intolerance and survival, and to support treatment decisions (48). Furthermore, only patients who were already selected for surgery or SABR were included in this study. This means that results were predominantly based on relatively fit patients. Therefore, caution is warranted when extrapolating the current results.

A worse physical and geriatric status is often associated with treatment intolerance and worse survival in patients with cancer, especially in those undergoing surgery (49). However, uncertainty remains in this study about the discriminative power of the used physical and geriatric screening and

assessment tools for selecting patients for the right treatment and to discuss the risks and benefits of the treatment with the patient. According to the current study results and results from a previous study (39), it appears to be useful to use pretreatment physical performance tests for assessing physical fitness (e.g., aerobic fitness, functional mobility) to select patients who might benefit from preventive interventions before and during treatment. For future research, it is recommended to conduct a large prospective multicenter study in which a large group of patients aged ≥70 years of age perform easy-to-use physical exercise tests and geriatric assessments before treatment initiation to clarify which (combination of) pretreatment parameters are predictive for treatment tolerance and survival. This may contribute to the development of a multimodal tool for pretreatment risk assessment.

Conclusions

Several physical and geriatric parameters were associated with treatment tolerance and survival in patients aged ≥70 years with stage I-II NSCLC undergoing surgery or SABR, in which worse scores indicate a higher risk for adverse treatment outcomes. An evaluation of pretreatment physical and geriatric performance seems highly recommended for shared decision-making and selecting patients who might benefit from preventive interventions before and/or during treatment. Further research is needed, particularly in patients receiving SABR, to investigate the ability of pretreatment physical exercise tests and geriatric assessments to accurately identify patients with stage I-II NSCLC who have an increased risk for treatment intolerance, as these patients might benefit from prehabilitation interventions to improve their physical performance status before treatment initiation.

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'I think it is important to provide support. You just do that as a partner. It is... we have been together for so long for a reason.'
-Informal caregiver-

Chapter 5

Associations of pretreatment physical status parameters with tolerance of concurrent chemoradiation and survival in patients with non-small cell lung cancer

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Abstract

Objective The aim of this study was to evaluate associations between pretreatment physical status parameters and tolerance of concurrent chemoradiation (cCHRT) and survival among patients with stage III non-small cell lung cancer (NSCLC).

Methods A retrospective cohort study was conducted among patients with stage III NSCLC who had received cCHRT between 2006 and 2015. Multivariate independent associations were analysed between the pretreatment parameters age, Charlson comorbidity index, World Health Organization performance status (WHO performance status), body mass index (BMI), fat-free mass index (FFMI), maximal handgrip strength, forced expiratory volume in one second and carbon monoxide lung diffusion capacity on the one hand with tolerance of cCHRT (defined as a received radiation dose at least equal to the prescribed radiation dose) and survival on the other hand.

Results 527 of 577 patients (91.3%) tolerated cCHRT. A WHO performance status ≥ 2 (odds ratio (OR) 0.43) and BMI < 18.5 kg/m^2 (OR 0.36) were associated with poorer tolerance of cCHRT. In the total group, a WHO performance status ≥ 2 (hazard ratio (HR) 1.73), low FFMI (HR 1.23) and intolerance of cCHRT (HR 1.55) were associated with poorer survival.

Conclusion In patients with stage III NSCLC receiving cCHRT, poor WHO performance status and BMI < 18.5 kg/m^2 were independently associated with tolerance of cCHRT. Physical status parameters and intolerance of cCHRT were independently associated with poorer survival. Besides using this information for treatment decisions, optimizing physical status in patients at risk for intolerance of cCHRT might be a next step for improving treatment outcomes.

Introduction

Lung cancer is the fourth most common type of cancer in the Netherlands (1), with 14,500 newly diagnosed patients in 2017 (2). Non-small cell lung cancer (NSCLC) accounts for 75% of all lung cancers (2). About one fourth presents with stage III which has a poor five-year survival rate (3). The preferred treatment for relatively fit patients with stage III NSCLC is concurrent chemoradiation (cCHRT) (4); however, this treatment option is very intensive and often accompanied by serious complications, including hospitalization and mortality (5).

The majority of patients are older (≥70 years). Patients at high risk for intolerance of CHRT are characterized as aged ≥70 years and those suffering from anorexia, dysphagia, fatigue, and physical inactivity (9-11). Although a geriatric assessment might identify older patients who are at risk for treatment complications (12), it is still unclear to what extent these tests individually, or in combination, are associated with treatment tolerance in patients with NSCLC (13-16). Evidence regarding treatment options and outcomes are scarce for older patients with NSCLC and evidence-based insights are highly needed for this vulnerable population. Older patients are under-represented in clinical trials, and those older patients who are included are generally selected fit patients without comorbidity. This means that the external validity of clinical trial results for the real-world population of older patients with cancer is low (6), especially since polypharmacy, frailty, poor performance status, long-term physical inactivity, and smoking-related comorbidities characterize patients with stage III NSCLC (5,7,8).

It is therefore important to gain real-world insight into modifiable parameters that might be prognostic for tolerance of cCHRT and survival, and identify patients at high risk for poor tolerance of cCHRT. Preferably, such parameters should be easily measured and cost-effective with a minimal burden for the patient. Such information can be used by medical specialists for identifying patients who are expected to tolerate cCHRT, which is important for shared decision-making. The aim of this study was to gain insight into the associations between pretreatment physical status parameters and tolerance of cCHRT and survival among patients with stage III NSCLC in everyday clinical practice.

Methods

Study design

This project concerned a retrospective cohort study for which anonymous data from the medical records from a clinic for radiotherapy were used. All patients who underwent cCHRT for stage III NSCLC between 2006 and 2015 and who had no objection for the use of their usual care data for research purposes were included. Baseline measurements and physical status parameters were usually scheduled on the day of the first irradiation. The internal review board of a clinic for radiotherapy decided that this study met their ethical policies and the regulations of the Dutch government.

Patients and data collection

Patients aged ≥18 years with stage III NSCLC, who received primary cCHRT between 2006 and 2015 in two teaching hospitals, two non-teaching hospitals, or a university medical centre, were included. Clinical tumour staging was performed according to the 7th TNM staging of the International Association for the Study of Lung Cancer (17). NSCLC was classified as squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and not otherwise specified. The following pretreatment patient characteristics and physical status parameters were collected from the electronic patient records: sex, age, body mass index (BMI), fat free mass index (FFMI), forced expiratory volume in one second (FEV_1), carbon monoxide lung diffusion capacity (DLCO), World Health Organization (WHO) performance status, Charlson comorbidity index, and maximal handgrip strength. In addition, prescribed and received radiation dose, date of diagnosis, date of first and last irradiation, and date of death or last registration were collected. After data collection, all data were checked for completeness and accuracy.

Treatment protocol

cCHRT was defined as treatment with chemotherapy and radiotherapy with any overlap between the two modalities. After one or two chemotherapy cycles, radiotherapy was given to the primary tumour and lymph nodes (18). In the first three weeks, 30 fractions of 1.5 Gray (Gy) were given twice daily, followed by fractions of 2 Gy once daily, with a minimum dose of 54 Gy and a maximum of 69 Gy (19). A mean radiation dose of 65 Gy delivered to the tumour and affected lymph nodes was given within 5.5 weeks. This corresponds to a biological equivalent of 72 Gy given in 36 daily fractions in 7.2 weeks (20).

Pretreatment physical status parameters

Anthropometry and body composition

Bioelectrical impedance analysis (Omron Healthcare Group, Hoofddorp, The Netherlands) with a single-frequency (50 kHz) was used for estimating body composition (21,22). Patients were standing with legs apart and arms straight forward, holding the device with both hands. Results are automatically corrected for body height, body mass, Fat-free mass (FFM), sex, and age. Body mass index was categorized as underweight (<18.5 kg/m^2) or normal weight/overweight (≥18.5 kg/m^2) (23). The fat-free mass index FFMI (kg/m^2) is a body height-adjusted assessment of FFM. Low FFMI was defined as a FFMI <17 kg/m^2 in male patients and <15 kg/m^2 in female patients, based on 10th-percentile values for healthy subjects (24).

Lung function

FEV_1 and DLCO measurements were performed by a pulmonary function technician and expressed as a percentage of predicted based on sex and age (25). Using spirometry, patients were asked to breathe in as deeply as possible, and then exhale as hard, quickly, and long as possible (26,27). The DLCO is a medical test that determines how much oxygen travels from the alveoli of the lungs to the blood stream (27). Scores ≤80% of predictive for FEV_1 and DLCO were classified as low (28).

Physical functioning

The WHO performance status was assessed by the radiation oncologist and used to indicate the level of physical functioning. Patients with a score ≥2 were classified as having a poor performance status (29). The Charlson comorbidity index was extracted from the medical records and classified as none to mild comorbidity (score 0-3) and severe comorbidity (score ≥4) (30). Handgrip strength as an indication of overall muscle strength was measured with a handheld dynamometer (JAMAR Hydraulic Hand Dynamometer, JA Preston Corporation, Jackson, MI, USA) (31). Patients were seated in a chair with their elbow flexed at 90° and the forearm in the neutral position without any arm support from the chair (32). A value below the 10th percentile of the UK Biobank reference values, was considered as low handgrip strength (33).

Outcome variables

Tolerance of cCHRT was classified as 'yes' when the received radiation dose was at least equal to the prescribed radiation dose. Five-year survival was defined

as the time from diagnosis to death of any cause or to date of last follow-up with a maximum of five years. Last date for checking date of death using the local hospital data registration or the Dutch Municipal Personal Records Database was June 1st 2019.

Statistical analyses

Data were analysed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were used to summarize patient characteristics and cross-tabulations were used to analyse associations between pretreatment physical status parameters and tolerance of cCHRT using chi2 tests (P<0.05 two sided). Univariate and multivariate binary logistic regression analyses were performed for analysing the associations between pretreatment physical status parameters and tolerance of cCHRT. In order to ensure sufficient power, the 'one in ten rule' was applied. The rule states that one predictive variable can be studied for every ten events (34). In this study, nine associated variables were studied. In case these were all included in multivariable analyses, a minimum number of 90 events should have occurred. Age, sex, and pretreatment physical status parameters with a P-value <0.10 in the univariate analyses were selected for the multivariate analyses. The odds ratio (OR) and corresponding 95% confidence interval (CI) was displayed for each parameter. An OR <1.0 indicated poorer tolerance of cCHRT. Overall survival during a five-year follow-up period was analysed according to Kaplan-Meier, and significant differences between groups were assessed by the log-rank test. Univariate and multivariate hazard ratios (HRs) and 95% CI for associations between physical status parameters and survival were calculated by Cox proportional hazards analyses. Age, sex, and pretreatment physical status parameters with a P-value <0.10 in the univariate analyses were selected for the multivariate regression analyses. Poorer survival was indicated by a HR >1.0. In multivariate analyses (backward conditional method; Pin=0.10, Pout=0.10), variables that were significant in univariate analyses were included. It was assumed that the associations between physical status parameters and survival could differ between sex and age groups. Therefore, multivariate analyses for overall survival were also stratified according to sex and age. P-values <0.10 were considered statistically significant.

Results

Data of 577 patients with stage III NSCLC, 357 male patients (61.9%) and 220 female patients (38.1%) with a mean age of 63.6 (standard deviation (SD) 9.2) years, receiving cCHRT were available for analysis. In Table 1, baseline characteristics of patients are summarized according to tolerance of cCHRT. WHO performance status 0-1, normal/overweight, and normal handgrip strength were significantly more present among patients who tolerated cCHRT (P<0.05). Due to the high proportion of missing cases, FEV_1 and DLCO were excluded from multivariable analyses (Table1).

Table 1. Pretreatment patient characteristics and physical status parameters according to tolerance of cCHRT.

Variable, number (%)	Tolerance of cCHRT		
	No[a] (n = 50)	**Yes[b] (n = 527)**	***P*-value**
Age (years)	63.9 ± 8.9 (45 to 80)	63.5 ± 9.2 (32 to 85)	
<70 years	35 (70.0)	368 (69.8)	0.98
≥70 years	15 (30.0)	159 (30.2)	
Sex			
Male	35 (70.0)	322 (61.1)	0.22
Female	15 (30.0)	205 (38.9)	
Histology			
Adenocarcinoma	15 (30.0)	139 (26.4)	0.47
Squamous cell carcinoma	20 (40.0)	173 (32.8)	
Large cell carcinoma	4 (8.0)	82 (15.6)	
Non-small cell lung cancer	9 (18.0)	120 (22.8)	
No histological diagnosis	2 (4.0)	13 (2.5)	
WHO performance status			
0-1	43 (86.0)	478 (90.7)	0.02[e]
≥2	7 (14.0)	29 (5.5)	
Unknown	0 (0.0)	20 (3.8)	
Charlson comorbidity index			
0-3	25 (50.0)	299 (56.7)	0.36
≥4	25 (50.0)	228 (43.3)	
BMI			
Underweight (<18.5 kg/m^2)	7 (14.0)	26 (4.9)	0.01
Normal/overweight (≥18.5 kg/m^2)	43 (86.0)	501 (95.1)	

Table 1. Continued

Variable, number (%)	Tolerance of cCHRT		
	No[a] (n = 50)	Yes[b] (n = 527)	*P*-value
FFMI			
Normal FFMI	35 (70.0)	395 (75.0)	0.52[e]
Low FFMI[c]	13 (26.0)	118 (22.4)	
Unknown	2 (4.0)	14 (2.7)	
Handgrip strength			
Normal	36 (72.0)	430 (81.6)	0.05[e]
Low[d]	13 (26.0)	80 (15.2)	
Unknown	1 (2.0)	17 (3.2)	
FEV_1			
<80% of predicted	25 (50.0)	191 (36.2)	0.18[e]
≥80% of predicted	20 (40.0)	233 (44.2)	
Unknown	5 (10.0)	109 (19.5)	
DLCO			
<80% of predicted	32 (64.0)	278 (52.8)	0.44[e]
≥80% of predicted	9 (18.0)	106 (20.1)	
Unknown	9 (18.0)	143 (27.1)	

Data are presented as mean ± SD or n (%).

Abbreviations: BMI=body mass index; DLCO=diffusing capacity for carbon monoxide FEV_1=forced expiratory volume in 1 second; FFMI=fat-free mass index; SD=standard deviation; WHO=World Health Organization.

[a] no: received radiation dose was less than the prescribed radiation dose.

[b] yes: received radiation dose was at least equal to the prescribed radiation dose.

[c] males FFMI <17 kg/m^2 and females <15 kg/m^2.

[d] <10th percentile of established normative values (35)

[e] Chi^2 test was calculated without missing values.

Tolerance of *cCHRT*

A total of 50 patients (8.7%) did not tolerate cCHRT. In univariate regression analyses, patients being underweight had a significantly poorer tolerance of cCHRT compared to patients with normal weight/overweight (OR 0.32). Patients with WHO performance status ≥2 had a significantly poorer tolerance of cCHRT compared to patients with WHO performance status 0-1 (OR 0.37). Finally, low handgrip strength was associated with poor tolerance of cCHRT (OR 0.52). In multivariable analyses, being underweight (OR 0.36) and WHO performance status ≥2 (OR 0.43) remained significantly associated with poorer tolerance of cCHRT. Results of the univariate and multivariate regression analyses for tolerance of cCHRT are shown in Table 2.

Table 2. Univariate and multivariate odds ratios for associations of pretreatment patient characteristics and physical status parameters with tolerance of cCHRT in patients with stage III NSCLC.

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age				
<70 years	Reference	0.98	NS	
≥70 years	1.01 (0.54 to 1.90)			
Sex				
Male	0.67 (0.36 to 1.26)	0.22	NS	
Female	Reference			
WHO performance status				
0-1	Reference	0.03	Reference	0.07
≥2	0.37 (0.15 to 0.90)		0.43 (0.17 to 1.07)	
Charlson comorbidity index				
0-3	Reference	0.36	NI[c]	
≥4	0.76 (0.43 to 1.36)			
BMI				
Underweight (<18.5 kg/m^2)	0.32 (0.13 to 0.78)	0.01	0.36 (0.15 to 0.90)	0.03
Normal /overweight (≥18.5 kg/m^2)	Reference		Reference	
FFMI				
Normal FFMI	Reference	0.52	NI[c]	
Low FFMI[b]	0.80 (0.41 to 1.57)			
Handgrip strength				
Normal	Reference	0.06	NS	
Low[c]	0.52 (0.26 to 1.02)			
FEV_1				
<80% of predicted	0.66 (0.35 to 1.22)	0.18	NI[c]	
≥80% of predicted	Reference			
DLCO				
<80% of predicted	0.74 (0.34 to 1.60)	0.44	NI[c]	
≥80% of predicted	Reference			

Abbreviations: BMI=body mass index; cCHRT=concurrent chemoradiation; CI=confidence interval; DLCO=diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FFMI=fat-free mass index; NI=not included; NS=not significant; NSCLC=non-small cell lung cancer; OR=odds ratio; WHO=World Health Organization.

[a] not included when *P*-value ≥0.10.

[b] males FFMI <17 kg/m^2 and females FFMI<15 kg/m^2.

[c] <10th percentile of established normative values (33).

Overall survival

Median overall survival for the whole group was 23 months, and at the time of analysis after five years, 404 patients (70%) had died. Median overall survival was 23 months for those who tolerated cCHRT and 11 months for those who did not tolerate cCHRT (P=0.007, Figure 1A). The one-, three-, and five-year survival rates for the whole group were 69%, 38%, and 30%, respectively. In univariate

analyses, age (HR 1.23), male sex (HR 1.24), low FFMI (HR 1.27), DLCO <80% (HR 1.42), WHO performance status ≥2 (HR 1.91), low handgrip strength (HR 1.32), and cCHRT intolerance (HR 1.56) were significantly associated with poorer survival. The following factors were analysed for their association with survival in multivariable analyses: age, sex, FFMI, WHO performance status, handgrip strength, and tolerance of cCHRT were analysed for their association with survival in multivariable analyses. Age ≥70 years (HR 1.22), WHO performance status ≥2 (HR 1.73), low FFMI (HR 1.23), and cCHRT intolerance (HR 1.55) remained significantly associated with poor survival. The results of univariate and multivariate Cox regression analyses for survival are shown in Table 3.

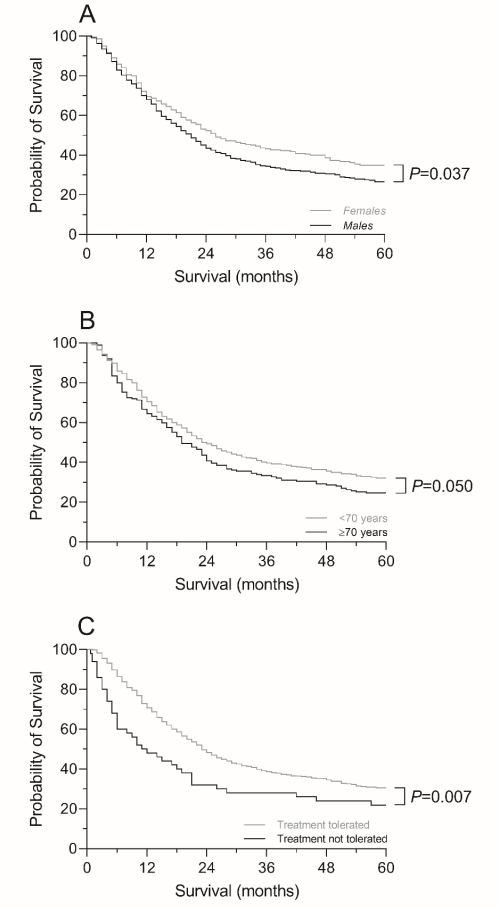

Figure 1. Kaplan-Meier survival curves. A. Kaplan-Meier survival curve according to sex in non-small cell lung cancer patients receiving concurrent chemoradiation (Log rank: P=0.04). B. Kaplan-Meier survival curve according to age groups in non-small cell lung cancer patients receiving concurrent chemoradiation (Log rank: P=0.05). C. Kaplan-Meier survival curve according to tolerance of cCHRT in non-small cell lung cancer patients receiving concurrent chemoradiation (Log rank: P=0.01

Table 3. Univariate and multivariate hazard ratios and 95% CI for associations between physical status parameters and survival in patients with stage III NSCLC.

	Median survival (months)	Univariate		Multivariate without tolerance of cCHRT		Multivariate with tolerance of cCHRT	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age							
<70 years	24	Reference	0.05	Reference	0.05	Reference	0.08
≥70 years	19	1.23 (0.98 to 1.51)		1.24 (1.00 to 1.54)		1.22 (0.98 to 1.51)	
Sex							
Male	21	1.24 (1.01 to 1.52)	0.04	NS		NS	
Female	26	Reference					
WHO performance status							
0-1	24	Reference	≤0.01	Reference	≤0.01	Reference	≤0.01
≥2	10	1.91 (1.33 to 2.74)		1.77 (1.23 to 2.57)		1.73 (1.19 to 2.51)	
Charlson comorbidity index							
0-3	21	Reference	0.31	NI[a]		NI[a]	
≥4	23	1.11 (0.91 to 1.35)					
BMI							
Underweight	15	1.28 (0.85 to 1.92)	0.23	NI[a]		NI[a]	
Normal/ overweight	23	Reference					
FFMI							
Normal FFMI	24	Reference	0.04	Reference	0.07	Reference	0.08
Low FFMI[b]	21	1.27 (1.02 to 1.56)		1.24 (0.98 to 1.57)		1.23 (0.97 to 1.56)	
Handgrip strength							
Normal	23	Reference	0.03	NS		NS	
Low[c]	17	1.32 (1.02 to 1.70)					
FEV_1							
<80% of predicted	21	1.13 (0.91 to 1.40)	0.28	NI[a]		NI[a]	
≥80%	23	Reference					
DLCO[f]							
<80%	21	1.42 (1.09 to 1.85)	0.01[e]	NI[a]		NI[a]	
≥80%	29	Reference					
Tolerance of cCHRT							
No[d]	11	1.56 (1.12 to 2.18)	0.01	NI[a]		1.55 (1.11 to 2.17)	0.01
Yes[e]	23	Reference				Reference	

Abbreviations: BMI=body mass index; cCHRT=concurrent chemoradiation; CI=confidence interval; DLCO=diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; FFMI=fat-free mass index; HR=hazard ratio; NI=not included; NS not significant; NSCLC=non-small cell lung cancer; WHO=World Health Organization.

[a] not included when *P*-value ≥0.10.

[b] males FFMI <17 kg/m^2 and females FFMI <15 kg/m^2.

[c] <10th percentile of established normative values (33).

[d] no=received radiation dose was less than the prescribed radiation dose.

[e] yes=received radiation dose was at least equal to the prescribed radiation dose.

[f] DLCO was not included in multivariate analysis, because of a high percentage of missing cases (26.3%) and because of violating the proportional hazards assumption.

Table 4. Multivariate hazard ratios without and with treatment tolerance for associations of pretreatment patient characteristics and physical status parameters with tolerance of cCHRT and survival in patients with stage III NSCLC stratified for sex and age.

	Multivariate without treatment tolerance		
	Male		**Female**
	HR (95% CI)	***P*-value**	**HR (95% CI)**
Age			
<70 years	Reference	0.08	NS
≥70 years	1.26 (0.97 to 1.63)		
WHO performance status			
0-1	NS		Reference
≥2			2.56 (1.38 to 4.76)
FFMI			
Normal FFMI	Reference	≤0.01	NS
Low FFMI[a]	1.65 (1.24 – 2.21)		
Handgrip strength			
Normal	NS		NS
Low[b]			
Tolerance of cCHRT			
No[c]	NI[e]		NI[e]
Yes[d]			
	Age <70 years		**Age ≥70 years**
	HR (95% CI)	*P*-value	HR (95% CI)
Age, continuous per year	NS		1.07 (1.01 to 1.13)
Sex			
Male	NS		NS
Female			
WHO performance status			
0-1	Reference	0.02	NS
≥2	1.76 (1.09 to 2.84)		
FFMI			
Normal FFMI	NS		Reference
Low FFMI[a]			1.60 (1.08 to 2.39)
Handgrip strength			
Normal	Reference	0.01	NS
Low[b]	1.52 (1.09 to 2.12)		
Tolerance of cCHRT			
No[c]	NI[e]		NS
Yes[d]			

Abbreviations: cCHRT=concurrent chemoradiation; CI=confidence interval; FFMI=fat-free mass index; HR=hazard ratio; NI=not included; NS=not significant; NSCLC=non-small cell lung cancer; WHO=World Health Organization.
[a] males FFMI <17 kg/m^2 and females FFMI <15 kg/m^2, [b] <10th percentile of established normative values (33), [c] no=received radiation dose was less than the prescribed radiation dose, [d] yes=received radiation dose was at least equal to the prescribed radiation dose, [e] not included as *P*-value ≥0.10.

	Multivariate with treatment tolerance			
	Male		Female	
***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
	NS		NS	
≤0.01	Reference 1.54 (0.97 to 2.42)	0.07	Reference 2.56 (1.38 to 4.76)	0-1
	Reference 1.60 (1.19 to 2.14)	≤0.01	NS	
	NS		NS	
	1.85 (1.24 to 2.77)	≤0.01	NS	
	Reference			
	Age <70 years		**Age ≥70 years**	
P-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
0.02	NS		1.07 (1.01 to 1.13)	0.02
	NS		NS	
	Reference 1.81 (1.12 to 2.92)	0.02	NS	
0.02	NS		Reference 1.60 (1.08 to 2.39)	0.02
	Reference 1.47 (1.06 to 2.06)	0.02	NS	
	1.89 (1.26 to 2.82)	≤0.01	NS	
	Reference			

Overall survival stratified for sex and age

Median overall survival was significantly lower in male patients compared to female patients (21 versus 26 months; P=0.037; Figure 1B). In male patients, WHO performance status ≥2 (HR 1.54), low FFMI (HR 1.60), and cCHRT intolerance (HR 1.85) were significantly associated with worse survival, whereas in female patients only WHO performance status ≥2 (HR 2.56) was significantly associated with worse survival (Table 4). Median overall survival was 24 months for patients aged <70 years and 19 months for those aged ≥70 years (P=0.050; Figure 1C). In patients aged <70 years, WHO performance status ≥2 (HR 1.81), low handgrip strength (HR 1.47), and cCHRT intolerance (HR 1.89) were significantly associated with worse survival, whereas in patients aged ≥70 years, only age per year as a continuous variable (HR 1.07) and low FFMI (HR 1.60) were significantly associated with worse survival (Table 4).

Discussion

Results from this study demonstrated that several physical status parameters were associated with outcome following cCHRT. In total, 8.7% of the patients did not tolerate cCHRT, especially those with poor WHO performance status or BMI<18.5 kg/m^2. Physical status parameters and tolerance of cCHRT were also associated with survival; however, associations differed between males and females and between younger and older patients.

A BMI <18.5 kg/m^2 and poor WHO performance status were independently associated with poor tolerance of cCHRT. Studies investigating the relationship between WHO performance status and tolerance of cCHRT in lung cancer are lacking. Furthermore, one study indicated that malnutrition, especially in overweight patients, negatively influences survival of stage III NSCLC (35). Although significance disappeared in multivariable analyses, low handgrip strength also seemed to be associated with poorer tolerance of cCHRT. This is in line with previous studies which have shown an association between low handgrip strength before treatment and an increased risk of poor treatment tolerance in patients with oesophageal and colorectal cancer (36-38). Results of the current study and previous studies therefore suggest that BMI <18.5 kg/m^2, poor WHO performance status, and low handgrip strength before treatment might have an added value in identifying patients at high risk of poor tolerance of cCHRT.

Additionally, poor tolerance of cCHRT was most significantly associated with poorer survival, even after adjustment for patient characteristics. These findings suggest that it is important to identify which patients are expected to benefit from this radical treatment with cCHRT for discussing the balance between quality of life and survival with patients. Low FFMI, poor WHO performance status, and low handgrip strength were significantly associated with worse survival; however, associations differed between males and females, and between younger and older patients. A previous study showed an association between low FFMI, poor WHO performance status, and low handgrip strength and worse survival in patients with NSCLC (39,40). In previous research (41), the prognostic value of low DLCO to predict worse survival in Japanese patients with stage III NSCLC has also been indicated. Although these results were also shown in univariate analyses in the current study, unfortunately DLCO could not be included in multivariable analyses due to missing values. Future studies should focus on this promising parameter.

Poor WHO performance status, low FFMI, and not tolerating cCHRT were significantly associated with poorer survival in male patients, whereas this was only poor WHO performance status in female patients. These differences might be explained by the small number of female patients in this study, resulting in a lack of statistical power. In patients <70 years, poor WHO performance status, low handgrip strength, and not tolerating cCHRT were significantly associated with poorer survival. In older patients, age (as a continuous variable) and low FFMI were significantly associated with poorer survival. It is plausible that relatively fit older patients aged ≥70 years were selected for cCHRT in this observational study in everyday clinical practice, which means that numbers of vulnerable older patients might have been too small for reaching significance (5).

Physical status parameters are often associated with treatment intolerance and worse survival in patients with cancer, especially in those undergoing surgery (43,44). Despite this, the association between a combination of these pretreatment physical status parameters and tolerance of cCHRT and survival among patients with stage III NSCLC has not been investigated before. The large sample size in this population truly reflected clinical practice, and quality and completeness of included data was high, except for DLCO. Using real-world data means that patients who were sufficiently fit for cCHRT were included as advised by European guidelines (45,46). Because of this possible selection bias, results for the associations between pretreatment physical performance

parameters and tolerance of CHRT might differ for vulnerable patients. This study demonstrates that pretreatment physical status parameters are associated with both tolerance of cCHRT and survival. However, in elderly patients, the impact of toxicities on quality of life (especially preserving independency) may be just as important as the prolongation of life expectancy. Future evidence on the associations between pretreatment physical status parameters and quality of life and functional recovery is essential to make adequate treatment decisions with patients. In addition, physical tests might also be used to identify high-risk patients who might benefit from lifestyle interventions before and during cancer treatment (47). Another limitation of this study is the lack of patient-related parameters such as nutritional status, psychological distress, and social support. These important functional status parameters are recommended by the American Society of Clinical Oncology (ASCO) guidelines for older and/or more vulnerable patients receiving chemotherapy (42). It is important to know the rate of adverse events in order to determine the definition of poor treatment tolerance. Ideally, this is derived from both the dose intensity of radiotherapy and the dose intensity for chemotherapy. Unfortunately, the latter was not available in the database from the clinic for radiotherapy. It is recommended to include this information in a subsequent study. Furthermore, it would be useful to determine whether these physical status parameters are also associated with treatment tolerance in stage III NSCLC patients undergoing less aggressive treatment, such as immunotherapy.

In conclusion, in patients with stage III NSCLC receiving cCHRT, poor WHO performance status and BMI <18.5 kg/m^2 were independently associated with tolerance of cCHRT, and both physical status parameters and intolerance of cCHRT were independently associated with poorer survival. Treatment selection for patients with stage III NSCLC is already well underway. Further improvements may be established by paying attention to the risk of intolerance of cCHRT, which increases the patient's risk of death and decreases quality of life. Optimizing physical status in patients at risk for intolerance of cCHRT can be a next step for improving treatment outcomes.

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Part II

Content and context of lifestyle interventions before, during, and after treatment

'If patients become more fit preoperatively due to prehabilitation, there will be a faster recovery after surgery and therefore a shorter length of hospital stay.'

-Healthcare professional-

Chapter 6

Evidence base for exercise prehabilitation suggests favourable outcomes for patients undergoing surgery for non-small cell lung cancer despite being of low therapeutic quality: a systematic review and meta-analysis

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Abstract

Objective The aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality, and length of hospital stay (LoS) in patients undergoing surgery for non-small cell lung cancer (NSCLC), thereby accounting for the quality of the physical exercise program.

Methods Two reviewers independently selected randomized controlled trials (RCTs) and observational studies and assessed them for methodological quality and therapeutic quality of the exercise prehabilitation program (i-CONTENT tool). Eligible studies included patients with NSCLC performing exercise prehabilitation and reported the occurrence of 90-day postoperative complications, postoperative mortality, and LoS. Meta-analyses were performed and the certainty of the evidence was graded (Grading of Recommendations Assessment, Development and Evaluation (GRADE)) for each outcome.

Results Sixteen studies, comprising 2,096 patients, were included. Pooled analyses of RCTs and observational studies showed that prehabilitation reduces postoperative pulmonary complications (OR 0.45), postoperative severe complications (OR 0.51), and LoS (mean difference -2.46 days), but not postoperative mortality (OR 1.11). The certainty of evidence was very low to moderate for all outcomes. Risk of ineffectiveness of the prehabilitation program was high in half of the studies due to an inadequate reporting of the dosage of the exercise program, inadequate type and timing of the outcome assessment, and low adherence.

Conclusion Although risk of ineffectiveness was high for half of the prehabilitation programs and certainty of evidence was very low to moderate, prehabilitation seems to result in a reduction of postoperative pulmonary and severe complications, as well as LoS in patients undergoing surgery for NSCLC.

Introduction

Lung cancer is the most common diagnosed cancer globally(1). Surgery is advised for patients with resectable early stage non-small cell lung cancer (NSCLC)(2, 3). In the Netherlands, approximately 35% of all patients with NSCLC who underwent surgery in 2018, developed a postoperative complication, of which 20% within 30 days postoperatively(4). The 30-day mortality rate is 2%(4). Postoperative complications are most common in older patients (≥70 years) who have a low physical fitness(5, 6), are physically inactive, malnourished, and have tobacco-related comorbidity(7-9). Especially patients with a high risk for adverse postoperative outcomes might benefit from preoperative interventions such as exercise prehabilitation.

Exercise prehabilitation in patients undergoing lung resection aims to improve a patient's health, including aerobic fitness level in the period between diagnosis and surgery in order to postoperatively reduce the risk for complications and reduce the length of hospital stay (LoS)(10). Recent systematic reviews in patients with NSCLC reported that exercise prehabilitation may be effective in reducing complications and LoS, but with inconsistent results(11-15). A better assessment of the quality of prehabilitation programs could potentially contribute to the certainty of evidence regarding the merit of prehabilitation to reduce postoperative complications, postoperative mortality, and LoS in patients undergoing surgery for NSCLC. In addition, there are no guidelines concerning the optimal content of an exercise prehabilitation program for preoperatively improving physical fitness to subsequently improve postoperative outcomes in patients with NSCLC. Finally, observational studies are frequently left out of systematic reviews while these studies might actually provide an additional perspective to RCTs(16).

Therefore, the aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality, and LoS in patients undergoing surgery for NSCLC, thereby accounting for the quality of the physical exercise program. To do so, we employed the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool in this systematic review to help understand, structure, and value the potential of preoperative physical exercises to improve the outcomes of NSCLC surgery(17).

Methods

A systematic review of the literature was performed according to the Cochrane guidelines for systematic reviews (18) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(19). The study protocol was registered at PROSPERO (CRD42021244223). Studies in which postoperative complications, postoperative mortality, and LoS after exercise prehabilitation was compared with usual care or between different frequencies of sessions in prehabilitation programs were selected.

Literature search

MEDLINE, Embase, and CINAHL databases were searched for eligible studies published up to December 2021. In addition, reference lists from retrieved studies were screened. The search strategy, which has been set up and optimized by the researchers and a librarian, contained a combination of controlled vocabulary (e.g., MeSH or EMTREE) and keyword terms and phrases searched in titles, abstracts, and key word fields, as appropriate. Key terms included in the search strategy are "non-small cell lung cancer" and "lung surgery", "prehabilitation", "postoperative complications", "postoperative mortality", and "length of hospital stay". Combinations of text words of the literature search are shown in supplementary file 1.

Study selection

Randomized controlled trials and observational studies in patients aged ≥18 years, with ≥95% patients with NSCLC undergoing elective surgery were included. The exercise prehabilitation program could be unimodal or multimodal, but should at least include physical exercise training that aimed to preoperatively improve physical fitness. Usual care groups consisted of patients who either received no intervention (usual care) or a comparison intervention (e.g., a different preoperative physical exercise program). Outcome measures of the studies should at least include postoperative complications, postoperative mortality, and/or LoS. Physical exercise training was defined as a structured form of either aerobic, interval, and/or resistance exercises, based upon validated measurements describing training intensity (e.g., heart rate, rating of perceived exertion, work rate), eventually supplemented with breathing exercises. Studies only involving health promotion initiatives without a structured professional follow-up were excluded in this review. Conference papers, case series, case reports, opinion studies (non-original research),

systematic reviews, and studies not published in English were also excluded. Two reviewers (M.V. and R.F.) independently screened titles and abstracts of retrieved records using Rayyan software (20) based on inclusion criteria and exclusion criteria. Thereafter, assessment of full-text articles according to eligibility criteria was performed by the two reviewers (M.V. and R.F.) independently. Any disagreements between reviewers were resolved through discussion and consensus. When no consensus was reached, a third party acted as an adjudicator (M.J.).

Data extraction

One reviewer (M.V.) extracted data from the included studies by using a standardized extraction form, after which another reviewer (R.F.) checked the extracted data. Extracted data included first author, publication year, number of participants, patient characteristics of the intervention group and control group, disease stage, age (mean; range), sex, type of surgery, and comorbidity. Items of the i-CONTENT tool were also described in terms of content. Characteristics of the physical exercise training program were extracted using the training frequency, training intensity, training time, training type, training volume, and training progression principles (FITT-VP) (21, 22) of the prescribed physical exercises of the intervention group and control group. Differences in postoperative pulmonary complications, any complications (Clavien-Dindo grade I-IV), severe complications (Clavien-Dindo grade II-IV), and postoperative mortality (Clavien-Dindo grade V) within 90 days, and LoS between the intervention group and usual care group were evaluated.

Methodological quality

The two reviewers (M.V. and R.F.) independently assessed the methodological quality of included studies by means of the Cochrane risk of bias tool for randomized controlled trials II (RoB2) (18) and observational studies of interventions for observational studies (ROBINS-I) tool(23). The RoB2 reviews six domains, and the ROBINS-I tool reviews seven domains. In the RoB2 tool, each item was rated as 'high', 'low', or 'some'. In the ROBINS-I tool, each item was rated as 'low', 'moderate', 'serious', 'critical', or 'no information'. Risk of bias of the included studies was assessed according to the outcomes postoperative complications, postoperative mortality, and LoS. No global score was given, but the score per study was given based on the relevant outcomes for this systematic review. Discrepancies were resolved by consensus. If no consensus was reached, a third person acted as an adjudicator (M.J.).

Therapeutic quality

Therapeutic quality of the physical exercise training module of the prehabilitation programs was assessed independently by two reviewers (M.V. and R.F.) using the i-CONTENT tool.(17) Using the i-CONTENT tool, the following eight items were substantively described: 1) patient selection, 2) dosage of the exercise program, 3) type of the exercise program, 4) qualified supervisor, 5) type and timing of outcome assessment, 6) safety of the exercise program, and 7) adherence to the exercise program. To ensure a uniform assessment of the assessors, basic guidelines for the application and interpretation were composed for each item of the i-CONTENT (Table 1) by all authors. The original authors of the i-CONTENT did not provide an aggregated cut-off for which studies could be considered of low, some, or high risk for ineffectiveness. A rating scheme was arbitrarily developed for this study (see supplementary file 2) to determine low and high risk for ineffectiveness per study.

Data synthesis

The effects of prehabilitation versus usual care on postoperative complications, postoperative mortality, and LoS, were analysed using random-effects meta-analysis models. Meta-analyses were performed separately for RCTs and observational studies.(18) For postoperative complications and postoperative mortality, the odds ratios (OR) and 95% CI were calculated using a Mantel-Haenszel model. For LoS, the mean differences (MD) and 95% confidence intervals (CI) were taken from the original studies. Meta-analyses were conducted using Review Manager (version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A P-value <0.05 was considered statistically significant. Heterogeneity was evaluated using the I^2 statistic. Results were classified as follows: 0% to 40% indicates low heterogeneity, 30% to 60% indicates moderate heterogeneity, 50% to 90% indicates substantial heterogeneity, and 75% to 100% indicates considerable heterogeneity(24).

Certainty of evidence

The two reviewers (M.V. and R.F.) independently rated the certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach(24). In order to interpret the findings, a GRADE summary of findings table was created in which the following outcomes were included: 1) pulmonary complications, 2) any complications, 3) severe complications, 4) postoperative mortality, and 5) LoS. The certainty of evidence was assessed for each outcome by downgrading based on the GRADE criteria for RCTs and upgrading for observational studies. Furthermore, the

current systematic review aimed to integrate the overall risk of ineffectiveness scores into the GRADE approach. Within the GRADE approach, risk of ineffectiveness of exercise prehabilitation programs was added under 'other considerations'. It was devised after consensus between the researchers that if at least 80% of the studies for a certain outcome measure had an overall risk of ineffectiveness of low or some, the GRADE level of certainty was upgraded by one level.

Table 1. Basic guidelines for the application and interpretation of therapeutic quality of the physical exercise training module of prehabilitation programs for each item of the i-CONTENT tool.(17)

	Low risk of ineffectiveness	**High risk of ineffectiveness**
1. Patient selection	A VO_{2peak} <20 mL/kg/min and/or a predicted postoperative VO_{2peak} <10 mL/kg/min or other selection criteria with clear rationale.	No preselection or selection (described).
2. Dosage of the training program	Intensity and duration of the exercise program must be clearly described and/or based on existing literature relevant to the target population of operable patients with NSCLC and/or an adequate exercise test (e.g., steep ramp test, CPET).	Not described where (the intensity of) the content of the exercise is based on and/or no physiological improvement can be expected due to low training dosage (frequency, intensity, time).
3. Type of the training program	At least aerobic exercise training with or without resistance exercise training.	An intervention inconsistent with the goal of physical exercise training for patients undergoing surgery for lung cancer.
4. Qualified supervisor (if applicable)	Guidance of a physical therapist who is specialized in supervising adult clinical populations.	Supervision is not reported or guidance was provided by a professional other than a physical therapist, or guidance is not described.
5. Type and timing of outcome assessment	30- to 90-day follow-up for postoperative complications, length of hospital stay, postoperative mortality. To measure change in preoperative physical fitness, a pre- and post-prehabilitation exercise test must be performed preoperatively, with at least two weeks between the measurements.	Less than 30 days or more than 90 days postoperatively description of follow-up.
6. Safety of the training program	Adverse events related to the exercise program are described and acceptable as would be expected in the studied population.	Adverse events related to the exercise program are higher than would be expected in the studied population.
7. Adherence to the training program	Adherence was determined separately for training frequency and deemed good in case of ≥80%.	Adherence to the training frequency was <80%.

Abbreviations: CPET=cardiopulmonary exercise test, i-CONTENT=international Consensus on Therapeutic Training aNd Training, NSCLC=non-small cell lung cancer, VO_{2peak}=oxygen uptake at peak training.

Results

Study characteristics

A total of 1,299 records were identified with the systematic search. After removing duplicates, 1,052 unique records were screened on title and abstract after which 47 full text articles were reviewed. Reasons for exclusion are described in Supplementary file 3. After full-text review, sixteen studies were included, of which twelve randomized controlled trials (RCTs) (25-37), three retrospective observational studies(26, 38, 39), and one prospective observational study(40). The studies included a total of 2,094 patients with operable NSCLC with pathological stage I, II, III, or IV. The sample size of the studies ranged from 19 to 939 patients, with a mean age-range between 56.2 and 74.4 years. Surgical procedures in the studies consisted of video-assisted thoracic surgery (n=9), open thoracotomy (n=5), lobectomy (n=2), robot-assisted thoracic surgery (n=2), pneumonectomy or bilobectomy (n=1), pneumonectomy (n=1), and segmentectomy (n=1). Fifteen studies compared exercise prehabilitation with usual care(25-39). One observational study (40) compared ≥3 prehabilitation sessions per week with <3 prehabilitation sessions per week. Postoperative complications and LoS were reported in all studies(25-40). Seven publications (26, 27, 29, 31, 32, 37, 38) reported postoperative complications according to the Clavien-Dindo classification(41), in one study (33) the Melbourne group scale had been used, and in six studies no classification system for postoperative complications had been used(25, 28, 30, 34-36, 39, 40). Postoperative mortality was reported in seven studies(28-32, 37, 38). General characteristics of the included studies are described in Table 2.

Exercise prehabilitation characteristics

Exercise prehabilitation consisted of aerobic exercises in fifteen studies (25-37, 39, 40) (94%), resistance exercises in nine studies (25, 26, 30, 31, 33, 36, 38-40) (56%), and breathing exercises in fourteen studies (25, 26, 28, 29, 31-40) (88%). In seven studies (25, 26, 28, 29, 34, 36, 37) (50%), breathing exercises consisted of inspiratory muscle strength training and in seven studies (31-33, 35, 38-40) (50%) of tidal volume training. Duration of prehabilitation programs varied between one and four weeks, with a training frequency between one and seven times per week. Training session duration (time) varied between 15-120 minutes per session. The exact content of the prehabilitation programs is reported in Table 3.

Methodological quality of the studies

Table 4 summarizes the risk of bias assessment. Of the included RCTs, two studies (30, 37) had an overall low risk of bias, two studies (25, 34) had some risk of bias, and eight studies (27-29, 31-33, 35, 36) had a high risk of bias. High risk of bias was mainly caused by an unclear description of the randomization process (n=5), unclear assignment to intended interventions (n=6), and poor adherence to intended interventions (n=7). Of the four included observational studies, two (38, 39) showed a moderate risk of bias and two (26, 40) a serious risk of bias. The latter was mainly caused by a high risk on the items confounding (n=2), patient selection (n=2), and a poor description of the intervention classification (n=1).

Therapeutic quality of the exercise prehabilitation programs

Assessment of the risk of ineffectiveness based on the content of the exercise prehabilitation programs is described in Table 4. One physical exercise training program (34) (6%), was classified as having a low risk of ineffectiveness. In seven exercise prehabilitation programs (26, 28, 30, 31, 33, 36, 37) (44%) there was some risk of ineffectiveness, and eight programs (25, 27, 29, 32, 35, 38-40) (50%) had a high risk of ineffectiveness. Main factors that increased the risk of ineffectiveness of exercise prehabilitation programs were inadequate patient selection (n=10), inadequate dosage of the physical exercise training program (n=10), inadequate description of type and timing of the outcome assessment (n=6), and low adherence to the physical exercise training program (n=5).

Table 2. General characteristics of the included studies

First author, year	Number of participants, n Study design Intervention	NSCLC stage of disease, n Inclusion/ participation of patients, n	Age, year, ±SD (range)
Benzo,(25) 2011	Prehab: 9, UC: 8 RCT Aerobic exercises, resistance exercises, breathing exercises	NR NR	Prehab: 70.2 ±8.6, UC: 72.0 ±6.7, p=0.71
Boujibar,(26) 2018	Prehab: 19, UC: 15 Observational study Aerobic exercises, resistance exercises, breathing exercises, education, smoking cessation	I-IIIa NR	Prehab: 69 (56-73), UC: 65 (59-71), p=0.61
Huang, (37) 2017	Prehab: 30, UC: 30 RCT Aerobic exercises, breathing exercises, psychological education	I: Prehab: 16, UC: 17 II: Prehab: 10, UC: 11 III: Prehab: 4, UC: 2 NR	Prehab: 63.0 ±8.7 UC: 63.6 ±6.5 p=0.75
Lai,(27) 2016	Prehab: 30, UC: 30 RCT Aerobic exercises	I: Prehab: 16, UC: 18 II: Prehab: 10, UC: 10 III: Prehab: 3, UC: 2 IV: Prehab: 1, UC: 0 67: did not meet the inclusive criteria, 38: refused to participate, 22: other reasons	Prehab: 72.5, ±3.4, UC: 71.6, ±1.9, p=0.23
Lai,(28) 2017	Prehab: 51, UC: 50 RCT Aerobic exercises, breathing exercises	I: Prehab: 30, UC: 20 II: Prehab: 14, UC: 25 III: Prehab: 6, UC: 5 IV: Prehab: 1, UC: 0 24: refuse to participate	Prehab: 63.8 ±8.2, UC: 64.6 ±6.6, p=0.58
Lai,(29) 2019	Prehab: 34, UC: 34 RCT Aerobic exercises, breathing exercises	I: Prehab: NR, UC: NR 22: refuse to participate	Prehab: 64.2 ±6.8, UC: 63.4 ±8.2, p=0.67

	Comorbidity, n (%)	Type of surgery, n	Postoperative outcomes
	Coronary artery disease: Prehab: 1 (10.0), UC: 3 (33.3), p=0.31 Diabetes: Prehab: 3 (30.0), UC: 3 (33.3), p=0.88	VATS, NR Open thoracotomy, NR	Postoperative complications[a] LoS
	COPD: Prehab: 9 (47.3), UC: 10 (66.7), p=0.49	VATS: Prehab: 15, UC: 13 RATS: Prehab: 4, UC: 2	30-day postoperative complications (Clavien-Dindo classification) LoS
	ASA score >3: Prehab: 3, UC: 2 p=1.00 COPD: Prehab: 5, UC: 6, p=0.73	VATS: Prehab: 17, UC:19 Open thoracotomy: Prehab: 13, UC: 11	30-day postoperative pulmonary complications (Clavien-Dindo classification) 30-day postoperative mortality LoS
	ASA score: Prehab: 3 (10.0) UC: 3 (10.0), p=1.00 COPD Prehab: 5 (17.0) UC: 4 (13), p=1.00	VATS: Prehab: 21, UC: 20 Open surgery: Prehab: 9, UC: 10	30-day postoperative pulmonary complications (Clavien-Dindo classification) 30-day postoperative mortality LoS
	Charlson comorbidity index 0-2: Prehab: 32 (63%), UC: 43 (86%), p=1.00 Charlson comorbidity index ≥3: Prehab 18 (35%), UC: 7 (14%), p=1.00	VATS: Prehab: 32, UC: 34 Open surgery: Prehab: 19, UC: 16	30-day postoperative complications LoS
	Hypertension: Prehab: 8 (25%), UC: 3 (9%), p=1.00 Diabetes: Prehab: 3 (9%), UC: 1 (3%), p=0.61 COPD: Prehab: 9 (28%), UC: 11 (34%), p=0.61	VATS: 64	30-day postoperative complications (Clavien-Dindo classification) 30-day postoperative mortality LoS

Table 2. Continued

First author, year	Number of participants, n Study design Intervention	NSCLC stage of disease, n Inclusion/ participation of patients, n	Age, year, ±SD (range)
Licker,(30) 2017	Prehab: 74, UC: 77 RCT Aerobic exercises, resistance exercises	I: Prehab: 33, UC: 40 II: Prehab: 28, UC: 27 III: Prehab: 13, UC: 10 12: not meeting the criteria, 8: refuse to participate, 5: short delay	Prehab: 64 ±10 UC: 64 ±13, p=0.74
Liu,(31) 2019	Prehab: 37, UC: 36 RCT Aerobic exercises, resistance exezrcises, breathing exercises, nutritional counselling, psychological adjustment, conventional guidance	I-III 6: ASA grade III, 4: stage IV, 5: neoadjuvant therapy, 2: declined to participate, 2: contraindications for 6MWT distance, 1: severe renal insufficiency	Prehab: 56.2 ±10.3, UC: 56.2 ±8.7, p=NR
Morano,(34) 2013	Prehab: 12, UC: 12 RCT Aerobic exercises, breathing exercises	I/II: Prehab: 11, UC: 9 IIIA: Prehab: 1, UC: 3 UC: 3: inoperable cancer	Prehab: 64.8 ±8, UC: 68.8 ±7.3, p=0.33
Pehlivan,(35) 2011	Prehab: 30, UC: 30 RCT Aerobic exercises, breathing exercises	IA to IIIB NR	Prehab 54.1 ±8.5 UC 54.8 ±8.5, p=0.70
Rispoli,(40) 2020	Prehab1: 13, Prehab2: 46 Observational study Aerobic exercises, resistance exercises, breathing exercises, stretching and relaxation, smoking cessation, ≥3 sessions a week prehabilitation is Prehab1, <3 sessions a week prehabilitation is Prehab2	I: Prehab1: 8, Prehab2: 32, p=0.48 II: Prehab1: 4, Prehab2: 10, p=0.61 III: Prehab1: 1, Prehab2: 4, p=0.90 3: refused to participate, 1: underwent bilobectomy instead of planned lobectomy	Prehab 1: 69.3 ±1.4, Prehab2: 69.7 ±3.5, p=0.74

	Comorbidity, n (%)	Type of surgery, n	Postoperative outcomes
	Hypertension: Prehab: 33 (45%), UC: 32 (42%), p=0.74 Diabetes: Prehab: 10 (14%), UC: 11 (14%), p=0.89 Cardiac arrhythmia: Prehab: 3 (4%), UC: 5 (7%), p=0.72 COPD: Prehab: 30 (41%), UC: 27 (35%), p=0.51 Coronary artery disease: Prehab: 10 (14%), UC: 8 (10%), p=0.62 Heart failure: Prehab: 8 (11%), UC 8 (10%), p=0.98 History of stroke: Prehab: 6 (8%), UC: 1 (1%), p=0.06	Pneumonectomy or bilobectomy: Prehab: 13, UC: 17 Lobectomy: Prehab: 49, UC: 46 Segmentectomy: Prehab: 1, UC: 15	30-day postoperative complications 30-day postoperative mortality LoS
	Hypertension: Prehab: 8 (22%), UC: 11 (31%) Diabetes: Prehab: 4 (11%), UC: 5 (14%) Ischemic heart disease: Prehab: 3 (8%), UC: 2 (6%) Cardiac arrhythmia: Prehab: 4 (11%), UC: 5 (14%) Cerebral infarction: Prehab 2 (5%), UC: 3 (8%) COPD: Prehab: 0 (0%), UC: 1 (3%) Asthma: Prehab: 5 (14%), UC: 2 (6%)	VATS: 73	30-day postoperative complications (Clavien-Dindo classification) 30-day postoperative mortality LoS
	COPD: Prehab: 9 (75%), UC: 9 (75%), p=0.62	VATS: NR Open thoracotomy: NR	30-day postoperative complications (Clavien-Dindo classification) LoS
	NR	Lobectomy: Prehab: 19, UC 2 Pneumonectomy: Prehab: 11, UC: 6, p=0.30	Postoperative complications LoS
	Charlson comorbidity index: Prehab1: mean 2.8 ±0.3, Prehab2: mean 2.77 ±0.3, p=0.69	VATS: Prehab1: 12, Prehab2: 38 Open surgery: Prehab1: 1, Prehab2: 8, p=0.98	Postoperative complications[a] LoS

Table 2. Continued

First author, year	Number of participants, n Study design Intervention	NSCLC stage of disease, n Inclusion/ participation of patients, n	Age, year, ±SD (range)
Saito,(39) 2017	Prehab: 51, UC: 65 Observational study Aerobic exercises, resistance exercises	I: Prehab: 31, UC: 40 II: Prehab: 10, UC: 12 IIIa: Prehab: 10, UC: 13, p=0.52 189: other type of surgery, 471: non-COPD	Prehab: 74.4 ±7.7, UC: 68.2 ±8.6, **p<0.01**
Saito,(38) 2021	Prehab: 51, UC: 93 Observational study Resistance exercises, breathing exercises	I: Prehab: 33, UC: 67 II: 10, UC: 14 III: Prehab: 7, UC: 12 IV: 1, UC: 0 2: superior sulcus tumour, 1: exploratory thoracotomy, 1: lack of preoperative lung function	Prehab: 73.0 ±6.0 UC: 71.3 ±7.3, p=0.15
Sebio Garcia,(33) 2016	Prehab: 10, UC: 12 RCT Aerobic exercises, resistance exercises, breathing exercises	NR Prehab: 2 referred to preoperative physical therapy, 2: not evaluated, 1: reconversion to thoracotomy, 1: not surgery, 1: not malignant disease. UC: 2: not malignant disease, 1: neoadjuvant therapy, 2 abandoned intervention, 2: surgery re-scheduled, 1 irresectable tumour, 1 excluded by the investigators, 1: other	Prehab: 70.9 ±6.1 UC: 69.0 ±4.4, p=NR
Tenconi,(36) 2021	Prehab: 70, UC: 70 RCT Aerobic exercises, resistance exercises, breathing exercises, therapeutic education	I-II NR	Prehab: 66.0 ±10.6 UC: 67.7 ±10.8, p=NR
Zhou (32) 2017	Prehab: 197, UC: 742 Observational study Aerobic exercises, breathing exercises	I: Prehab: 16, UC: 18 II: Prehab: 10, UC: 10 III Prehab: 3, UC: 2 IV: Prehab: 1, UC: 0 NR	Prehab: 58.5 ±9.6, UC: 58.8 ±9.3, p=0.56

Bold = considered significant with p<0.10.

Abbreviations: 6MWT=six-minute walk test, ASA=American Society of Anesthesiologists score, COPD=chronic obstructive pulmonary disease, LoS=length of hospital stay, NR=not reported, NSCLC=non-small cell lung cancer, Prehab=prehabilitation group, RATS= robot-assisted thoracic surgery, RCT=randomized controlled trial, SD=standard deviation, UC=usual care group, VATS=video-assisted thoracic surgery.

[a]: follow-up time is not described.

	Comorbidity, n (%)	Type of surgery, n	Postoperative outcomes
	COPD GOLD I: Prehab: 26 (51%), UC: 54 (83%) COPD GOLD II: Prehab: 25 (49%), 11 (17%) in UC **p<0.01**	VATS: Prehab: 18, UC: 28 Open surgery: Prehab: 33, UC: 37	90-day postoperative complications LoS
	Charlson comorbidity index 0: Prehab: 15 (29%), UC: 33 (36%) 1-2: Prehab: 27 (53%), UC: 45 (48%) 3-4: Prehab: 7 (14%), UC: 14 (15%) ≥5: Prehab: 2 (4%), UC: 1 (1%) **p=0.08**	Open thoracotomy: Prehab: 1, UC: 4 VATS: Prehab: 39, UC: 66 RATS: Prehab: 11, UC: 23, p=0.37	90-day postoperative complications 90-day postoperative mortality LoS
	Colinet comorbidity score: Prehab: mean 9.3 ±4.3, UC: mean 8.7 ±4.2, p=NR	VATS: Prehab: 10, UC: 12	90-day postoperative complications LoS
	NR	VATS RATS	30-day postoperative complications LoS
	Hypertension or/and coronary disease: Prehab 10 (5%), UC: 37 (5%), p=0.63 COPD: Prehab: 22 (11%), UC: 92 (12%), p=0.64 Diabetes Prehab: 13 (7%), UC: 49 (7%), p=0.99	VATS: Prehab: 122, UC: 489, p=0.30 Open surgery: Prehab 75, UC: 253	30-day postoperative complications (Clavien-Dindo classification) 30-day postoperative mortality LoS

Table 3. Content of exercise prehabilitation according to the items of therapeutic quality on the i-CONTENT tool.

First author, year	Patient selectionEligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)
Benzo, (25) 2011	Low-risk group[a]: Moderate to severe COPD and FEV_1 <80%	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 2/day, **I**: NR, **T**:20 min, **T**: treadmill or cross-trainer (Nu-Step) and arm-R-size exercises or arm-ergometer **Resistance exercises**: **F**: 2/day, **I**: at least light intensity on the Borg scale, **T**: 2 x 10-12 repetitions, **T**: Thera band **Breathing exercises**: **F**: 1/day, **I**: perceived exertion of somewhat hard on the Borg scale, **T**: 15-20 repetitions, **T**: Threshold Inspiratory Muscle Trainer or P-Flex valve
Boujibar, (26) 2018	High-risk group[a]: ≥18 years and VO_{2peak} ≤20 mL/kg/min	Based on: international recommendations (42) Program duration: NR **Aerobic exercises**: **F**: 3-5/week, **I**: tailored to the ventilatory threshold (VT1) on the CPET, **T**: 45 min, **T**: cycling **Resistance exercises**: **F**: 3-5/week, **I**: 70% of 1RM, **T**: 3 x 12 repetitions, **T**: NR, **Breathing exercises**: **F**: 3-5/week, **I**: 30% of maximum inspiratory pressure, **T**: NR, **T**: Threshold Inspiratory Muscle Trainer
Huang, (37) 2017	High-risk group[a]: Age >70 years, BMI >30, COPD with heavy smoking history (≥20 pack-years) FEV_1 ≤70%, or prior thoracic surgery	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 7/week, **I**: own speed and power, progressively increased the resistance range, **T**: 20 min, **T**: cross-trainer (NuStep) **Breathing exercises**: **F**: 2-3/day, **I**: NR, **T**: 15-20, **T**: Threshold Inspiratory Muscle Trainer
Lai, (27) 2016	Low-risk group[a]: ≥70 years	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 1/day, **I**: self-preferred speed and power, **T**: 30 min, **T**: cross-trainer (Nu-Step)
Lai, (28) 2017	High-risk group[a]: >75 years and >20 pack-year smoking history and BMI >30 kg/m^2 and ppoFEV_1 <60% and ppoDLCO <60% and COPD	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 1/day, **I**: not clearly reported, **T**: 30 min, **T**: cross-trainer (Nu-Step) **Breathing exercises**: **F**: 2-3/day, **I**: NR, **T**: 15-20 min, **T**: Threshold Inspiratory Muscle Trainer and manual deep breathing exercises

	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
	Physical therapist	Postoperative complications[b] Postoperative mortality[b] LoS	Safety: no adverse events Dropouts: none Exercise adherence: all participants completed all sessions
	Physical therapists	30-day postoperative complications LoS	Safety: no adverse events No dropouts Exercise adherence: mean number of exercise sessions was 17 (14-20). 10 (52%): received >17 exercise sessions, 9 (47%): received ≤17 exercise sessions
	Aerobic exercises in hospital with a physical therapist, breathing exercises with trained nurses.	30-day postoperative complications 30-day postoperative mortality LoS	Safety: NR Dropouts: Prehab: 1 (3%): acute COPD exacerbation, 2 (7%): knee pain Exercise adherence: NR
	Aerobic exercises supervised by a physical therapist	30-day postoperative complications 30-day postoperative mortality LoS	Safety: NR Dropouts: Prehab: 4 (13%) could not endure the high-intensive regimen, 1 (3%): perceived lack of benefit, 1 (3%): knee pain Exercise adherence: NR
	Physical therapist dedicated to thoracic surgery patients	30-day postoperative complications LoS	Safety: no adverse events Dropouts: Prehab: 6 (12%): not completion Exercise adherence: NR

Table 3. Continued

First author, year	Patient selectionEligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)
Lai,(29) 2019	Low-risk group[a]: 45-80 years and ppoFEV_1 <60%,	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 7/week, **I**: NR, **T**: 30 min, **T**: cross-trainer (Nu-Step) **Breathing exercises**: **F**: 3/day, **I**: NR, **T**: 20 breaths/session, **T**: Threshold Inspiratory Muscle Trainer
Licker,(30) 2017	Low-risk group[a]: All patients	Based on: (43) Program duration: NR **Aerobic exercises**: **F**: 2-3/week, **I**: 80-100% of peak work-rate near-maximal heart rates toward the end of each series of sprints based on the individual's exercise response, **T**: 2 series of 10 min with 15-sec work-interval and 15 sec rest-interval with 4-min rest between series, **T**: cycling **Resistance training**: **F**: 2-3/week, **I**: NR, **T**: NR, **T**: leg press, leg extension, back extension, seat row, biceps curls, or chest and shoulder press
Liu,(31) 2019	Low-risk group[a]: <70 years	Based on: (44) Program duration: 2 weeks **Aerobic exercises**: **F**: 3/week, **I**: based on Borg-score 13-16 and 70% of heart rate reserve, **T**: 30 min, **T**: jogging or walking or cycling **Resistance exercises**: **F**: 2/week, **I**: Borg-score moderate to high (13-16), **T**: 3 x 3-12 repetitions, **T**: major muscle groups with Thera band **Breathing exercises**: **F**: 2/day, **I**: NR, **T**: 10 minutes, **T**: 1) A Tri-Ball Respiratory Training (Leventon S.A., Barcelona, Spain) for breathing exercises; 2) cough exercises; 3) blowing up a small balloon in 1 breath and holding for >5 seconds
Morano,(34) 2013	High-risk group[a]: Previous pulmonary disease, interstitial lung disease, COPD with impaired spirometry function	Based on: NR Program duration: 4 weeks **Aerobic exercises**: **F**: 5/week, **I**: 80% on the maximum work rate achieved during a treadmill incremental test, **T**: 10 min in the first week with increments of 10 min every week, **T**: walking on a treadmill **Breathing exercises**: **F**: 1/day, **I**: 20% on the maximal inspiratory pressure (MIP), increased 5-10% each session, to reach 60% of their MIP, **T**: 10-30 min, **T**: Threshold Inspiratory Muscle Trainer

	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
	Aerobic exercises supervised by a physical therapist, respiratory exercises supervised by a trained nurse	30-day postoperative complications 30-day postoperative mortality LoS	Safety: no adverse events Dropouts: Prehab: 2 (6%): exercise intensity to high Exercise adherence: NR
	Physical therapist specialized in rehabilitation	30-day postoperative complications 30-day postoperative mortality LoS	Safety: no adverse events Dropouts: Prehab: 3 (4%): patient withdrawal, 3 (4%): operation cancelled, UC: 5 (7%): patient withdrawal, 2 (3%): operation cancelled Exercise adherence: to the prescribed exercise sessions: 87% ±18%, median 8 sessions
	Home-based, instruction and resistance exercises supported by a physical therapist	30-day postoperative complications 30-day postoperative mortality LoS	Safety: no adverse events Dropouts: Prehab: 2 (6%) did not receive surgery, UC: 2 (6%) did not receive surgery Exercise adherence: NR
	NR	Postoperative complications[b] LoS	Safety: NR Dropouts: UC: 3 (3%) inoperable cancer Exercise adherence: NR

Table 3. Continued

First author, year	Patient selectionEligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)
Pehlivan,(35) 2011	Low-risk group[a]: ASA I-II	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 3/day, **I**: according to patient's tolerance to training speed and time, **T**: NR, **T**: walking on a treadmill **Breathing exercises**: **F**: 2/day, **I**: NR, **T**: NR, **T**: incentive spirometry
Rispoli,(40) 2020	Low-risk group[a]: COPD stage I	Based on: (45, 46) Program duration: 4 weeks **Aerobic exercises**: **F**: ≥3/week, **I**: at least 15 minutes or dyspnoea-limited, **T**: 30 min, **T**: walking outside or treadmill **Resistance exercises**: **F**: ≥3/week, **I**: NR, **T**: NR, **T**: abdominal exercises, lower limbs exercises **Breathing exercises**: **F**:NR, **I**: NR, **T**: NR, **T**: incentive spirometry
Saito,(39) 2017	Low-risk group[a]: COPD gold ≥II and FEV_1 <100% and ECOG ≥2	Based on: NR Program duration: 2 to 4 weeks **Aerobic exercises**: **F**: 5/week, **I**: NR, **T**: 30 min, **T**: cycling **Resistance exercises**: **F**: 5/week, **I**: NR, **T**: NR, **T**: bronchodilator, training for chest expansion, shoulder girdle mobilization
Saito,(38) 2021	Low-risk group[a]: All patients	Based on: NR Program duration: 2 to 4 weeks preoperative **Resistance exercises**: **F**: 7/week, **I**: 15 repetitions, **T**: NR, **T**: abdominal crunch **Breathing exercises**: **F**: 7/week, **I**: NR, **T**: based on vital capacity 50-100 breaths/session, **T**: incentive spirometry coach2
Sebio Garcia (33), 2016	High-risk group[a]: FEV1 80%, BMI 30; (c) age 75 years or two or more co-morbidities identified in the Colinet Comorbidity Score.	Based on: (47) Program duration: NR **Aerobic exercises**: **F**: 3-5/week, **I**: interval training (one minute at high intensity (80% of WR_{peak}) plus four minutes of active rest (performed at 50% of WR_{peak}) measured with the CPET, **T**: 30 min, **T**: cycling **Resistance exercises**: **F**: 3-5/week, **I**: 25 repetition maximum test, **T**: 3x 15 repetitions, **T**: six training using Thera band and body mass for the large muscle groups **Breathing exercises**: **F**: 2/day, **I**: 80% of vital capacity, **T**: 6 cycles of 5 repetitions, **T**: incentive spirometry coach2

	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
	Physical therapist	Postoperative complications[b] LoS	Safety: NR No dropouts Exercise adherence: NR
	Home-based instruction and weekly phone calls supported by a physical therapist	Postoperative complications[b] LoS	Safety: NR Dropouts: no Exercise adherence: Prehab1: 13 (22%) performed <3 sessions per week, Prehab2: 46 (78%) performed ≥3 sessions per week
	Aerobic exercises supervised by a physical therapist	90-day postoperative complications LoS	Safety: NR Dropouts: NR Exercise adherence: NR
	Physical therapist at the first instance of home-based exercises	90-day postoperative complications 90-day postoperative mortality LoS	Safety: NR Dropouts: NR Exercise adherence: NR
	Physical therapist	90-day postoperative complications LoS	Safety: no adverse events Dropouts: Prehab: 2 (17%): lost to follow up, UC: 1 (10%): clinical deterioration Exercise adherence: NR

Table 3. Continued

First author, year	Patient selectionEligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)
Tenconi, (36) 2021	Low-risk group[a]: All patients	Based on: (48) Program duration: 2-3 weeks **Aerobic exercises**: **F**: 2-3/week, **I**: 60–80% peak workload previously determined with shuttle walking test and adapted to the patient's tolerance, **T**: 30-40 minutes, **T**: outpatient clinic cycling, home-based: walking **Resistance exercises**: **F**: 2-3/week, **I**: maximal load (previously determined with the 10-repetition maximum test), **T**: 2-3x 10 repetitions, **T**: lower limbs (extensor muscle group), upper limbs (biceps, triceps, deltoids, latissimus dorsi, pectoralis) and abdominal wall **Breathing exercises**: **F**: 1/day, **I**: ≥30% of maximal predicted inspiratory pressure and adapted to the patient's tolerance, **T**: 15-30 minutes, **T**: Threshold Inspiratory Muscle Trainer
Zhou, (32) 2017	High-risk group[a]: ≥50 years and ≥20 pack-year smoking history and BMI ≥28 kg/m^2 and FEV_1 ≤60% and COPD, asthma or airway hyper reactivity	Based on: NR Program duration: 1 week **Aerobic exercises**: **F**: 1/day. **I**: according to own speed and power, then increasing progressively, **T**: 30 min, **T**: cross-trainer (Nu-Step) **Breathing exercises:F**: 2-3/day: **I**: NR, **T**: 15-20 min, **T**: Volume training: abdominal breathing and inspiratory training with the Voldyne 2500

Abbreviations: 1RM=one repetition maximum, BMI=body mass index, COPD=chronic obstructive pulmonary disease, CPET=cardiopulmonary exercise test, DLCO=carbon monoxide lung diffusion capacity, ECOG=Eastern cooperative oncology group, FEV_1=forced expiratory volume in one second, i-CONTENT=international Consensus on Therapeutic Training aNd Training, min=minute, LoS=length of hospital stay, NR=not reported, ppoDLCO=predicted postoperative carbon monoxide lung diffusion capacity, ppoFEV_1=predicted postoperative forced expiratory volume in one second, Prehab=prehabilitation group, UC=usual care group, VO_{2peak}=oxygen uptake at peak training, WR_{peak}=work rate at peak exercise.

[a]: including a low, moderate, or high-risk group was interpreted according to the patient selection in the included studies and the score on the i-CONTENT tool.

[b]: follow-up time was not described.

	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
	Physical therapist	30-day postoperative complications LoS	Safety: Adverse events: Prehab: 2 (7%): mild, 17 (55%): moderate, 11 (37%): severe, UC: 2 (4%): mild, 37 (69%): moderate, 15 (28%): severe Dropouts: Prehab: 6 (9%): adjuvant treatment, 5 (7%): disease progression, 5 (7%): non-primary lung neoplasm, 8 (11%): lost to follow-up, 1 (1%): other, UC: 15 (21%): adjuvant treatment, 2 (3%): disease progression, 3 (4%): non-primary lung neoplasm, 9 (13%): lost to follow-up, 1 (1%): other Exercise adherence: 90% of the patients had accomplished 80% session adherence
	Education and teaching supported by a nursed specialized in lung cancer, aerobic exercise supervised by a physical therapist	30-day postoperative complications 30-day postoperative mortality	Safety: NR Dropouts: Prehab: 7 (19%): required for advancing the surgery, 9 (24%): perceived lack of benefit, 11 (30%): could not endure the high-intensive regimen, 7 (19%): considered time/expense cost and suspended, 3 (8%): other reasons Exercise adherence: NR

Table 4. Results of methodological quality according to the Cochrane risk of bias tool and the Robins-1 tool, and therapeutic quality according to the i-CONTENT tool.

Methodological quality for randomized controlled trials on the Cochrane risk of bias tool 2

	Risk assessed for outcome[a]	Randomization process	Assignment to intended interventions	Adherence to intended interventions
Benzo (25)	Primary	Some	Low	Low
Huang (37)	Primary	Low	Low	Low
Lai (27)	Primary	Some	Low	High
Lai (28)	Secondary	Low	High	High
Lai (29)	Secondary	Some	Some	High
Licker (30)	Primary	Low	Low	Low
Liu (31)	Secondary	Low	High	High
Morano (34)	Primary	Some	Low	Low
Pehlivan (35)	Primary	Low	Low	High
Sebio Garcia (33)	Side issue	Some	High	Low
Tenconi (36)	Secondary	Some	Some	Some

Methodological quality for observational studies on the Robins-1 tool[a]

First author		Confounding	Selection	Intervention classification	Deviation from interventions
Boujibar (26)	Secondary	Serious	No information	Low	Low
Rispoli (40)	Secondary	Moderate	Serious	Moderate	Low
Saito (39)	Primary	Moderate	Low	Moderate	Low
Saito (38)	Primary	Moderate	Low	Moderate	Low
Zhou (32)	Primary	Moderate	Low	Moderate	Serious

Therapeutic quality

First author	1. Patient selection	2. Dosage of the exercise program	3. Type of the exercise program	4. Qualified supervisor (if applicable)
Benzo (25)	**High**	**High**	**Low**	**Low**
Boujibar (26)	**Low**	**Low**	**Low**	**Low**
Huang (37)	**Low**	**High**	**Low**	**Low**
Lai (27)	**High**	**High**	**Low**	**Low**
Lai (28)	**Low**	**High**	**Low**	**Low**
Lai (29)	**High**	**High**	**Low**	**Low**
Licker (30)	**High**	**Low**	**Low**	**Low**
Liu (31)	**High**	**Low**	**Low**	**Low (home)**
Morano (34)	**Low**	**Low**	**Low**	**High**
Pehlivan (35)	**High**	**High**	**High**	**Low**
Rispoli (40)	**High**	**High**	**Low**	**Low**
Saito (39)	**High**	**High**	**Low**	**Low (home)**
Saito (38)	**High**	**High**	**Low**	**Low (home)**
Sebio Garcia (33)	**Low**	**Low**	**Low**	**Low (home)**
Tenconi (36)	**High**	**Low**	**Low**	**Low (home)**
Zhou (32)	**Low**	**High**	**Low**	**Low**

Methodological quality: low=low risk of bias, some= some concerns; high=high risk of bias, moderate=moderate risk of bias, serious=serious risk of bias.
Therapeutic quality: low=low risk of ineffectiveness; high=high risk of ineffectiveness.
[a]: Risk of bias was assessed in each study based on the relevant outcomes for this systematic review.
[b]: Overall risk of ineffectiveness:
Low risk of ineffectiveness= Item 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND ≥2 of the items 4, 5, 6

	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias	Direction of bias of the study outcome
	Low	Low	Low	**Some**	Unpredictable
	Low	Low	Low	**Low**	Unpredictable
	Low	Low	Low	**High**	Favours comparator
	Low	Low	Low	**High**	Unpredictable
	Low	Low	Low	**High**	Favours comparator
	Low	Low	Low	**Low**	Not applicable
	Low	Low	Low	**High**	Unpredictable
	Low	Low	Low	**Some**	Favours experimental
	Low	Some	Low	**High**	Unpredictable
	High	Low	Low	**High**	Favours comparator
	Low	Low	Some	**High**	Unpredictable

	Missing outcome data	Measurement of outcome	Selection of reported results	Overall risk of bias	
	Low	Low	Low	**Serious**	Favours comparator
	Low	Low	Moderate	**Serious**	Favours experimental
	Low	Low	Low	**Moderate**	Unpredictable
	Low	Low	Low	**Moderate**	Unpredictable
	Low	Low	Low	**Serious**	Favours comparator

	5. Type and timing of outcome assessment	6. Safety of the exercise program	7. Adherence to the exercise program	Overall risk of ineffectiveness[b]
	High	**Low**	**Low**	**High**
	Low	**Low**	**High**	**Some**
	Low	**Low**	**Low**	**Some**
	High	**Low**	**Low**	**High**
	High	**Low**	**Low**	**Some**
	High	**Low**	**Low**	**High**
	Low	**Low**	**Low**	**Some**
	Low	**Low**	**Low**	**Some**
	Low	**Low**	**Low**	**Low**
	Low	**Low**	**Low**	**High**
	Low	**Low**	**Low**	**High**
	High	**Low**	**High**	**High**
	Low	**Low**	**High**	**High**
	Low	**Low**	**High**	**Some**
	Low	**Low**	**Low**	**Some**
	High	**Low**	**High**	**High**

scored a "low risk of ineffectiveness"
Some risk of ineffectiveness= Item 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND 1 of the items 4, 5, 6 scored a "low risk of ineffectiveness" OR 3 of the items 1, 2, 3, and 7 scored a "low risk of ineffectiveness" AND ≥1 of the items 4, 5, 6 scored a "low risk of ineffectiveness"
High risk of ineffectiveness= ≤2 of the items 1, 2, 3, and 7 scored a "low risk of ineffectiveness"

Effects of prehabilitation on postoperative complications, length of hospital stay, and postoperative mortality

Postoperative pulmonary complications

Postoperative pulmonary complications were assessed in eight RCTs (25, 27-30, 33-35) and two observational studies (32, 39) (Figure 1.A). The pooled result of these studies showed a statistically significant lower incidence of postoperative pulmonary complications in the prehabilitation groups compared to the usual care groups in RCTs (OR 0.31, 95% CI 0.20 to 0.48; I^2 0%) and observational studies (OR 0.60, 95% CI 0.41 to 0.88; I^2 0%). Certainty of the evidence according to the GRADE approach was moderate and very low for RCTs and observational studies, respectively (see Table 5). The one observational study (40) which compared a different number of prehabilitation session with each other was not included in the meta-analysis reported that ≥3 prehabilitation sessions per week significantly reduced postoperative pulmonary complications compared to performing <3 sessions a week ($p<0.01$).

Table 5. Summary of findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

Certainty assessment						
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**1. Publications bias* 2. Residual confounding 3. Dose-response gradient 4. Risk of ineffectiveness**
Postoperative pulmonary complications (follow up: 90 days)						
8	Randomized controlled trials	Serious[a, b]	Not serious	Not serious	Not serious	1. Publication bias 2. Strongly suspected 3. Strong association[a] 4.<80%
Postoperative pulmonary complications (follow up: 90 days)						
2	Observational studies	Very serious[a, c]	Not serious	Not serious	Not serious	1. Publication bias 2. Strongly suspected 4.<80%
Postoperative any complications (follow up: 90 days)						
11	Randomized controlled trials	Very serious[a, b]	Not serious	Not serious[b]	Not serious	1. Publication bias 2. Strongly suspected 3. Strong association[a] 4.<80%
Postoperative any complications (follow up: 90 days)						
4	Observational studies	Very serious[a, c]	Not serious	Not serious	Serious	1. Publication bias 2. Strongly suspected 4.<80%
Postoperative severe complications (follow up: 90 days)						
4	Randomized controlled trials	Very serious[a,b]	Not serious	Not serious	Not serious	3. Strong association 4.<80%
Postoperative severe complications (follow up: 90 days)						
3	Observational studies	Very serious[a, c]	Not serious	Not serious	Not serious	2. All plausible residual confounding would suggest spurious effect, while no effect was observed 4.<80%
Postoperative mortality (follow up: 90 days)						
6	Randomized controlled trials	Very serious[a, b]	Not serious	Not serious	extremely serious[f]	1. Publication bias 2. Strongly suspected 4.<80%
Postoperative mortality (follow up: 90 days)						
2	Observational studies	Very serious[a, c]	Not serious	Not serious	extremely serious[f]	1. Publication bias 2. Strongly suspected 4.<80%
Length of hospital stay						
15	Randomized controlled trials	Very serious[a, b]	Serious[c]	Not serious	Not serious	1. Publication bias 2. Strongly suspected 3. Strong association[a] 4.<80%
Length of hospital stay						
3	Observational studies	Very serious[a, c]	Serious[d]	Not serious	Serious[d,e]	1. Publication bias 2. Strongly suspected 4.<80%

Abbreviations: CI=confidence interval, OR=odds radio.

*: funnel plots have been added in supplementary file 4

a: most studies showed a high risk of bias favouring the usual care group.

b: unclear process and no description of the assignment, and undescribed exercise adherence to the intended interventions.

Number of patients		Effect		Certainty
Exercise prehabilitation with event/ total	Usual care with event/ total	Relative (95% CI)	absolute (95% CI)	
41/248 (16.5%)	95/251 (37.8%)	**OR 0.31** (0.20 to 0.48)	**220 fewer per 1.000** (from 270 less to 152 less)	⊕⊕⊕○ Moderate
39/248 (15.7%)	204/807 (25.3%)	**OR 0.60** (0.41 to 0.88)	**84 fewer per 1.000** (from 131 less to 23 less)	⊕○○○ Very low
112/387 (28.9%)	116/300 (38.7%)	**OR 0.37** (0.23 to 0.61)	**198 fewer per 1.000** (from 260 less to 109 less)	⊕⊕○○ Low
116/300 (38.7%)	468/915 (51.1%)	**OR 0.58** (0.35 to 0.97)	**134 fewer per 1.000** (from 243 less to 8 less)	⊕○○○ Very low
19/131 (14.5%)	41/130 (31.5%)	**OR 0.36** (0.20 to 0.68)	**173 fewer per 1.000** (from 231 less to 77 less)	⊕⊕⊕○ Moderate
96/267 (36.0%)	422/850 (49.6%)	**OR 0.56** (0.29 to 1.06)	**141 fewer per 1.000** (from 274 less to 15 less)	⊕⊕○○ Low
2/235 (0.9%)	4/235 (1.7%)	**OR 0.63** (0.14 to 2.83)	**28 fewer per 1.000** (from 15 less to 30 more)	⊕○○○ Very low
3/248 (1.2%)	5/835 (0.6%)	**OR 1.11** (0.39 to 3.14)	**1 more per 1.000** (from 4 less to 13 more)	⊕○○○ Very low
232	230	-	MD **3.02 lower** (4.82 less to 1.22 less)	⊕○○○ Very low
299	900	-	MD **0.6 lower** (3.95 lower to 2.75 higher)	⊕○○○ Very low

c: high risk on confounding and classification of intervention status can be affected by knowledge of the outcome or risk of the outcome.
d: wide pooled effects of the confidence intervals.
e: small minimal important difference.
f: very imprecise estimate due to the low rate of such event in this small sample size

Any postoperative complications

Incidence of any postoperative complication was assessed in eleven RCTs (25, 27-31, 33-37) and four observational studies (26, 32, 38, 39) (Figure 1.B). The meta-analysis showed that the incidence of any complications was significantly lower in patients receiving prehabilitation compared to patients receiving usual care (OR 0.44, 95% CI 0.30 to 0.64; I^2 42%). The GRADE certainty of evidence was low based on RCTs and very low based on observational studies (see Table 5).

Severe postoperative complications

Four RCTs (27, 29, 31, 37) and three observational studies (26, 32, 38) separately assessed severe complications (Figure 1.C). The pooled results showed that prehabilitation significantly reduced the risk of severe complications in RCTs (OR 0.36, 95% CI 0.20 to 0.68; I^2 0%) and observational studies (OR 0.56, 95% CI 0.29 to 1.06; I^2 32%). The GRADE certainty of evidence was moderate based on RCTs and low based on observational studies (see Table 5).

Postoperative mortality

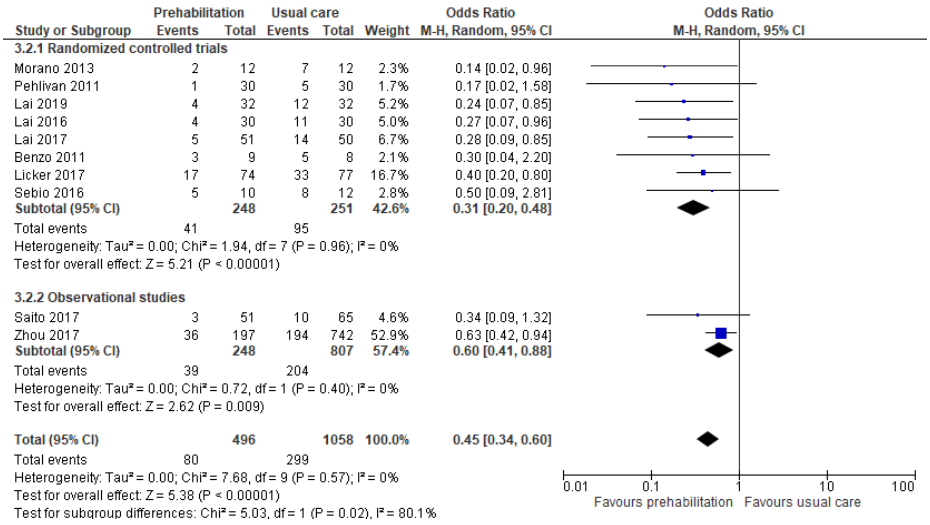
The effect of prehabilitation on postoperative mortality was assessed in six RCTs (27, 29-31, 35, 37) and two observational studies (32, 39) (Figure 1.D). The effect of prehabilitation on postoperative mortality was not significant in both the RCTs and observational studies (RR 0.63, 95% CI 0.14 to 2.83; I^2 0% and RR 1.88, 95% CI 0.44 to 8.05; I^2 0%) with a very low certainty of evidence according to GRADE (see Table 5).

Length of hospital stay

LoS was assessed in seven RCTs (25, 27, 28, 34-37) and three observational studies (32, 38, 39) (Figure 1.E). LoS was shorter in the prehabilitation groups compared to usual care in RCTs (mean difference (MD) –3.02 days, 95% CI –4.82 to –1.22; I^2 85%) with a very low certainty according to the GRADE approach (see Table 5). In observational studies, no significant differences were found between prehabilitation and usual care (MD -0.60 days, 95% CI -3.95 to 2.75; I^2 54%) with a very low certainty according to the GRADE approach. The one study that was not included in the meta-analysis (40) found a significant reduction (3.5 days) of LoS in the group that performed ≥3 prehabilitation sessions a week compared to the prehabilitation group that performed <3 sessions a week.

Figure 1. The effect of exercise prehabilitation compared to usual care on postoperative pulmonary complications (A), any postoperative complications (B), any postoperative severe complications (C) postoperative mortality (D), and length of hospital stay (E).

A



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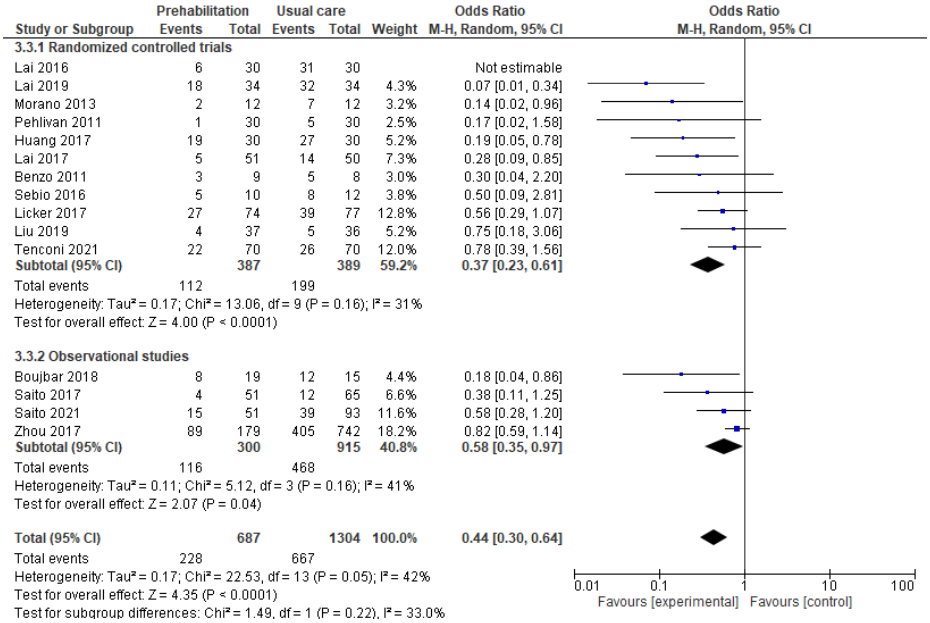
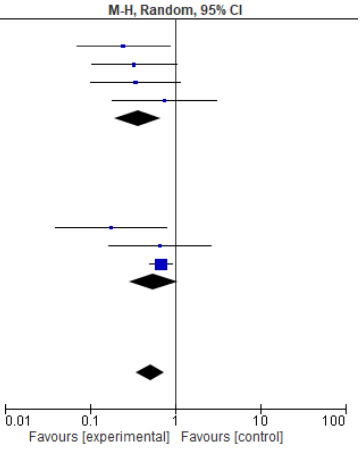


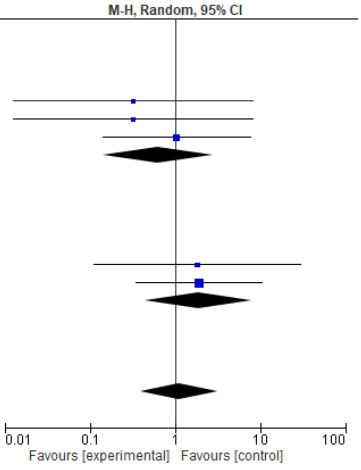
C

Study or Subgroup	Prehabilitation Events	Prehabilitation Total	Usual care Events	Usual care Total	Weight	Odds Ratio M-H, Random, 95% CI
3.4.1 Randomized controlled trials						
Lai 2019	4	34	12	34	8.4%	0.24 [0.07, 0.86]
Lai 2016	6	30	13	30	9.8%	0.33 [0.10, 1.03]
Huang 2017	5	30	11	30	8.9%	0.35 [0.10, 1.16]
Liu 2019	4	37	5	36	6.9%	0.75 [0.18, 3.06]
Subtotal (95% CI)		**131**		**130**	**33.9%**	**0.36 [0.20, 0.68]**
Total events	19		41			
Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.18 (P = 0.001)						
3.4.2 Observational studies						
Boujbar 2018	4	19	9	15	6.0%	0.18 [0.04, 0.81]
Saito 2021	3	51	8	93	7.1%	0.66 [0.17, 2.62]
Zhou 2017	89	197	405	742	52.9%	0.69 [0.50, 0.94]
Subtotal (95% CI)		**267**		**850**	**66.1%**	**0.56 [0.29, 1.06]**
Total events	96		422			
Heterogeneity: Tau² = 0.14; Chi² = 2.94, df = 2 (P = 0.23); I² = 32%						
Test for overall effect: Z = 1.77 (P = 0.08)						
Total (95% CI)		**398**		**980**	**100.0%**	**0.51 [0.35, 0.75]**
Total events	115		463			
Heterogeneity: Tau² = 0.05; Chi² = 7.07, df = 6 (P = 0.31); I² = 15%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
Test for subgroup differences: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%						



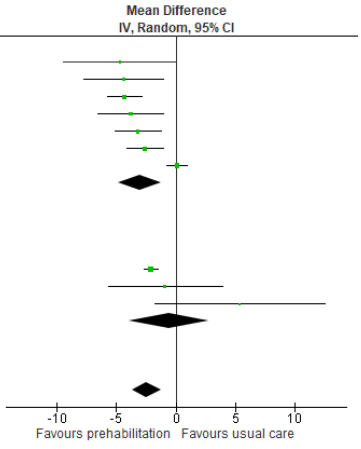
D

Study or Subgroup	Prehabilitation Events	Prehabilitation Total	Usual care Events	Usual care Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Randomized controlled trials						
Lai 2019	0	34	0	32		Not estimable
Liu 2019	0	37	0	36		Not estimable
Pehlivan 2011	0	30	0	30		Not estimable
Huang 2017	0	30	1	30	10.4%	0.32 [0.01, 8.24]
Lai 2016	0	30	1	30	10.4%	0.32 [0.01, 8.24]
Licker 2017	2	74	2	77	27.7%	1.04 [0.14, 7.59]
Subtotal (95% CI)		**235**		**235**	**48.4%**	**0.63 [0.14, 2.83]**
Total events	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.1.2 Observational studies						
Saito 2021	1	51	1	93	14.0%	1.84 [0.11, 30.05]
Zhou 2017	2	197	4	742	37.6%	1.89 [0.34, 10.41]
Subtotal (95% CI)		**248**		**835**	**51.6%**	**1.88 [0.44, 8.05]**
Total events	3		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**483**		**1070**	**100.0%**	**1.11 [0.39, 3.14]**
Total events	5		9			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.7%						



E

Study or Subgroup	Prehabilitation Mean	Prehabilitation SD	Prehabilitation Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 Randomized controlled trials								
Benzo 2011	6.3	3	9	11	6.3	8	4.8%	-4.70 [-9.49, 0.09]
Morano 2013	7.8	4.8	12	12.2	3.6	12	7.5%	-4.40 [-7.79, -1.01]
Pehlivan 2011	5.4	2.7	30	9.7	3.1	30	13.7%	-4.30 [-5.77, -2.83]
Lai 2016	6.9	4.4	30	10.7	6.4	30	9.2%	-3.80 [-6.58, -1.02]
Huang 2017	5.8	3	30	9	4.6	30	11.9%	-3.20 [-5.17, -1.23]
Lai 2017	6.1	3	51	8.7	4.6	50	13.5%	-2.60 [-4.12, -1.08]
Tenconi 2021	6.6	2.7	70	6.5	2.4	70	15.7%	0.10 [-0.75, 0.95]
Subtotal (95% CI)			**232**			**230**	**76.4%**	**-3.02 [-4.82, -1.22]**
Heterogeneity: Tau² = 4.44; Chi² = 39.09, df = 6 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 3.29 (P = 0.001)								
3.1.2 Observational studies								
Zhou 2017	6.2	3.3	197	8.3	5.6	742	16.3%	-2.10 [-2.71, -1.49]
Saito 2021	13.1	13.6	51	14	14.9	93	4.8%	-0.90 [-5.71, 3.91]
Saito 2017	19	24.8	51	13.6	9.8	65	2.5%	5.40 [-1.81, 12.61]
Subtotal (95% CI)			**299**			**900**	**23.6%**	**-0.60 [-3.95, 2.75]**
Heterogeneity: Tau² = 4.96; Chi² = 4.34, df = 2 (P = 0.11); I² = 54%								
Test for overall effect: Z = 0.35 (P = 0.73)								
Total (95% CI)			**531**			**1130**	**100.0%**	**-2.46 [-3.71, -1.22]**
Heterogeneity: Tau² = 2.38; Chi² = 43.88, df = 9 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 3.88 (P = 0.0001)								
Test for subgroup differences: Chi² = 1.56, df = 1 (P = 0.21), I² = 35.8%								



Discussion

The aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality and LoS in patients undergoing surgery for NSCLC, thereby accounting for the quality of the physical exercise programs. The pooled estimates of the RCTs show that prehabilitation results in a reduction of postoperative pulmonary complications, severe postoperative complications, and postoperative LoS. Pooled estimates of the included observational studies also indicate that exercise prehabilitation may reduce postoperative complications and LoS. However, the GRADE certainty of evidence of each outcome was very low to moderate.

Results of the current review are in line with previous research, as several systematic reviews have shown that exercise prehabilitation might be an effective intervention for reducing postoperative complications and LoS in NSCLC/lung resection(11-14). Furthermore, in a recently published systematic review(15), the certainty of evidence was described. However, the certainty of evidence was described without an explanation to which content it was assessed on, which is a major limitation. Nevertheless, previous reviews neither described nor assessed the quality of the content of the physical exercise training module of included prehabilitation studies. Although prehabilitation seems effective, it remains unclear how an optimally effective exercise prehabilitation program should be designed.

The finding that prehabilitation improved most postoperative outcomes, despite the fact that half of the included studies in this systematic review had a high risk of ineffectiveness, might suggest that the full potential of prehabilitation might not have been unlocked. Main concerns with regard to the risk of ineffectiveness were that most included studies (63%) did not specially select patients with a higher risk for postoperative complications and even seemed to exclude them(25, 27, 29-31, 35, 36, 38-40). Because especially patients who are at a high risk for complications and functional decline after surgery might benefit most from prehabilitation(49), patient selection should start preoperatively with an adequate assessment of treatment-associated risk factors for a personalized approach(50-52).

The description of the dosage of prehabilitation programs was unclear in 63% of the included articles(25, 27-29, 32, 35, 37-40). Full reporting of the

prescription and adherence to of exercise prehabilitation is eminent for adequate estimation of the risk of ineffectiveness, and thereby the quality of the exercise program. Merely three studies offered a personalized physical exercise prescription based on outcomes of the cardiopulmonary exercise test of any other formal exercise test (26, 33, 53). In addition, the progression principle was applied in only three studies(34, 36, 37). Both personalization, as well as adequate progression of exercises are of major importance to allow for sufficient overload to improve physical fitness(54). Previous research in patients undergoing elective surgery for abdominal cancer recommends personalized and well-controlled high-intensity interval training to achieve the greatest improvements in physical fitness in the short preoperative time period(55). Overall, prehabilitation programs of the included studies were safe, as no serious adverse events were reported and there were no relevant dropouts due to the nature of the programs.

Strength and limitations

A strength of this systematic review was the inclusion of both RCTs and observational studies. RCTs often have high internal validity but limited generalizability due to the strict inclusion criteria, while observational studies are more generalizable due to the use of real-life data. Another strength was the detailed assessment and description of the content of prehabilitation programs, thereby indicating shortcomings in the development and reporting of prehabilitation programs so that they can receive attention in future studies. This will contribute to further improve the content and effectiveness of the programs, as well as the reproducibility of studies. A limitation of this systematic review involves the choice to only include studies with prehabilitation programs that met a certain minimum set of requirements (i.e., at least a physical exercise module). However, this is considered the cornerstone of an effective (multimodal) prehabilitation program, especially in unfit (high-risk) patients. A second limitation was that the two reviewers did not independently extracted data from each of the included studies. The extraction has been carefully checked by another reviewer and therefore no bias is expected. A third imitation was that the included studies included different types of surgery without specifying how many postoperative complications occurred per type of surgery, making stratification impossible. The risk of ineffectiveness of the prehabilitation programs was moderate to high, and therefore a meta-analysis could not be stratified by risk of ineffectiveness (i.e., low, moderate, or high) of the prehabilitation programs. The latter also precluded a comparison between different training types (e.g., aerobic exercises, resistance exercises, breathing exercises).

Future studies

The description of the FITT-VP principles of the exercise prehabilitation programs was incomplete in the included studies, making it difficult to truly assess the risk of ineffectiveness by means of the i-CONTENT scale. Therefore, it is recommended to use the i-CONTENT tool not only to evaluate exercise prehabilitation programs but also to improve the quality and description of prehabilitation programs already at the stage of study design. Gaining more insight into which content of exercise prehabilitation is most effective could be applied in a RCT with a large sample size, in which different exercise programs (e.g., high-intensity interval training, resistance exercises, and breathing exercises) individually and/or in combination are performed.

Conclusion

Based on the results of the current review, exercise prehabilitation effectively reduces the occurrence of postoperative pulmonary complications, postoperative severe complications, and reduce LoS in patients undergoing surgery for NSCLC, despite the high risk of ineffectiveness. However, results should be interpreted with caution as the certainty of evidence is very low to moderate for all outcomes. Future research should focus on the quality and reporting of prehabilitation programs, which is expected to improve postoperative outcomes through exercise prehabilitation with higher certainty.

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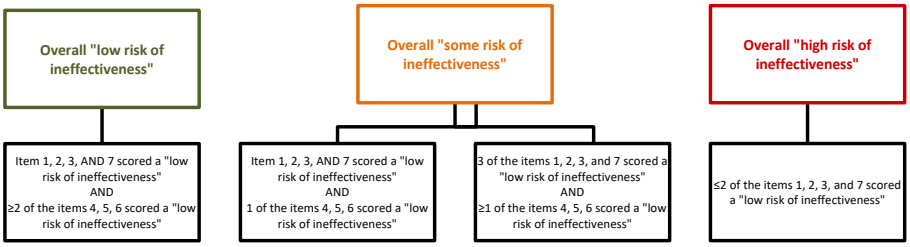
Supplementary files

Supplementary file 1. Combinations of text words of the literature search according to the PICO-structure.

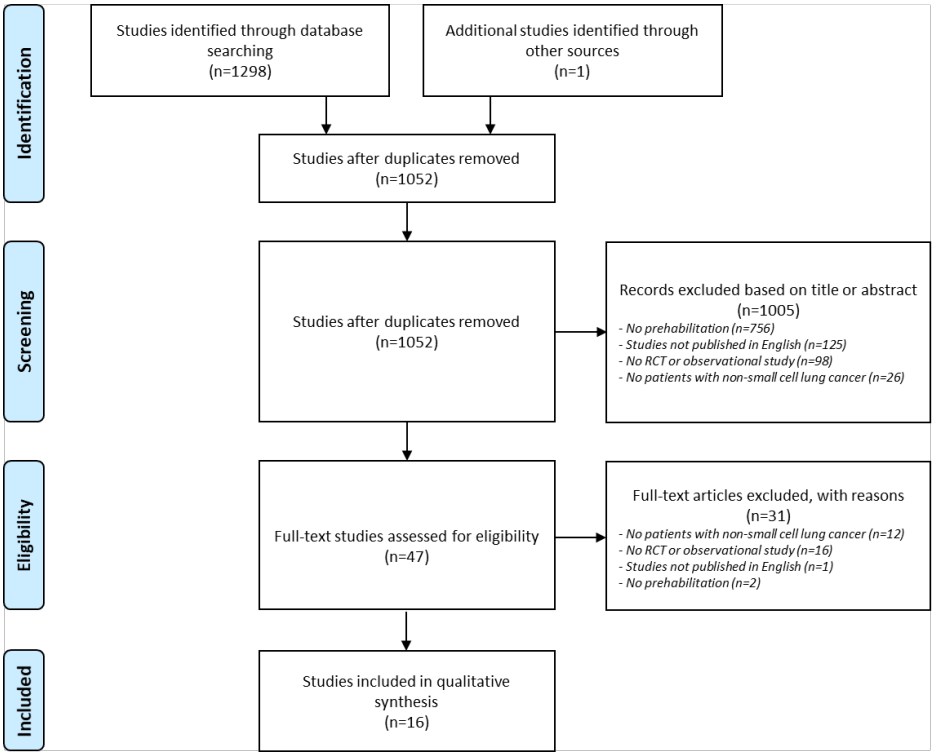
Databases [a]	Population	Intervention	Outcome
Embase, PubMed, Cinahl,	"lung neo plasms"(MeSH Terms:NoExp) OR "Carcinoma, Non-Small-Cell Lung"(Mesh) OR lung-neoplasm*(tiab) OR lung-cancer*(tiab) OR pulmonary-cancer*(tiab) OR pulmonary-neoplasm*(tiab) OR cancer-of-the-lung*(tiab) OR cancers-of-the-lung*(tiab) OR non-small-cell-lung-carcinoma*(tiab) OR NSCLC(tiab) OR non-small-cell-lung-cancer*(tiab) OR lung-tum*(tiab) OR lung-malignanc*(tiab) OR lung-tumor(tiab) OR lung-tumour(tiab) AND Pulmonary-surgical-procedures(MeSH) OR Pneumonectomy(Mesh) OR thoracic-surgical-procedures(MeSH) pulmonary-surgical-procedure*(tiab) OR lung-resection(tiab) OR lobectomy(tiab) OR pneumonectomy(tiab)	Prehab*(tiab) OR before-surgery(tiab) OR training-training(tiab) OR physical-training(tiab) OR physical-training(tiab) OR training(tiab) OR Training-therapy(tiab) OR physical-fitness(tiab) OR physical-therapy-modalities OR training(tiab) OR physical-activity(tiab) OR physical-fitness(Mesh) OR training-therapy(tiab) OR aerobic-training(tiab) OR aerobic-training(tiab) OR training(tiab) OR "perioperative care"(MeSH Terms) OR ("High-intensity Interval Training"(MeSH) OR high-intensity-interval(tiab) OR interval-training(tiab) OR interval-training(tiab) OR high-intensity-intermittent(tiab) OR HIIT(tiab) OR HIIE(tiab) OR sprint-interval-training*(tiab) OR Prehabilitation(tiab) OR Prehabilitative(tiab) OR pre-conditioning(tiab) OR preconditioning(tiab) OR "endurance training"(MeSH) OR endurance-training*(tiab) OR rehabilitation(tiab) OR "physical endurance"(MeSH) OR physical-endurance(tiab) OR MICT(tiab) OR MIE(tiab) OR moderate-intensity-training(tiab) OR training-training(tiab) OR physical-training(tiab) OR training-intervention*(tiab) OR training-program*(tiab))	"complications"(MeSH Subheading) OR complication*(tiab) OR associated-conditions(tiab) OR coexistent-disease(tiab) OR "mortality"(MeSH Terms) OR mortality(tiab) OR mortalities(tiab) OR "mortality"(MeSH Subheading) OR "death"(MeSH Terms) OR death*(tiab) OR fatal*(tiab) OR "hospitalization"(MeSH Terms) OR hospitalization(tiab) OR hospitalisation(tiab) OR "length of stay"(MeSH Terms) OR length-of-stay(tiab) OR length-of-hospital-stay(tiab)

[a]: search presented for PubMed only: the search strategy has been adjusted for searching in the other databases.

Supplementary file 2. Therapeutic quality according to the i- CONTENT tool.

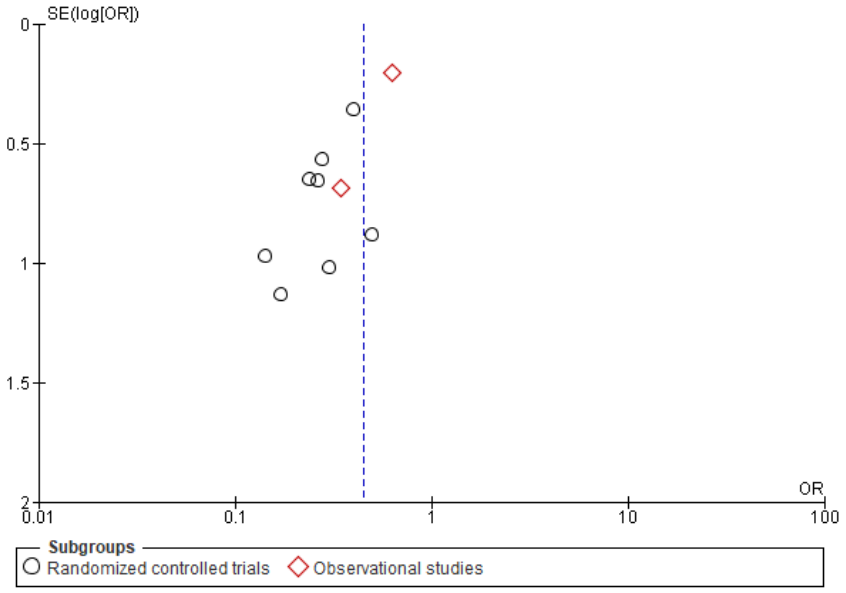


Supplementary file 3. PRISMA Flow diagram displaying the selection of studies and reason for exclusion.



Supplementary file 4. Funnel plots. Postoperative pulmonary complications (A), any postoperative complications (B), any postoperative severe complications (C) postoperative mortality, (D), and length of hospital stay (E).

A



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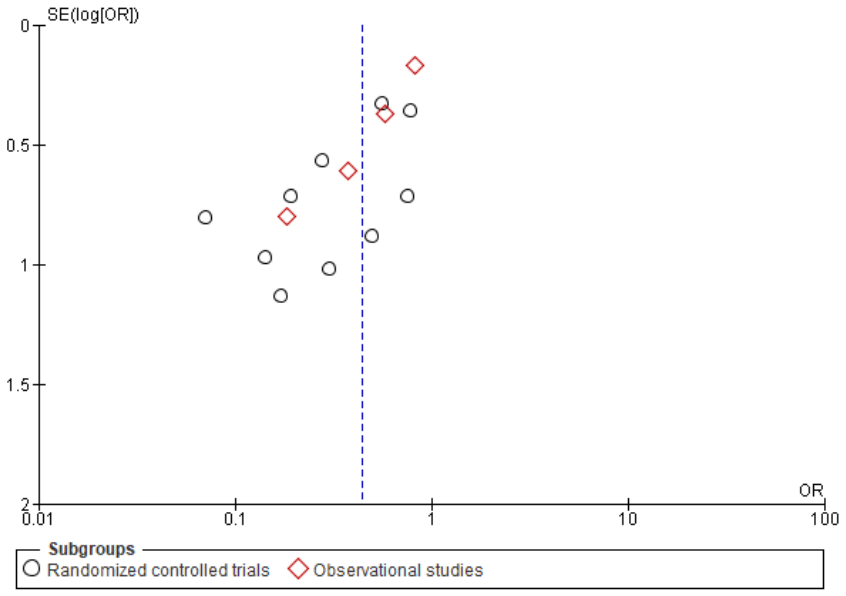

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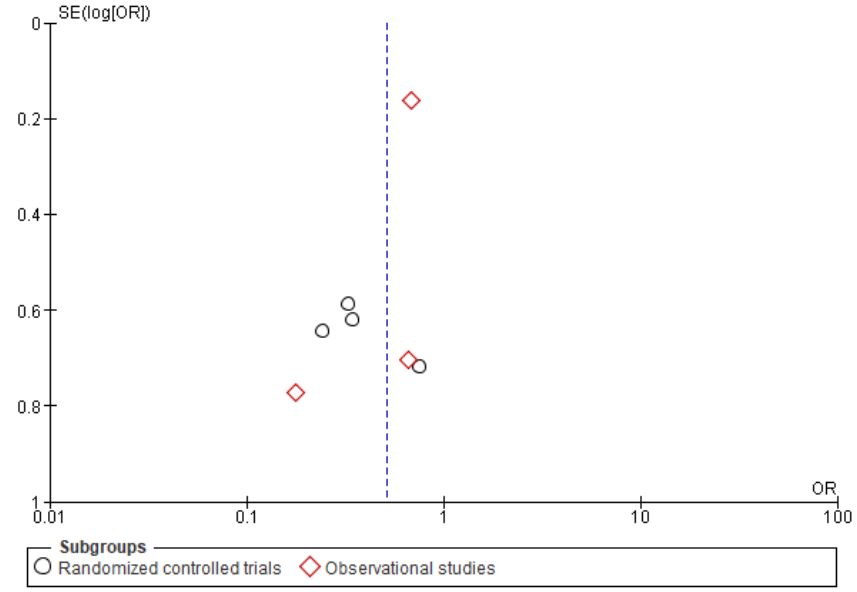
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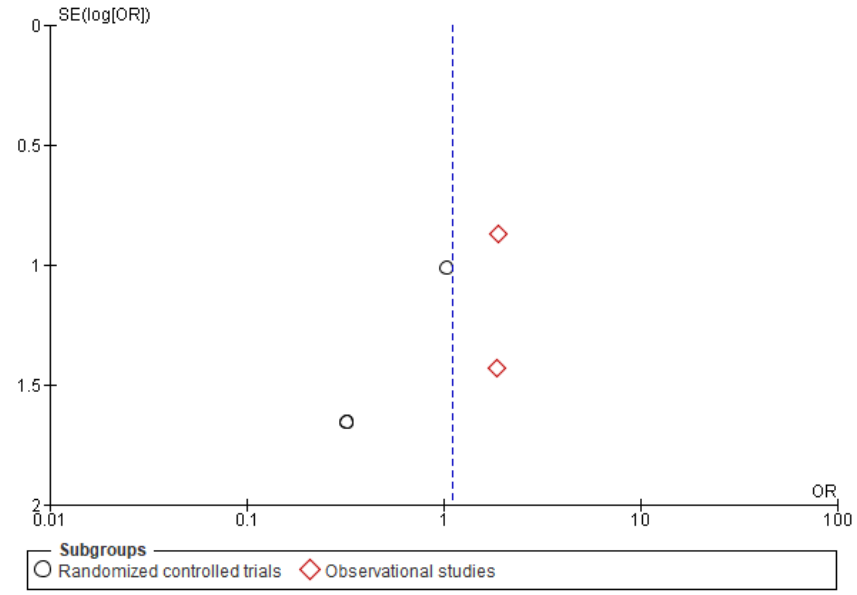
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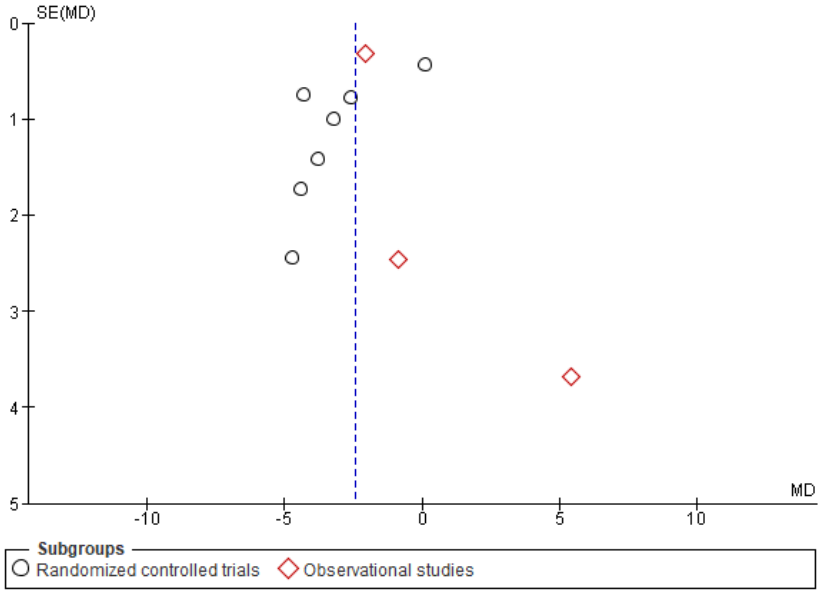
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Randomized controlled trials
Observational studies

Supplementary file 5. Postoperative outcomes in patients undergoing surgery for non-small cell lung cancer

First author, year. Study design	Number of participants Risk group	Risk of biasRisk of ineffectiveness
Benzo, (25) 2011 RCT	Prehab: 9 UC: 8 Non-high-risk group[a]	Some High
Boujibar, (26) 2018 Observational study	Prehab: 19 UC: 15 High-risk group[a]	Serious Some
Huang, (37) 2017 RCT	Prehab: 30 UC: 30 High-risk group[a]	Low Some
Lai, (27) 2016 RCT	Prehab: 30 UC: 30 Non-high-risk group[a]	High High
Lai, (28) 2017 RCT	Prehab: 51 UC: 50 High-risk group[a]	High Some
Lai, (29) 2019	Prehab: 34 UC: 34 Non-high-risk group[a]	High High

	Postoperative complications, n (%)	Postoperative mortality, n (%)	Length of hospital stay, days, ±SD
	Pulmonary complications: Prehab: 3 (30%), UC: 5 (56%), p=0.23 Ventilation hours, mean: Prehab: 6.0 (18%), UC: 33.3 (62%), p=0.39 Prolonged chest tube (>7days): Prehab: 1 (10%), UC: 5 (56%), **p=0.03** Average number of days with chest tubes mean (SD): Prehab: 4.3 (2), UC 8.8 (5), **p=0.04** Respiratory failure: Prehab: 1 (10%), UC: 2 (22%), p=0.45 Pneumonia: Prehab: 1 (10%), UC: 2 (22%), p=0.45 Requiring bronchoscopy for atelectasis: Prehab: 1 (10%), UC: 2 (22%), p=0.45	-	Prehab: 6.3 ±3.0 UC: 11.0 ±6.3 **p=0.06**
	Clavien-Dindo classification, **p=0.03**: Grade 0: Prehab: 11 (58%), UC: 3 (20%) Grade I: Prehab: 4 (21%), UC: 3 (20%) Grade II: Prehab: 2 (11%), UC: 2 (13%) Grade IIIa: Prehab: 0 (0%), UC: 5 (33%) Grade IIIb: Prehab: 1 (5%), UC: 0 (0%) Grade IV: Prehab: 1 (5%), UC: 2 (13%) Complications: Prehab: 8 (42%), UC: 12 (80%), **p=0.04** Number of complications, **p<0.01**: 0: Prehab: 11 (58%), UC: 3 (20%) 1: Prehab: 8 (42%), UC: 5 (33%) 2: Prehab: 0 (0%), UC: 6 (40%) 3: Prehab: 0 (0%), UC: 1 (7%)	-	Prehab: median 5 UC: median 7 **p<0.08**
	Pulmonary complications: Clavien-Dindo classification: Grade I: Prehab: 14 (47%), UC: 16 (53%), p=0.61 Grade II: Prehab: 4 (13%), UC: 8 (27%), p=0.20 Grade III: Prehab: 3 (10%), UC: 2 (7%), p=1.00 Grade IV: Prehab: 1 (3%), UC: 2 (7%), p=1.00 Grade II-IV: Prehab: 5 (13%), UC: 12 (40%), **p=0.05**	Prehab: 0 (0%) UC: 1 (3%) p=1.00	Prehab: 5.8 ±3.0 UC: 9.4 ±4.6 **p<0.01**
	Pulmonary complications: Prehab: 4 (13%), UC: 11 (37%), **p=0.04** Pulmonary complications: Clavien-Dindo classification: Grade I: Prehab: 15 (50%), UC: 16 (53%), p=0.80 Grade II: Prehab: 4 (13%), UC: 8 (60%), p=0.20 Grade III: Prehab: 2 (7%), UC: 4 (13%), p=0.39 Grade IV: Prehab: 0 (0%), UC: 1 (3%), p=1.00	Prehab: 0 (0%) UC: 1 (3%) p=1.00	Prehab: 6.9 ±4.4 UC: 10.7 ±6.4 **p=0.01**
	Pulmonary complications: Prehab: 5 (10%), UC: 14 (28%), **p=0.02** Risk of pulmonary complications after prehabilitation: **OR 0.16 (95% CI 0.04-0.65, p=0.01)**	-	Prehab: 6.1 ±3.0 UC: 8.7 ±4.6 **p<0.01**
	Clavien-Dindo classification: Grade I: Prehab 14 (41%), UC: 20 (59%), p=0.15 Grade II: Prehab: 4 (12%), UC: 10 (29%), **p=0.07** Grade III: Prehab: 0 (0%), UC: 3 (9%), p=0.24 Grade IV: Prehab: 0 (0%), UC: 1 (2.9%), p=1.00 Grade II-V pulmonary complications: Prehab: 4 (11.8), UC: 12 (35.3), **p=0.02**	Prehab: 0 (0%) UC: 0 (0%) P=1.00	Prehab: median 5 UC: median 8 **p<0.01**

Supplementary file 5. Continued

First author, year. Study design	Number of participants Risk group	Risk of biasRisk of ineffectiveness
Licker,(30) 2017 RCT	Prehab: 74 UC: 77 Non-high-risk group[a]	**Low** **Some**
Liu,(31) 2019 RCT	Prehab: 37 UC: 36 Non-high-risk group[a]	**High** **Some**
Morano,(34) 2013 RCT	Prehab: 12 UC: 12 High-risk group[a]	**Some** **Low**
Pehlivan (35), 2011 RCT	Prehab: 30 UC: 30 Non-high-risk group[a]	**High** **High**
Rispoli (40), 2020 Observational study	Prehab1: 13[b] Prehab2: 46 Non-high-risk group[a]	**Serious** **High**
Saito,(39) 2017 Observational study	Prehab: 51 UC: 65 Non-high-risk group[a]	**Moderate** **High**
Saito,(38) 2021 Observational study	Prehab: 51 UC: 93 Non-high-risk group[a]	**Moderate** **High**

	Postoperative complications, n (%)	Postoperative mortality, n (%)	Length of hospital stay, days, ±SD
	Pulmonary complications: Prehab: 17 (23%), UC: 33 (45%), **p<0.01** All complications: Prehab: 27 (23%), UC: 39 (51%) Cardiovascular complications: Prehab: 13 (18%), UC: 10 (14%), p=0.58 Surgical complications: Reoperation: Prehab: 8 (2%), UC 2 (3%), **p=0.09** Bronchopleural fistula: Prehab: 3 (4%), UC: 3 (3.9), p=0.71 Wound infections: Prehab: 3 (4%), UC: 4 (5%), p=0.96 Renal dysfunction: Prehab: 2 (3%), UC: 4 (5%), **p<0.01**	Prehab: 2 (3%) UC: 2 (3%) p=0.64	Prehab: median 10 UC: median 9 p=0.22
	Clavien-Dindo classification, p=0.16 Grade 0-I: Prehab: 33 (89%), UC: 31 (86%) Grade II: Prehab: 4 (11%), UC: 2 (6%) Grade III: Prehab: 0 (0%), UC: 3 (8%) Pneumonia: Prehab: 0 (0%), UC: 1 (4%), p=0.31 Atelectasis: Prehab: 0 (0%), UC: 1 (4%), p= 0.31 Cardiac complications: Prehab: 2 (5%), UC: 2 (7%), p=0.67	Prehab: 0 (0%) UC: 0 (0%)	Prehab: median 8 UC: median 8 p=0.57
	Pulmonary complications: Prehab 2 (17%), UC: 7 (77%), **p=0.01** Days with chest tubes: Prehab: 4.2 ±2.9, UC: 7.4, **p=0.03** Pneumonia: Prehab: 0 (0%), UC: 2 (22%), p=0.17 Ventilation >48 h: Prehab: 1 (8%), UC: 3 (33%), p=0.20 Bronchopleural fistula: Prehab: 2 (17%), UC: 7 (78%), **p<0.01** Atelectasis: Prehab: 0 (0%), UC: 3 (33%), **p=0.06** Bronchospasm: Prehab: 0 (0%), UC: 6 (66%), **p<0.01**	-	Prehab: 7.8 ±4.8 UC: 12.2 ±3.6 **p=0.04**
	Pulmonary complications: Prehab: 1 (3.3), UC: 5 (16.6) All complications, **p=0.04**: Atelectasis: Prehab: 0 (0%), UC: 1 (3%) Fever: Prehab: 1 (3%), UC: 2 (7%) Dyspnoea: Prehab: 0 (0%), UC: 1 (3%) Haemorrhagic drainage: Prehab: 0 (0%), UC: 1 (3%)	Prehab: 0 (0%) UC: 0 (0%)	Prehab: 5.40 ±2.67, UC: 9.66 ±3.09 **P<0.01**
	Pulmonary complications: Prehab1: 6 (46%), Prehab2: 3 (7%), **p<0.01** Other complications (atrial fibrillation): Prehab1: 1 (8%), Prehab2: 3 (6%), p=0.88	-	Prehab1: 10.0 ±8.4 Prehab2: 6.5 ±2.1 **p=0.01**
	All complications: Prehab: 4 (13%), UC: 12 (39%), **p=0.10** Pulmonary complications: Prehab: 3 (10%), UC: 10 (32%), p=0.11	-	Prehab: 19.0 ±24.8 UC: 13.6 ±9.8 **p=0.05**[c]
	Clavien-Dindo classification: Grade 0: Prehab: 35 (69%), UC: 49 (53%), **p=0.06** Grade I: Prehab: 12 (24%), UC: 31 (33%), p=0.22 Grade II: Prehab: 1 (2%), UC: 6 (7%), p=0.23 Grade IIIa: Prehab: 2 (4%), UC: 1 (1%), p=0.73 Grade IVa: Prehab: 0 (0%), UC: 1 (1%), p=NR	Prehab: 1 (2%) UC: 1 (1%) p=1.80	Prehab: 13.1 ±13.6 UC: 14.0 ±14.9 P=0.33

Supplementary file 5. Continued

First author, year. Study design	Number of participants Risk group	Risk of biasRisk of ineffectiveness
Sebio Garcia,(33) 2016 RCT	Prehab: 10 UC: 12 High-risk group[a]	**Serious** **Some**
Tenconi,(36) 2021 RCT	Prehab: 70 UC: 70 Non-high-risk group[a]	**High** **Some**
Zhou,(32) 2017 Observational study	Prehab: 197 UC: 742 High-risk group[a]	**High** **High**

Abbreviations: CI=confidence interval, ICU=intensive care unit, OR=odds ratio, Prehab=prehabilitation group, UC=usual care group, RCT=randomized controlled trial, SD=standard deviation, VO_{2peak}=oxygen uptake at peak exercise

[a]: low, moderate, or high-risk group was interpreted according to the patient selection in the included studies and the score on the i-CONTENT tool.

[b]: <3 sessions a week prehabilitation is Prehab1, ≥3 sessions a week prehabilitation is Prehab2

[c]: significant shorter length of hospital stay in the usual care group

	Postoperative complications, n (%)	Postoperative mortality, n (%)	Length of hospital stay, days, ±SD
	Melbourne Group Scale Pulmonary complications: Prehab 5 (50%), UC: 8 (66%), p=0.36	-	Prehab: 2 (median) UC: 3 (median) p=0.54
	Complications: Prehab: 22 (31%), UC: 26 (37%), p=0.59	-	Prehab: 6.6 ±2.7 UC6.5 ±2.4 p=0.78
	Pulmonary complications: Prehab: 36 (18%), UC: 194 (26%), **p=0.02** Clavien-Dindo classification: Grade II Pneumonia: Prehab: 22 (11%), UC 128 (17%), **p=0.02** Pleural effusion needing drainage: Prehab: 14 (7%), UC: 49 (7%), p=0.80 Atelectasis needing bronchoscope: Prehab: 13 (7%), UC: 91 (12%), **p=0.04** Air leak ≥7 days: Prehab: 14 (7%), UC:49 (7%), p=0.92 Grade III Empyema: Prehab 6 (3%), UC: 30 (4%), p=0.52 Mechanical ventilation >48h: Prehab 8 (4%), UC: 27 (4%), p=0.78 Bronchopleural fistula: Prehab 4 (2%), UC: 13 (2%), p=0.77 Grade IV Return to ICU: Prehab 4 (2%), UC: 7 (1%), p=0.26 Pulmonary embolism: Prehab 0 (0%), UC: 3 (9%), p=1.00 ARDS: Prehab 4 (2%), UC: 8 (1%), p=0.29 Pulmonary complications: **OR 0.57 (95% CI 0.47-0.93, p=0.03)** Pneumonia**: OR 0.62 (95% CI 0.38-1.02, p=0.06)** Atelectasis: **OR 0.49 (95% CI 0.26-0.91, p=0.02)**	Prehab: 2 (1%) UC: 4 (1%) p=0.61	Prehab: 6.2 ±3.3 UC: 8.3 ±5.6 **p<0.01**

'I think physical exercise also contributes in a psychological sense, because I think it gives people a hold that they can do something themselves. Moreover, physical exercise also releases endomorphins so that that's just incredibly positive.'
-Healthcare professional-

Chapter 7

Effects of exercise prehabilitation and/or rehabilitation on healthrelated quality of life and fatigue in patients with non-small cell lung cancer undergoing surgery: a systematic review

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Abstract

Background This systematic review aimed to appraise the current available evidence regarding the effects of exercise prehabilitation and rehabilitation on perceived health-related quality of life (HRQoL) and fatigue in patients undergoing surgery for non-small cell lung cancer (NSCLC).

Methods Studies were selected according to Cochrane guidelines and assessed for methodological quality and therapeutic quality (the international CONsensus on Therapeutic Exercise aNd Training (i-CONTENT)). Eligible studies included patients with NSCLC performing exercise prehabilitation and/or rehabilitation and postoperative HRQoL and fatigue up to 90-days postoperatively.

Results Thirteen studies were included. Exercise prehabilitation and rehabilitation significantly improved postoperative HRQoL in almost half of the studies (47%), although none of the studies demonstrated a decrease in fatigue. Methodological quality and therapeutic quality were poor in respectively 62% and 69% of the studies.

Conclusion There was an inconsistent effect of exercise prehabilitation and exercise rehabilitation on improving HRQoL in patients with NSCLC undergoing surgery, with no effect on fatigue. Due to the low methodological and therapeutic quality of included studies, it was not possible to identify the most effective training program content to improve HRQoL and reduce fatigue. It is recommended to investigate the impact of a high therapeutic qualified exercise prehabilitation and exercise rehabilitation on HRQoL and fatigue in larger studies.

Introduction

Lung cancer is the fourth most common type of cancer in the Netherlands with 14,573 newly diagnosed patients in 2020 (1, 2).Non-small cell lung cancer (NSCLC) concerns 85% of all patients with lung cancer (3). According to European guidelines (4), surgery is advised for relatively fit patients with operable early-stage NSCLC. About half of the patients is aged 70 years or older and this proportion is expected to increase due to aging (5). Characteristics of patients with NSCLC are smoking-related comorbidities, frailty, poor physical performance status, and long-term physical inactivity (6). These characteristics can increase postoperative complications, and decrease survival and health-related quality of life (HRQoL) (7-9).

In addition, NSCLC and its treatment is often accompanied with physical and psychological symptoms. Pain, fatigue, insomnia, and/or mood disturbances are the four most commonly reported postoperative and distressing symptoms (10, 11).These symptoms can severely reduce perceived HRQoL and daily functioning after surgery (12). This accounts especially for patients with NSCLC who are physically inactive and/or malnourished and therefore have a low physiological reserve capacity (6). Prehabilitation (physical exercise training before surgery) and rehabilitation (physical exercise training after surgery) in patients with NSCLC are emerging disciplines, which may positively influence long-term HRQoL, fatigue, and exercise capacity (9, 11, 13, 14). Previous systematic reviews reported a minimal improvement in HRQoL after prehabilitation and/or rehabilitation in patients with NSCLC (15-17), with a limited number and low quality of evidence of included trials. However, systematic evidence regarding the effects of exercise prehabilitation and rehabilitation on HRQoL and fatigue in patients with NSCLC is scarce. Therefore, the aim of this study was to systematically review the literature regarding the effects of exercise prehabilitation and rehabilitation on perceived HRQoL and fatigue in patients undergoing surgery for NSCLC.

Methods

Cochrane and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. The study protocol was registered at PROSPERO (CRD42018087073).

Data sources and searches

Articles were systematically searched in PubMed and EMBASE till May 2022. Search terms were related to the research question, including patients with NSCLC performing (a combination of) preoperative and/or postoperative aerobic exercise training, resistance exercise training, and breathing exercises in whom HRQoL and fatigue were assessed (see Supplementary file 1). No filters were applied for study design, and date, as this could eliminate useful articles.

Study selection

Randomized and non-randomized controlled trials in patients with NSCLC, aged ≥18 years, in which of ≥95% patients with NSCLC underwent elective surgery were included. Search results were combined and duplicates removed. Two reviewers (E.D. and R.R. until March 2018, M.V. and E.D. until May 2022) independently assessed titles, abstracts, and full texts regarding eligibility. Studies were included when patients were diagnosed with stage I-III NSCLC and participated in a physical exercise training intervention (aerobic exercise training, resistance exercise training, and/or breathing exercises) before and/or after surgery, that evaluated the effect on HRQoL and/or fatigue. Furthermore, only randomized controlled trials (RCT), cohort studies, or pilot studies written in English or Dutch were included. Studies were excluded when the physical exercise training intervention was not described or when studies were case reports or systematic reviews. Discrepancies between the three reviewers (M.V., E.D., and R.R.) were discussed until consensus.

Assessment of methodological quality

Three reviewers (M.V., E.D., and R.R.) independently assessed the methodological quality of included studies by means of the Cochrane risk of bias tool for randomized controlled trials II (RoB2) (18) and non- randomized controlled trials of interventions for non-RCTs (ROBINS-I) tool (19). The RoB2 reviews six domains and the ROBINS-I tool reviews seven domains. In the RoB2 tool, each item was rated as 'high', 'low', or 'some'. In the ROBINS-I tool, each item was rated as 'low', 'moderate', serious', 'critical', or 'no information'. Discrepancies

were resolved by consensus. If no consensus was reached, a fourth person acted as an adjudicator (M.J.).

Therapeutic quality

Therapeutic quality of exercise prehabilitation programs was assessed independently by the same reviewers (M.V., E.D.) using the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool (20). Using the i-CONTENT tool, the following eight items were substantively described: 1) patient selection, 2) dosage of the exercise program, 3) type of the exercise program, 4) qualified supervisor, 5) type and timing of outcome assessment, 6) safety of the exercise program, and 7) adherence to the exercise program. A score could be given as low or high risk for ineffectiveness on each of the seven items. An overall risk of ineffectiveness was calculated based on the weight per item that applies to estimate the content of an exercise prehabilitation and/or rehabilitation program. The used criteria for grading the overall risk of ineffectiveness are shown in Table 1.

Data extraction

Information collected included the name of the first author, year of publication, number of participants, study design, used exercise intervention, age of participants, comorbidity, type of surgery, type and dosage of the exercise program (e.g., frequency, intensity, time, and type), qualified supervisor of the exercise program, type and timing of the outcome assessment, adherence to the physical exercise training sessions, and safety of the exercise program. The outcome measures HRQoL and fatigue were presented as reported in the original studies. A meta-analysis was intended to be performed by use of the Review Manager (version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Table 1. Interpretation of therapeutic quality of exercise prehabilitation, rehabilitation program, or a combination of prehabilitation and rehabilitation for patients with NSCLC scheduled for surgery, based on the i-CONTENT tool (20).

	Low risk of ineffectiveness	High risk of ineffectiveness
1. Patient selection	A VO_{2peak} <20 mL/kg/min and/or a predicted postoperative VO_{2peak} <10 mL/kg/min for prehabilitation or other selection criteria with a clear rationale for prehabilitation and/or rehabilitation.	No preselection or selection (described).
2. Dosage of the exercise program	Intensity and duration of the physical exercise training program must be clearly described and/or based on existing literature relevant to the target population of operable patients with NSCLC and/or an adequate exercise test (e.g., steep ramp test, CPET).	Intensity and duration of the physical exercise training program is not (adequately) described and/or no physiological improvement can be expected due to a low training dosage (frequency, intensity, time).
3. Type of the exercise program	At least aerobic training with or without resistance training.	An intervention inconsistent with the goal of training therapy for patients undergoing surgery for lung cancer.
4. Qualified supervisor (if applicable)	Guidance of a physical therapist who is specialized in supervising adult clinical populations.	Supervision or guidance is not reported or supervision or guidance was provided by a professional other than a physical therapist.
5. Type and timing of outcome assessment	Follow-up for HRQoL and/or fatigue before and after exercise prehabilitation and/or before and after exercise rehabilitation.	Follow-up for HRQoL and/or fatigue was not clearly described.
6. Safety of the exercise program	Adverse events related to the exercise program are described and acceptable as would be expected in the studied population.	Adverse events related to the exercise program are higher than would be expected in the studied population or adverse events were not described.
7. Adherence to the exercise program	Adherence was determined separately for training frequency and deemed good in case of ≥80%.	Adherence to the training frequency was <80%.

Abbreviations: CPET=cardiopulmonary exercise test; HRQoL=health-related quality of life; i-CONTENT=the international Consensus on Therapeutic Exercise aNd Training; NSCLC=non-small cell lung cancer; VO_{2peak}=oxygen uptake at peak exercise.

Results

Study characteristics

Study Selection

The PubMed and EMBASE search provided respectively 380 and 232 hits, and 247 hits were found through other sources. After removal of duplicates, there were 756 unique hits. The reasons for exclusion based on title, abstract, and full-text analyses are described in the PRISMA flow diagram (Figure 1). After full-text review, thirteen studies (21-33) were included. Study designs included eight RCTs (22, 25, 26, 28-30, 32, 33) and five cohort studies (21, 23, 24, 27, 31). A total of 633 patients with lung cancer were included (98% NSCLC), consisting of patients with (pathological) stage I (33%), II (14%), III (4%), IV (1%), I-II (28%), I-IIIa (3%), or unknown stage of disease (15%). The sample size ranged from 9 to 101 participants, with an overall age-range between 44 and 79 years. Medical treatment consisted of surgery (99%) (21, 22, 24-33), whereas two studies included (palliative) chemotherapy and one study palliative chemoradiotherapy after surgery as well (23). General characteristics of the included studies are described in Table 2. A meta-analysis could not be performed due to a lack of accurate reporting of HRQoL and fatigue outcomes and heterogeneity of the content of physical exercise training programs in the included studies.

Exercise prehabilitation and rehabilitation

Patients followed exercise prehabilitation in eight studies (21-23, 25, 28-30, 33), exercise rehabilitation in three studies (26, 31, 32), and a combination of exercise prehabilitation and rehabilitation in two studies (24, 27). The postoperative follow-up time differed between 21 days (26), 30 days (21, 22, 25, 27-30, 33), two months (21, 24, 32), three months (22, 31), and six months (32), whereas one study did not describe the length of postoperative follow-up (23). Physical exercise training interventions included aerobic exercise training (21-33), resistance exercise training (21-24, 26, 27, 31, 33), and breathing exercises (22, 25, 26, 28-30, 32, 33). The intervention period for exercise prehabilitation lasted one week (25, 28-30), two weeks (33), or four weeks (23), whereas this was two weeks (26) or eight to twelve weeks (31, 32) for exercise rehabilitation and nine weeks for a combination of exercise prehabilitation and rehabilitation (24).The number of sessions varied from two or three times a day for breathing exercises (25, 31-33), three to five times a week for aerobic, resistance, and breathing exercises (21-24, 26), and six or seven times a week for aerobic and breathing exercises (27-30), with a training session duration between 30

and 90 minutes. All physical exercise training interventions were prescribed at a moderate or high training intensity. Supervision of the intervention was applied by physical therapists (21, 22, 24, 30, 31, 33), trained nurses (25, 29, 30), or a consult by phone (23). The content of exercise prehabilitation and/or rehabilitation programs is reported in Table 3.

Table 2. General characteristics of the included studies.

First author, year	• Number of participants, n • Study design • Intervention	• Stage of disease, n	Mean age, year, ±SD (range)
Exercise prehabilitation			
Coats (23), 2013	• 13 • Prospective cohort • Aerobic exercises, resistance exercises	I: 5 II: 4 IV: 2 Unknown: 2	59 ±9
Huang (25), 2017	• IG: 30, UC: 30 • RCT • Aerobic exercises, breathing exercises	I: IG: 16, UC: 17 II: IG: 10, UC: 11 III: IG: 4, UC: 2	IG: 63.0 ±8.7 UC: 63.6 ±6.5
Lai (28), 2016	• IG: 30, UC: 30 • RCT	I: IG: 16, UC: 18 II: IG: 10, UC: 10 III: IG: 3, UC: 2 IV: IG: 1, UC: 0	IG: 72.5, ±3.4 UC: 71.6, ±1.9 p=0.23
Lai (29), 2017	• IG: 51, UC: 50 • RCT • Aerobic exercises, breathing exercises	I: IG: 30, UC: 20 II: IG: 14, UC: 25 III: IG: 6, UC: 5 IV: IG: 1, UC: 0	IG: 63.8 ±8.2 UC: 64.6 ±6.6 p=0.58
Lai (30), 2019	• IG: 32, UC:32 • RCT • Aerobic exercises, breathing exercises	I: NR	IG: 64.2 ±6.8 UC: 63.4 ±8.2 p=0.67
Peddle (21), 2009	• 9 • Prospective cohort • Aerobic exercises, resistance exercises, breathing exercises	• NSCLC: 6 Kidney: 1 Hamartoma: 1 Spindle cell sarcoma: 1	64 ±8 p=NR
Sebio Garcia (22), 2017	IG: 10, UC: 12 RCT Aerobic exercises, resistance exercises, breathing exercises	NR	IG: 69.4 ±9.4 UC: 70.9 ±6.1

	Comorbidity, n	Type of surgery, n	Outcome measures
	• COPD: 5 (38%)	• Awaiting surgery: 10 • CT: 1 • Postoperative palliative CT: 1 • Postoperative palliative RT and CT: 1	• HRQoL • Fatigue
	• ASA score >3: IG: 3 (10%), UC: 2 (7%), p=1.00 • COPD: IG: 5 (17%), UC: 2 (7%), p=0.49	• VATS: IG: 17, UC: 9 • Open surgery: IG: 13, UC: 11	• HRQoL • Fatigue
	• ASA score: IG: 3 (10%) UC: 3 (10%) (p 1.00) • COPD: IG: 5 (17%) UC: 4 (13%), p=1.00	• VATS: IG: 21, UC: 20 • Open surgery: IG: 9, UC: 10	• HRQoL
	• Charlson comorbidity index 0-2: IG: 32 (63%), UC: 43 (86%), p=1.00 • Charlson comorbidity ≥3: IG 18 (35%), UC: 7 (14%), p=1.00	• VATS: IG: 32, UC: 34 • Open surgery: IG: 19, UC: 16	• HRQoL
	• Hypertension: IG: 8 (25%), UC: 3 (9%), p=1.00 • DM II: IG: 3 (9%), UC: 1 (3%), p=0.61 • COPD: IG: 9 (28%), UC: 11 (34%), p=0.61	• VATS	• HRQoL • Fatigue
	• COPD: 3 (33%) • Charlson comorbidity index >3: (100%)	• Lobectomy: 6 • Pneumonectomy: 1 • Wedge resection: 2	• HRQoL • Fatigue
	• Respiratory disease: IG: 7 (70%), UC: 4 (33%), p=NR • Cardiovascular disease: IG: 8 (80%), UC: 9 (75%), p=NR • DM II: IG: (10%), UC: 1 (8%), p=NR	• VATS	• HRQoL

Table 2. Continued

First author, year	• Number of participants, n • Study design • Intervention	• Stage of disease, n	Mean age, year, ±SD (range)
Tenconi (33), 2021	IG: 70, UC: 70 RCT Aerobic exercises, resistance exercises, breathing exercises, therapeutic education	I and II: NR	IG: 66.0 ±10.6 UC: 67.7 ±10.8 p=NR
Exercise rehabilitation			
Jastrzebski (26), 2018	• IG: 22, UC: 21 • RCT • Aerobic exercises, resistance exercises, breathing exercises	• NR	IG: 69.8 ±6.0 UC: 69.0 (±9.6) p=NR
Lu (31), 2020	• 16Prospective cohort • Aerobic exercises, resistance exercises, Tai-Chi	• I, II, and IIIa: NR	59 (44-63) p=NR
Messagi-Sartor (32), 2019	• IG: 16, UC: 21 • RCT • Aerobic exercises, breathing exercises	• I and II: NR	IG: 64.2 ±8.1 UC: 64.8 ±8.9 p>0.05
Combination of exercise prehabilitation and exercise rehabilitation			
Granger (24), 2018	• 37 • Prospective cohort • Aerobic exercises, resistance exercises	• I: 22 II: 5 III: 2 IV: 3 Unknown: 5	62.7 ±10.5 P=NR
Kadiri (27), 2019	• 31 • Prospective cohort • Aerobic exercises, resistance exercises	• NSCLC: 17 Stage IV NSCLC: 1 Other lung cancer type: 7 Benign: 6	64 ±12

Abbreviations: ASA=American Society of Anesthesiologists; DM=diabetes mellitus; COPD=chronic obstructive pulmonary disease; CT=chemotherapy; HRQoL=health-related quality of life; IG=intervention group; NR=not reported; NSCLC=non-small cell lung cancer; RATS=robot assisted thoracic surgery; RCT=randomized clinical trial; RT=radiotherapy; SD=standard deviation; UC=usual care group; VATS=video-assisted thoracic surgery.

	Comorbidity, n	Type of surgery, n	Outcome measures
	• NR	• VATS • RATS	• HRQoL
	• NR	• Lobectomy	• HRQoL
	• NR	• Lobectomy: 8 • Wedge resection: 3 • Segmentectomy: 2 • Lobectomy and wedge resection: 3 • Segmentectomy and wedge resection: 1	• HRQoL • Fatigue
	• COPD (27%): IG: NR, UC: NR	• VATS: IG: 2, UC: 1Thoracotomy: IG: 14 UC: 20	• HRQoL • Fatigue
	• NR	• Lobectomy: 20 • Wedge resection: 10 • Segmentectomy: 3 • Pneumonectomy: 2 • Other:2	• HRQoL • Fatigue
	• Ischemic heart disease: 2 (6%) • COPD: 9 (29%)	• NR	• HRQoL • Fatigue

Table 3. Content of exercise prehabilitation and rehabilitation according to the items of therapeutic quality.

First author, year	Patient selection	Type and dosage of the preoperative exercise program ▪ **(F:** Frequency**, I:** intensity**, T:** Time**, T:** Type**)**
Exercise prehabilitation		
Coats (23), 2013	45-80 years, SpO_2 <80% during CPET, comorbidities	▪ Based on: NR ▪ Program duration: 4 weeks ▪ **Aerobic exercises**: **F**: 3-5/week, **I**: 60-80% of CPET WR_{peak}, with reduction of intensity in case of a 1-10 Borg dyspnea scores ≥6, **T**: 30 min, **T**: Cycle ergometer **Resistance exercises**: ▪ **F**: 3-5/week, **I**: 2-3 kg, progressively increasing, **T**: 2 x 10-15 repetitions, **T**: gravity-resisted exercises
Huang (25), 2017	>70 years, BMI >30, COPD with heavy smoking history, FEV_1/FVC ratio ≤70%	▪ Based on: NR ▪ Program duration: 1 week ▪ **Aerobic exercises**: **F**: 7/week, **I**: Own speed and power, progressively increased the resistance range, **T**: 20 min, **T**: cross-trainer **Breathing exercises**: ▪ **F**: 2-3/day, **I**: NR, **T**: 15-20, **T**: threshold inspiratory muscle trainer
Lai (28), 2016	≥70 years	▪ Based on: NR ▪ Program duration: 1 week ▪ **Aerobic exercises**: ▪ **F**: 1/day, **I**: self-preferred speed and power, **T**: 30 min, **T**: cross-trainer
Lai (29) 2017	>75 years and >20 pack-year smoking history and BMI >30 kg/m^2 and $ppoFEV_1$ <60% and ppoDLCO <60% and COPD	▪ Based on: NR ▪ Program duration: 1 week ▪ **Aerobic exercises**: **F**: 1/day, **I**: not clearly reported, **T**: 30 min, **T**: cross-trainer **Breathing exercises**: **F**: 2-3/day, **I**: NR, **T**: 15-20 min, **T**: threshold inspiratory muscle trainer and manual deep breathing exercises
Lai (30) 2019	45-80 years and $ppoFEV_1$ <60%	▪ Based on: NR ▪ Program duration: 1 week ▪ **Aerobic exercises**: **F**: 7/week, **I**: NR, **T**: 30 min, **T**: cross-trainer **Breathing exercises**: **F**: 3/day, **I**: NR, **T**: 20 breaths/session, **T**: threshold inspiratory muscle trainer

	Qualified supervisor	▪ Primary outcome of the study ▪ Type and timing of outcome assessment	Safety
	Consult by phone by the researchers	▪ HRQoL ▪ HRQoL and fatigue: at baseline and after four weeks (before surgery)	No adverse events
	Trained nurses	▪ Postoperative pulmonary complications ▪ HRQoL and fatigue: at baseline and after one week (before surgery)	NR
	Aerobic exercises supervised by a physical therapist	▪ Change in 6MWD ▪ HRQoL: at baseline and after one week (before surgery)	NR
	Physical therapist dedicated to thoracic surgery patients	▪ Postoperative pulmonary complications ▪ HRQoL: at baseline and after one week (before surgery)	No adverse events
	Aerobic exercises supervised by a physical therapist, respiratory exercises supervised by a trained nurse	▪ Postoperative pulmonary complications ▪ HRQoL and fatigue: at baseline and after one week (before surgery)	No adverse events

First author, year	Patient selection	Type and dosage of the preoperative exercise program ▪ **(F:** Frequency**, I:** intensity**, T:** Time**, T:** Type**)**
Peddle (21), 2009	≥18 years	▪ Based on: NR ▪ Program duration: NR ▪ **Aerobic exercises**: **F**: 5/week, **I-T**: week 1: increasing duration and intensity from 20 min at 60% of CPET VO_{2peak} to 30 min at 65% of CPET VO_{2peak}, weeks 2 and 3: 4 sessions of 25-30 minutes at 60-65% of CPET VO_{2peak} and 1 session of 20 minutes at the ventilatory anaerobic threshold. After week 3: 3 sessions of 60-65% of CPET VO_{2peak} for 30-35 minutes, 1 threshold workout, and 1 interval workout per week, **T**: cycle ergometer
Sebio Garcia (22), 2017	≥18 years, at least one of the following: (a) FEV_1 ≤80% of predicted value or BMI ≥30 or age ≥75 years or two or more co-morbidities identified in the Colinet Comorbidity Score	▪ Based on: (34) ▪ Program duration: NR ▪ **Aerobic exercises**: **F**: 3-5/week, **I**: interval training (one minute at high intensity (80% of CPET WR_{peak}) plus four minutes of active rest (performed at 50% of CPET WR_{peak}), **T**: 30 min, **T**: cycling **Resistance exercises**: **F**: 3-5/week, **I**: 25 repetition maximum test, **T**: 3 × 15 repetitions, **T**: six exercises using Thera bands and body mass for the large muscle groups **Breathing exercises**: **F**: 2/day, **I**: 80% of vital capacity, **T**: 6 cycles of 5 repetitions, **T**: incentive spirometry coach2
Tenconi (33), 2021	All patients	▪ Based on: (35) ▪ Program duration: 2-3 weeks ▪ **Aerobic exercises**: **F**: 2-3/week, **I**: NR, **T**: 30-40 minutes, **T**: at the outpatient clinic: cycling; home-based: walking **Resistance exercises**: **F**: 2-3/week, **I**: maximal load (previously determined with the 10-repetition maximum test), **T**: 2-3 sets of 10 repetitions, **T**: lower limbs (extensor muscle group), upper limbs (biceps, triceps, deltoids, latissimus dorsi, pectoralis), and abdominal wall **Breathing exercises**: **F**: 1/day, **I**: ≥30% of maximal predicted inspiratory pressure and adapted to the patient's tolerance, **T**: 15-30 minutes, **T**: threshold inspiratory muscle trainer

	Qualified supervisor	▪ **Primary outcome of the study** ▪ **Type and timing of outcome assessment**	Safety
	Exercise physiologist	▪ HRQoL and fatigue ▪ HRQoL and fatigue: at baseline and after prehabilitation (before surgery)	No adverse events
	Physical therapist	▪ HRQoL ▪ HRQoL: at baseline and after prehabilitation (before surgery)	No adverse events
	Physical therapist	▪ Change in 6MWD ▪ HRQoL: at baseline and 6 months after surgery	Adverse events: IG: 2 (7%): mild, 17 (55%): moderate, 11 (37%): severe, UC: 2 (4%): mild, 37 (69%): moderate, 15 (28%): severe

First author, year	Patient selection	Type and dosage of the preoperative exercise program ▪ **(F:** Frequency**, I:** intensity**, T:** Time**, T:** Type**)**
Exercise rehabilitation		
Jastrzebski (26), 2018	ECOG 0-1	▪ Based on: NR ▪ Program duration: 2 weeks, 10 (±4) weeks after surgery **Aerobic exercises**: **F**: 5/week, **I**: 30-80% of HR_{peak}, **T**: 20-30 min, **T**: cycle ergometer or treadmill **Resistance exercises**: **F**: 5/week, **I**: 40-70% of 1RM, **T**: NR, **T**: Nordic walking **Breathing exercises**: **F**: 5/week, **I**: NR, **T**: 30, **T**: breathing, a prolonged exhalation exercise, and chest percussion
Lu (31), 2020	18-75 years, ECOG 0-2	▪ Based on: NR ▪ Program duration: 12 weeks, 6-12 weeks after surgery ▪ **Aerobic exercises**: **F**: 2/week, **I**: 15 min on 80% of baseline mean walk speed on the 6MWT and increased at moderate intensity (Borg-score 4-10, somewhat hard), **T**: 90 min, **T**: treadmill **Resistance exercises**: **F**: NR, **I**: Borg-score 4-10, somewhat hard, **T**: 3 sets of 8-15 repetitions, **T**: major limb movement
Messagi-Sartor (32), 2019	<80 year	▪ Based on: NR ▪ Program duration: 8 weeks, 6 weeks after surgery ▪ **Aerobic exercises**: **F**: 3/week, **I**: 60% of baseline WR_{peak} on the CPET, **T**: 30 min, **T**: cycle ergometer **Breathing exercises**: **F**: 3/week, 2/day, **I**: 50% of PI_{max} and PE_{max} and adjusted weekly by 10 cm cm H_2O, **T**: 5 sets of 10 repetitions, **T**: inspiratory and expiratory muscle trainer
Combination of exercise prehabilitation and rehabilitation		
Granger (24), 2018	≥18 years	▪ Based on: NR ▪ Program duration: 9 weeks: ≤7 days preoperative and until 8 weeks postoperative ▪ **Aerobic exercises**: **F**: 5/week, **I**: moderate, **T**: 30 min, **T**: walking **Resistance exercises**: **F**: 3/week, **I**: moderate (1-10 Borg dyspnea scale 4-6, somewhat hard), **T**: 2 sets of 10-15 repetitions, **T**: major muscle groups

	Qualified supervisor	▪ Primary outcome of the study ▪ Type and timing of outcome assessment	Safety
	NR	▪ Change in 6MWD and HRQoL ▪ HRQoL: at the first day of exercise rehabilitation and after exercise rehabilitation at day 21	Minor adverse events: arthritis: n=1, knee pain: n=2
	Specialized physical therapist	▪ Feasibility and safety of delivering rehabilitation ▪ HRQoL and fatigue: at the start of exercise prehabilitation and after exercise rehabilitation at 12 weeks	No adverse events
	Physical therapist	▪ HRQoL ▪ HRQoL and fatigue: at the start of exercise rehabilitation and after exercise rehabilitation at 8 weeks	No adverse events
	Specialized physical therapist	▪ Feasibility and safety of delivering prehabilitation and rehabilitation ▪ HRQoL and fatigue: at baseline before prehabilitation (before surgery) and at 8 weeks after rehabilitation (after surgery)	No adverse events

First author, year	Patient selection	Type and dosage of the preoperative exercise program ▪ **(F:** Frequency**, I:** intensity**, T:** Time**, T:** Type**)**
Kadiri (27), 2019	All patients	▪ Based on: (36) ▪ Program duration: NR ▪ **Aerobic and** **F**: 1/day, **I**: at a midly short of breath, **T**: at least 20 min, **T**: walking, swimming, exercise classes or cycling **Resistance exercises**: **F**: 1/day, **I**: heart rate >60% of the age-predicted maximum, **T**: 10 × 3 min per exercise, **T**: upper and lower limb

Abbreviations: 1RM=one-repetition maximum; 6MWT=six-minute walk test; 6MWD=six-minute walk distance; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CPET=cardiopulmonary exercise test; IG=intervention group; HR_{peak}=heart rate at peak exercise; HRQoL=health-related quality of life; ECOG=Eastern cooperative oncology group; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; NR=not reported; PI_{max}=maximal inspiratory mouth pressure; PE_{max}=maximal expiratory mouth pressure; ppoDLCO=predicted postoperative diffusing capacity of the lung for carbon monoxide; ppoFEV_1=predicted postoperative forced expiratory volume in one second; SpO_2=peripheral oxygen saturation; UC=usual care; VO_{2peak}=oxygen uptake at peak exercise; WR_{peak}=work rate at peak exercise.

	Qualified supervisor	▪ Primary outcome of the study ▪ Type and timing of outcome assessment	Safety
	Physical therapist	▪ Postoperative pulmonary complications and length of hospital stay ▪ HRQoL and fatigue: at baseline (before surgery) and 6 weeks after rehabilitation (after surgery)	No adverse events

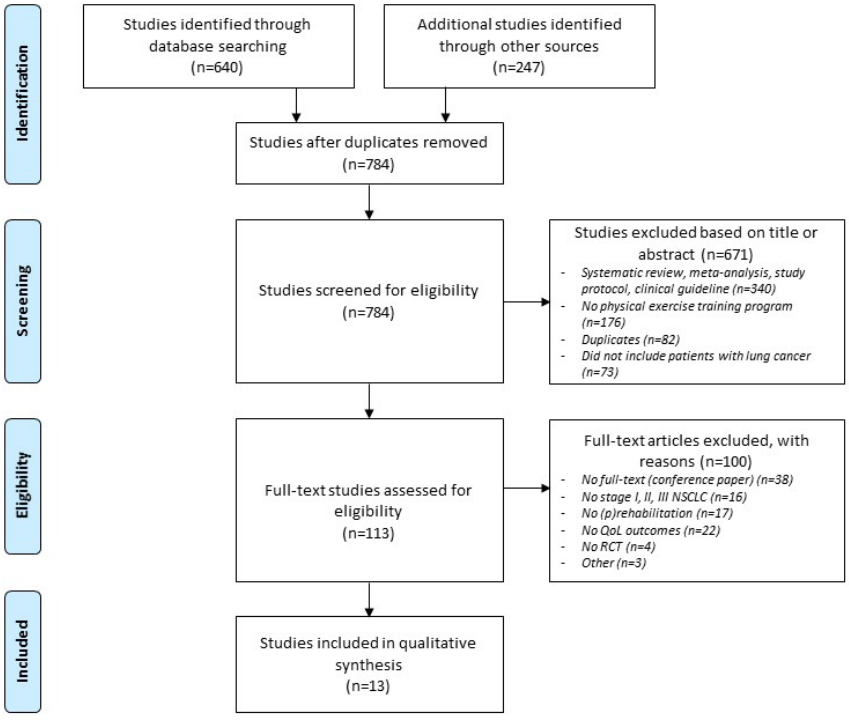

Figure 1. PRISMA flow diagram displaying the selection of studies and reasons for exclusion.

Table 4. Results of methodological quality according to the Cochrane risk of bias tool and the Robins-1 tool, and therapeutic quality according to the i- CONTENT tool.

Methodological quality (Cochrane risk of bias tool)				
First author	**Randomization process**	**Assignment to intended interventions**	**Adherence to intended interventions**	**Missing outcome data**
Exercise prehabilitation				
Huang (25)	Low	Low	Low	Low
Lai (28)	Some	Low	High	Low
Lai (29)	Low	High	High	Low
Lai (30)	Some	Some	High	Low
Sebio Garcia (22)	Some	High	Low	High
Tenconi (33)	Some	Some	Some	Low
Exercise rehabilitation				
Jastrzebski (26)	High	Low	High	high
Messagi-Sartor (32)	Low	Low	High	Low

Methodological quality (Robins-1 tool)				
First author	**Confounding**	**Selection**	**Intervention classification**	**Deviation from interventions**
Exercise prehabilitation				
Coats (23)	Moderate	Low	Moderate	Low
Peddle (21)	Moderate	Moderate	Moderate	Low
Exercise rehabilitation				
Lu (31)	Moderate	Moderate	Moderate	Low
Combination of exercise prehabilitation and rehabilitation				
Granger (24)	Moderate	Moderate	Moderate	Low
Kadiri (27)	Moderate	No information	Moderate	Low

Therapeutic quality (i-CONTENT scale)[a]				
First author	**1. Patient selection**	**2. Dosage of the exercise program**	**3. Type of the exercise program**	**4. Qualified supervisor (if applicable)**
Exercise prehabilitation				
Coats (23)	High	High	High	Low
Huang (25)	Low	High	Low	Low
Lai (28)	High	High	Low	Low
Lai (29)	Low	High	Low	Low

	Measurement of the outcome	Selection of the reported result	Overall risk of bias
	Low	Low	Low
	Low	Low	Some
	Low	Low	Low
	Low	Low	Some
	Low	Low	Some
	Low	Some	Some
	High	High	High
	Low	Low	Low

	Missing outcome data	Measurement of outcome	Selection of reported results	Overall risk of bias
	Low	Low	Low	Moderate
	Low	Low	Moderate	Serious
	Low	Low	Low	Moderate
	Low	Low	Low	Moderate
	Low	Low	Low	Moderate

	5. Type and timing of outcome assessment	6. Safety of the exercise program	7. Adherence to the exercise program	Overall risk of ineffectiveness
	High	High	High	High
	Low	Low	Low	Some
	High	Low	Low	High
	High	Low	Low	Some

Table 4. Continued

First author	1. Patient selection	2. Dosage of the exercise program	3. Type of the exercise program	4. Qualified supervisor (if applicable)
Lai (30)	High	High	Low	Low
Peddle (21)	High	High	High	High
Sebio Garcia (22)	High	High	High	High
Tenconi (33)	High	Low	Low	Low
Exercise rehabilitation				
Jastrzebski (26)	High	High	High	Low
Lu (31)	High	High	Low	Low
Messagi-Sartor (32)	Low	Low	Low	Low
Combination of exercise prehabilitation and exercise rehabilitation				
Granger (24)	High	High	High	High
Kadiri (27)	Low	High	High	High

Methodological quality: low=low risk of bias, some= some concerns; high=high risk of bias, moderate=moderate risk of bias, serious=serious risk of bias.**Therapeutic quality**: low=low risk of ineffectiveness; high=high risk of ineffectiveness.[a]: Overall risk of ineffectiveness: Low risk of ineffectiveness: items 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND ≥1 of the items 4, 5, 7 scored a "low risk of ineffectiveness"Some risk of ineffectiveness: items 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND 1 of the items 4, 5, 7 scored a "low risk of ineffectiveness" OR 3 items with a score of "low risk of ineffectiveness" on item 1, 2, 3, and 7 AND ≥1 of the items 4, 5, 7 scored a "low risk of ineffectiveness"High risk of ineffectiveness: ≤2 items with a score of "low risk of ineffectiveness" on item 1, 2, 3, and 7

	5. Type and timing of outcome assessment	6. Safety of the exercise program	7. Adherence to the exercise program	Overall risk of ineffectiveness
	High	Low	Low	High
	Low	High	High	High
	High	High	Low	High
	Low	Low	Low	Some
	High	Low	Low	High
	High	Low	Low	High
	Low	Low	High	Some
	High	High	High	High
	High	Low	High	High

Table 5. Effects of exercise prehabilitation and rehabilitation on health-related quality of life and fatigue.

Author, year	▪ Risk of bias ▪ Risk of ineffectiveness	Exercise intervention		
		Aerobic exercises	Resistance exercises	Breathing exercises
Exercise prehabilitation				
Coats (23), 2013, Prospective cohort	▪ Low ▪ High			
Huang (25), 2017, RCT	▪ Low ▪ Some			
Lai (28), 2016, RCT	▪ Some ▪ High			
Lai (29) 2017, RCT	▪ Low ▪ Some			
Lai (30) 2019, RCT	▪ Some ▪ High			
Peddle (21), 2009, prospective observational	▪ Some ▪ High			
Sebio Garcia (22), 2017, RCT	▪ Some ▪ High			

Outcomes on quality of life and/or fatigue	▪ **Non-participation in the study** ▪ **Drop-outs** ▪ **Training adherence**
HRQoL: EORTC-QLQ-C30 No statistically significant improvement **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically but a clinically significant reduction	▪ n=20 (35%) (n=6 lack of time, n=6 not specified, n=5 lack of interest about engaging in a research project, n=3 high level of anxiety, n=3 scheduled surgery within one week of consent, n=1 clinical deterioration) ▪ n=3 (n=2 clinical deteriorations, n=1 psychological distress) ▪ 125% for aerobic and 83% for resistance exercise
HRQoL: EORTC-QLQ-C30 A statistically significant improvement in the IG compared to UC, **p=0.04** **Fatigue: fatigue index** No statistically significant reduction in the IG compared to UC	▪ NR ▪ IG: n=3, (n=1 acute COPD exacerbation, n=2 worsening knee pain, n=2 loss of motivation), UC: n=0 ▪ 90%
HRQoL: EORTC-QLQ-C30 No statistically significant increase was observed in the IG compared to UC	▪ n=22 (refuse to participate) ▪ IG: n=4 (n=1 lack of perceived benefit, n=1 knee pain, n=2 unknown) ▪ NR
HRQoL: EORTC QLQ-C30 No statistically significant increase was observed in the IG compared to UC	▪ n=24 (refuse to participate) ▪ IG: n=6 (n=6 did not complete the follow-up assessment) ▪ NR
HRQoL: EORTC QLQ-C30 A statistically significant improvement in emotional function in the IG compared to UC, **p<0.01** **Fatigue: fatigue index** No statistically significant reduction in the IG compared to UC	▪ n=22 (refuse to participate) ▪ IG: n=2 (n=2 exercise intensity too high) ▪ NR
HRQoL: FACT-L A statistically significant improvement in the lung cancer subscale after prehabilitation compared with baseline, **p<0.01** **Fatigue: FACT subscale for fatigue** No statistically significant reduction after prehabilitation compared with baseline	▪ n=13 (n=6 lack of interest, n=2 already exercising, n= 2 work, n=2 no transportation, n=1= languages) ▪ n=3 (n=1 surgical complication, n=2 death) ▪ Mean 88%
HRQoL: SF-36 A statistically significant improvement in the physical component summary in the IG compared to the UC, **p<0.01**	▪ n=30 (n=14 surgery in 1 week, n=16 declined to participate), n=2 after randomization in UC (referred to physical therapy) ▪ IG: n=1 (n=1 clinical deterioration), UC: n=2 (n=2 lost to follow-up) ▪ Median of 16 sessions (range 8-25): mean 50%

Table 5. Continued

Tenconi (33), 2021, RCT	▪ Some ▪ Some				
Exercise rehabilitation					
Jastrzebski (26), 2018, RCT	▪ High ▪ High				
Lu (31), 2020 prospective cohort	▪ High ▪ High				
Messagi-Sartor (32), 2019, RCT	▪ Low ▪ Some				
Combination of exercise prehabilitation and exercise rehabilitation					
Granger (24), 2018, prospective cohort	▪ Some ▪ High				
Kadiri (27), 2019, prospective cohort	▪ Low ▪ High				

Abbreviations: EORTC-QLQ-30=European for and of QLQ-C30; FACT=functional assessment of cancer therapy; FACT-L=functional assessment of cancer therapy of the lung; HRQoL=health-related quality of life; IG=intervention group; NR=not reported; NS=not significant; UC=usual care group

	HRQoL: SF-12 No statistically significant improvement in the IG compared to UC	▪ NR ▪ IG: n=25 (n=6 adjuvant treatment, n=5 disease progression, n=5 non primary lung neoplasm, n=8 lost to follow-up, n=1 other). UC: n=30 (n=15 adjuvant treatment, n=2 disease progression, n=3 non primary lung neoplasm, n=9 lost to follow-up, n=1 other) ▪ 90% of the patients had accomplished 80% session adherence
	HRQoL: SF-36 A statistically significant improvement within the IG and/or UC on the subscales: Pain: IG: **p=0.04**, UC: **p<0.01** Physical functioning: IG: **p=0.02** Physical health: IG: **0.05** General health: IG: **p<0.01** Vitality: UC: **p=0.02** Mental health: UC: **p<0.01**	▪ NR ▪ No dropouts ▪ NR
	HRQoL: EORTC QLQ-C30 A statistically significant improvement on emotional function compared with before rehabilitation**, p<0.01** **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction compared with before rehabilitation	▪ n=61 (n=23 travel to far, n=22 busy with personal affairs, n=9 still hospital inpatient, n=3 busy with work, n=3 incorrect phone number, n=1 do not want to participate) ▪ n=1 (unable to contact) ▪ 47% of the participants attended at least 70% of the scheduled supervised exercise sessions, total attendance rate was 53% (181/340 possible supervised sessions).
	HRQoL: EORTC-QLQ-30 No statistically significant difference between the IG and UC A clinically significant improvement within the IG and UC **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction between the IG and UC	▪ n=19 (n=2 postoperative complications, n=4 no preoperative assessment, n=6 declined to participate, n=7 other reasons) ▪ IG: n=5 (n=3 declined participations, n= 2 chemotherapy), UC: n=8 (n=5 declined participations, n=2 chemotherapy, n=1 postoperative complications) ▪ >80% completion
	HRQoL: EORTC-QLQ-30 No statistically significance improvement **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction	▪ n=4 ▪ n=10 (n=10 did not complete the follow-up assessment) ▪ Median of 4 sessions
	HRQoL: EORTC-QLQ-30 A statistically significant improvement at 5 months postoperative compared with preoperative **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction	▪ NR ▪ Before surgery 32%, after surgery 79% (pain, lack of motivation and generally feeling unwell) ▪ Median of 4 (range 1-7) sessions a week. 32% did not use the app postoperative

Therapeutic quality

Results of the therapeutic quality assessment of the physical exercise training programs are depicted in Table 4. Four studies (25, 29, 32, 33) (38%) scored some risk of ineffectiveness and nine studies (21-24, 26-28, 30, 31) (62%) a high risk of ineffectiveness. Often, physical exercise training programs scored a high risk of ineffectiveness on the items patient selection (n=9), description of the dosage of the physical exercise training program (n=10), type and timing of the outcome assessment (n=6), and low adherence to the program (n=5).

Health-related quality of life and fatigue

Effects of exercise prehabilitation and/or rehabilitation on HRQoL and fatigue are shown in Table 5. HRQoL was the primary outcome in four studies (21-23, 32) and a secondary outcome in nine studies (24-31, 33). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ- C30) questionnaire for HRQoL was used in nine studies (23-25, 27-32), whereas the short form 36 questionnaire (SF-36) was used in two studies (22, 26), and both the functional assessment of cancer therapy-lung (FACT-L) (21) and short-form 12 questionnaire (SF-12) in one study (33). Fatigue was measured with the EORTC QLQ- C30 subscale for fatigue in five studies (23, 24, 27, 31, 32), the fatigue index in two studies (25, 30), and the FACT-L subscale for fatigue in one study (21).

Exercise prehabilitation

Six RCT's (22, 25, 28-30, 33) and two prospective cohort studies (21, 23) investigated the effect of exercise prehabilitation on HRQoL. One study (21) showed that exercise prehabilitation significantly improved HRQoL on the EORTC-QLQ-C30 lung cancer subscale. Other studies found a significantly higher overall HRQoL measured with the EORTC-QLQ-C30 (25), emotional function on the EORTC-QLQ-C30 (30), and a significant improvement in the physical component summary on the SF-36 (22) after exercise prehabilitation as compared to the usual care group. Fatigue was measured in four studies (21, 23, 25, 30) with the subscale fatigue on the EORTC QLQ-C30, the fatigue index in two studies (25, 30), and with the FACT-L subscale for fatigue in one study (21), in which there was no statistically significant effect of exercise prehabilitation on fatigue.

Exercise rehabilitation

Two RCTs (26, 32) and one prospective cohort study (31) investigated the effect of exercise rehabilitation on HRQoL. The subscales 'global quality of

life' and 'emotional functioning' of the EORTC-QLQ-C30 significantly improved during exercise rehabilitation (31). These subscales improved in the exercise rehabilitation group compared to usual care in one study (26). Fatigue was measured in two studies by the EORTC QLQ-C30 (31, 32), in which there was no statistically significant effect of exercise rehabilitation on fatigue.

Combination of exercise prehabilitation and rehabilitation
In two prospective cohort studies (24, 27), HRQoL was measured with the EORTC-QLQ-C30. One of these studies (27) showed an improvement in HRQoL five months after combined exercise prehabilitation and rehabilitation compared to preoperative HRQoL. Fatigue was measured in both studies by the EORTC QLQ-C30 (24, 27) in which there was no statistically significant effect of exercise prehabilitation and rehabilitation on fatigue.

Discussion

The aim of this systematic review was to appraise current available evidence regarding the effects of exercise prehabilitation and rehabilitation on perceived HRQoL and fatigue in patients undergoing surgery for NSCLC. Half of studies that applied exercise prehabilitation or exercise rehabilitation reported small statistically significant improvements in HRQoL, but in most studies this only concerned different subscales of the used questionnaire which make the clinical usefulness of the changes unclear. None of the studies reported a statistically significant decrease in fatigue. Due to the large heterogeneity of physical exercise training programs, the short intervention duration in some studies, the generally high risk of bias concerning methodological quality, and the high risk of ineffectiveness regarding therapeutic quality in most studies, the results of this systematic review must be interpreted with caution.

This is the first systematic review that examined the effect of exercise prehabilitation and/or rehabilitation on postoperative HRQoL and fatigue thereby accounting for the quality of the exercise intervention (i-CONTENT tool). Regardless of the risk of ineffectiveness score for the applied prehabilitation and/or rehabilitation programs, there was an inconsistent effect of exercise prehabilitation and/or rehabilitation on HRQoL. Heterogeneity across the items of the i-CONTENT tool, along with the risk of bias regarding HRQoL and fatigue, influences the certainty ratings supporting the efficacy and effectiveness of exercise prehabilitation and/or rehabilitation. Previous

systematic reviews also reported a minimal improvement in HRQoL after prehabilitation and/or rehabilitation in patients with NSCLC undergoing surgery (15-17), which is possibly caused by the limited number and the low quality of evidence of included trials. In addition, in this systematic review, the duration of the exercise program was only one week in four studies (25, 28-30) and two weeks in two studies (26, 33). In a previous systematic review (37) in which exercise training was performed by patients with NSCLC undergoing surgery, a duration of an exercise program of at least four weeks was recommended to improve HRQoL. Thus, those programs with a duration of merely one or two weeks might not be expected to improve HRQoL. In a previous study (38), it was reported that regained muscle mass associated with aging improved a patient's performance of activities of daily living, reduced cancer-related fatigue, and improved HRQoL after sixteen-weeks whole-body resistance training. Moreover, in a qualitative study (39) among patients with NSCLC, benefits of exercise rehabilitation were reported by participants such as improvements in muscle strength, aerobic fitness, and motivation, making sense of a goal that prevented boredom, feeling more prepared for future challenges, and improved ability to manage surgery-related symptoms. Most participants reported the exercise program to be feasible and to appreciate the individualized prescription and monitoring support from experienced physical therapists, as well as partly supervised exercises in a home-based setting (39). Furthermore, fatigue is one of the most frequently mentioned barriers to adherence to exercise interventions among patients with lung cancer (17, 40). Exercises or tools decreasing these symptoms are very important for both patients and clinicians to incorporate as goals in the exercise intervention (17, 40).

Strengths and limitations

A strength of this study was the use of i-CONTENT tool, leading to a more appropriate evaluation of the quality of the interventions next to methodological quality applied despite the heterogeneity of the used exercise programs (41, 42). Regarding study limitations, there was a large heterogeneity of physical exercise training programs and measures used to assess HRQoL (domains). Furthermore, there was a high risk of ineffectiveness of the exercise interventions (e.g., inadequate description or lack of supervision, personalization, objective monitoring of training intensity, monitoring of adherence) and a high risk of bias in many studies. The generally poor methodological and therapeutic quality of the included studies was mainly due to the non-description or incomplete description of the population, as well as the representativeness of the exercise intervention (e.g., frequency, intensity, type,

time). There was considerable variation between studies concerning the type of surgery and the used outcome variables of HRQoL and fatigue questionnaires. This variation may have influenced the effects of exercise prehabilitation and/or rehabilitation on HRQoL and fatigue. Moreover, it should be mentioned that three studies took place at the same hospital in China (25, 28, 29). This could have influenced expectations of researchers, physical therapists, (part of the) patients, methods, collection, and data analyses. As these three studies did not mention this potential overlap, it is important to raise awareness regarding both publication and reporting bias across these studies.

As mentioned earlier, the results of this systematic review must be interpreted with caution because of the heterogeneity of exercise programs and measures used to assess HRQoL and HRQoL domains, the high risk of ineffectiveness of the exercise interventions (e.g., caused by not describing or inserting of supervision, personalization, objective monitoring of exercise intervention and exercise intensity, training adherence), and the high risk of bias in many studies. Further research is required to investigate how to sustain positive effects of exercise over time and to determine essential attributes of exercise (mode, intensity, frequency, duration, timing) in patients with NSCLC, for an optimal effect on HRQoL and its subdomains.

Conclusion

There was an inconsistent effect of exercise prehabilitation and exercise rehabilitation on HRQoL in patients with NSCLC undergoing surgery, and no effect on fatigue. Due to the high risk of ineffectiveness of the exercise interventions, especially in case of a short duration of an exercise intervention, this systematic review cannot provide a definitive conclusion regarding the best form of exercises to improve HRQoL and reduce fatigue. It is recommended to investigate the impact of an exercise prehabilitation and/or rehabilitation program with high methodological and therapeutic quality (e.g., a duration of at least four weeks and a moderate- or high-exercise intensity) on HRQoL and fatigue in patients with NSCLC undergoing surgery in larger studies.

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Supplementary file

Supplementary file 1. Combinations of text words of the literature search according to the PICO-structure.

Databases [a]	Population	Intervention	Outcome
Embase, PubMed, Cinahl	("lung neoplasms"[MeSH Terms] OR lung cancer[tiab]) OR ("carcinoma, non-small-cell lung"[MeSH Terms] OR non-small-cell lung[tiab] OR nsclc[tiab])	((("resistance exercise"[MeSH Terms] OR "resistance exercise"[tiab] OR "strength exercise"[tiab]) OR (((("exercise therapy"[MeSH Terms] OR exercise therapy[tiab]) OR ("exercise"[MeSH Terms] OR exercise[tiab])) OR physical activity[tiab]) OR physical therapy[tiab]) OR (aerobic exercise[tiab] OR aerobic exercise[tiab]))) OR (("respiratory therapy"[MeSH Terms] OR respiratory therapy[tiab]) OR respiratory exercise[tiab]))	("quality of life"[MeSH Terms] OR quality of life[tiab]

[a]: search presented for PubMed only: the search strategy has been adjusted for searching in the other databases.

'I would have liked to do physical exercises in a group guided by the physical therapist, because in a group you can talk to other patients and it helps to stay motivated.'

-Patient who underwent surgery for NSCLC-

Chapter 8

A qualitative stakeholder analysis of beliefs, facilitators, and barriers for a feasible prehabilitation program before lung cancer surgery

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Abstract

Background In order to develop a feasible prehabilitation program before surgery of NSCLC, this study aimed to gain insight into beliefs, facilitators, and barriers of 1) healthcare professionals to refer patients to a prehabilitation program, 2) patients to participate in and adhere to a prehabilitation program, and 3) informal caregivers to support their loved ones.

Methods Semi-structured interviews were conducted with healthcare professionals, patients who underwent surgery for NSCLC, and their informal caregivers. The capability, opportunity, and motivation for behavior-model (COM-B) guided the development of the interview questions. Results were analyzed thematically.

Results The interviews were conducted with twelve healthcare professionals, seventeen patients, and sixteen informal caregivers. Four main themes were identified: 1) content of prehabilitation and referral, 2) organizational factors, 3) personal factors for participation, and 4) environmental factors. Healthcare professionals mentioned that multiple professionals should facilitate the referral of patients to prehabilitation within primary and secondary healthcare involved in prehabilitation, considering the short preoperative period. Patients did not know that a better preoperative physical fitness and nutritional status would make a difference in the risk of postoperative complications. Patients indicated that they want to receive information about the aim and possibilities of prehabilitation. Most patients preferred a group-based physical exercise training program organized in their living context in primary care. Informal caregivers could support their loved one when prehabilitation takes place by doing exercises together.

Conclusion A prehabilitation program should be started as soon as possible after the diagnosis of lung cancer. Receiving information about the purpose and effects of prehabilitation in a consult with a physician seems crucial to patients and informal caregivers to be involved in prehabilitation. Support of loved ones in the patient's own living context is essential for adherence to a prehabilitation program.

Introduction

Lung cancer has increased significantly in recent decades, contributing to approximately 13% of all cancer diagnoses worldwide (1). Non-small cell lung cancer (NSCLC) constitutes the majority (85%) of lung cancers (2). The primary curative treatment for patients with early-stage NSCLC is surgical tumor resection (3-5). Despite advances in surgery, such as video-assisted thoracic surgery, the incidence of postoperative complications remains high and occurs in 35% of patients with NSCLC (6). Research has shown that the risk for postoperative complications is higher in patients over 70 years with a low expiratory volume in one second (FEV_1), a poor preoperative aerobic fitness, tobacco-related comorbidity, cognitive impairment, and/or comorbidities (e.g., chronic obstructive pulmonary diseases, cardiovascular diseases, and/or diabetes mellitus) (7-9). Postoperative complications are associated with a delayed or incomplete recovery of physical fitness levels after surgery (10).

A multimodal prehabilitation program, including aerobic, resistance, and/or inspiratory muscle training, nutritional advice, and/or support for smoking-cessation, can reduce the risk of postoperative complications after surgery in patients with NSCLC (8, 11, 12). Moreover, prehabilitation can decrease the length of hospital stay and facilitate postoperative recovery (12-14). Despite the effectiveness of prehabilitation, it is not yet part of usual care. Previous studies in patients with NSCLC have shown that the ability to participate in a prehabilitation program is low (between 28% and 56% (15)) and that program adherence is only moderate (between 53% and 73% (16)). In addition, to improve participation and adherence in prehabilitation, it is important to gain insight into preferences and possible facilitators and barriers of a prehabilitation program among patients, their informal caregivers, and healthcare professionals.

Surgeons see benefits of prehabilitation in order to decrease the risk of postoperative complications in patients with NSCLC and are willing to delay surgery with two weeks; however, it is unclear for surgeons when and where to refer to for prehabilitation (17). Research in patients with colorectal cancer has shown that, next to ensuring a therapeutically valid program content, it is important to identify the barriers and preferences of patients in order to develop a feasible and (cost-)effective prehabilitation program in the proper context (18, 19). Therefore, this study aimed to gain insight into beliefs, facilitators, and barriers of 1) healthcare professionals to refer patients to a

prehabilitation program, 2) patients with NSCLC to participate in and adhere to a prehabilitation program, and 3) informal caregivers to support their loved ones in prehabilitation.

Methods

Study design

A qualitative interview study was performed to develop a feasible prehabilitation program, including physical exercise training, nutritional and psychological support, and/or coaching towards lifestyle changes for patients with operable NSCLC. Healthcare professionals, patients, and informal caregivers were interviewed to explore beliefs, facilitators, and barriers to prehabilitation. Included patients did not perform prehabilitation but had the experience of a perioperative period and could reflect on facilitating factors and barriers. In order to gain a respectable representation of beliefs, no exclusion criteria were set. This study was approved by the Medical Research Ethics Committee Zuyderland (reference number: 2021-2879). All participants were recruited between September 2021 and February 2022.

Study population

Healthcare professionals

Healthcare professionals of disciplines involved in the treatment of patients with NSCLC with experience in prehabilitation of patients with cancer varied from pulmonologists, rehabilitation physicians, pulmonary nurses, psychologists, dieticians, and physical therapists. Names of these specialists were provided by the researcher (MV) of VieCuri Medical Center, Venlo, The Netherlands, and a pulmonologist (GB) of the Zuyderland Medical Center, Heerlen, The Netherlands.

Healthcare professionals were informed and invited to participate in the study by e-mail by the researcher. After e-mail consent, the researcher contacted the included healthcare professionals to schedule an interview. Written informed consent was provided at the start of the interview.

Patients with NSCLC who underwent lung resection

Potentially eligible patients were identified in the multidisciplinary team meeting in the VieCuri Medical Center or Zuyderland Medical Center by the researcher (MV), case manager (nurse specialist in lung oncology) by

screening surgery schedules. Eligibility criteria were 1) patients who underwent lung resection for NSCLC, 2) ≥18 years of age, 3) adequate understanding of the Dutch language, and 4) able to participate within 30 days after surgery. The pulmonologist provided information regarding the study during the first consultation after hospital discharge following lung resection. Interested patients received a patient information letter. Thereafter, the researcher contacted the patient to verify the willingness to participate and to schedule an interview after oral consent. Written informed consent was obtained before interviewing.

Informal caregivers of patients with NSCLC

During the first consultation after discharge from the hospital following lung resection, interested patients were asked to identify an informal caregiver who had been vital to them in the perioperative period. This could be a spouse, an adult child, a close friend, or a relative. The researcher contacted the informal caregiver by phone to ask for oral consent to schedule an interview. Written informed consent was signed at the start of the interview.

Data collection

Data was collected through one-to-one semi-structured interviews at a time and place suited for each participant. Interviews with healthcare professionals were conducted via video consulting online. For patients and informal caregivers this was at their home or before or after a scheduled usual care appointment at the hospital. One researcher (MV) conducted the interviews with patients and informal caregivers separately. The other researcher (EB) conducted the interviews with healthcare professionals. The number of interviews intended to perform was based on inductive thematic saturation. Saturation was considered when interviews did not lead to new themes. It was expected that approximately ten interviews with healthcare professionals, fifteen interviews with patients, and fifteen with informal caregivers were required. Preoperative and postoperative patient characteristics were derived from the electronic patient files. When applicable, a patient's postoperative complications were graded according to the Clavien-Dindo classification (20) to provide insight into treatment characteristics and treatment outcomes of the patients.

Content of the interviews

The interviews were conducted based on a semi-structured interview guide (developed by MV, CS, BB, and MJ) using open-ended questions that initially defined the areas explored. Interview topics are shown in Table 1. These initial

topics were chosen based on an existing behavior model. The capability, opportunity, motivation, and behavior (COM-B) model (21) guided the categories of questions regarding three types of behavior: 1) participating in multimodal prehabilitation, 2) referring to a prehab program, or 3) to support a loved one during prehab. The COM-B model (21) suggests that engagement in a behavior is determined by capability (e.g., physical skills, knowledge), opportunity (e.g., environment, social norms), and motivation (e.g., habits, beliefs, general attitude towards multimodal prehabilitation). Three test interviews were conducted for the study population, after which the topics and interview guides were optimized. The researchers (MV and EB) discussed changes in the interview guides.

Healthcare professionals were asked about the facilitators and barriers concerning their ability and available opportunities to refer patients to prehabilitation. Additionally, their opinion about which subgroup(s) of patients benefits the most from prehabilitation was asked. Information requested included patient characteristics, previous experiences with physical exercise training, nutritional advice, and smoking-cessation. Moreover, the occurrence of postoperative complications and their opinion about surgical delay to gain time for prehabilitation were questioned. Informal caregivers were interviewed about barriers and facilitators to support their loved ones to adhere to a prehabilitation program.

Table 1. Interview topic guide

1A. Healthcare professionals	
BEHAVIOR	1. Do you refer patients for prehabilitation, physical therapy, nutritional support, smoking cessation? To whom/what most? 2. Do you think patients would participate in prehabilitation? 3. Which element of prehabilitation is the most important for your patients?
MOTIVATION	4. Do you think it makes sense to offer prehabilitation to your patients? 5. In your opinion, is aerobic fitness related to the development of complications and recovery after surgery? 6. For which group of patients do you think referral to prehabilitation would be useful/not useful? 7. Are you planning to refer your patients with operable non-small cell lung cancer to prehabilitation? 8. How often do patients suffer from complications after lung surgery?

Table 1. Continued

CAPABILITY	9. Would it be difficult or easy for you to estimate whether someone qualifies for prehabilitation? 10. Do you think all operable patients with NSCLC are eligible? 11. What are barriers for you to refer patients to prehabilitation? 12. What would make it easier for you to refer patients for prehabilitation?
OPPORTUNITY	13. Do you think it is logistically feasible to set up multimodal prehabilitation for patients preparing for lung cancer surgery, in combination with the appointments that patients have regarding diagnostics and treatment? 14. Do you know what the procedure is to refer patients for prehabilitation? Is this difficult or easy to figure out and implement?
Other questions	15. Do you think that preparing patients for surgery is needed by means of prehabilitation? 16. Which healthcare providers could best guide the patient in the preoperative period? 17. What are your thoughts about a lifestyle clinic in the hospital? 18. What are your thoughts about professional guidance for patients in preparation of surgery? 19. What are your thoughts about extending a delay before surgery to make more time for prehabilitation? How long might this delay be?
1B. Patients	
BEHAVIOR	20. How did you experience the period around your surgery? 21. Did you do anything specific in preparation for your surgery in the period before prior to your surgery (e.g., physical exercise training, nutritional adjustments)? 22. How do you look back on this period? Would you do anything else with today's knowledge? 23. Did your physician advise you to be physically active/perform physical exercise training, adjust your diet, and/or stop smoking in preparation of your surgery? 24. Have you heard of prehabilitation? What are your thoughts about such a program?
CAPABILITY	25. Were you able to perform physical exercise training before your surgery? Did you do this? 26. Do you think you were able to follow a prehabilitation program at least 3 times a week? 27. Do you think you were able to follow a protein-rich diet? *For smokers*: 28. Did you stop smoking before surgery? Did you consider stopping? 29. Do you think you were able to stop smoking?

Table 1. Continued

MOTIVATION	30. Do you think it makes sense to perform physical exercise training prior to your surgery? 31. Do you think it is useful (for you) to eat a protein-rich diet and to adjust your eating behavior prior to your surgery? 32. Do you think it makes sense (for you) to get support from a psychologist prior to your surgery? 33. If you had to do it all over, how would you estimate the chance that you would follow a physical exercise training program in preparation of your surgery? *For smokers:* 34. If applicable: do you think it would be beneficial (for you) to quit smoking prior to your surgery?
OPPORTUNITY	35. Were you able to perform physical exercise training before your surgery? 36. Were you able/possible to follow a protein-rich diet before your surgery? 37. Did you have enough time to perform physical exercise training before your surgery? *For smokers:* 38. Were you able to quit smoking before the surgery?
Other questions	39. Did you have information before the operation about physical exercise training, nutrition, smoking cessation, psychological counseling, prehabilitation programs? 40. How physically fit did you feel before surgery after being diagnosed with lung cancer? 41. How physically fit did you feel after surgery? 42. Have you had any complications? 43. What do you think about guidance from a healthcare provider about prehabilitation programs? 44. What if the preoperative time period before surgery was extended in order to be able to participate in prehabilitation to be better prepared?
1C. Informal caregivers	
BEHAVIOR	45. How are you? How did your loved one experience the period around his/her surgery? 46. Did you and your loved one do anything specific in preparation for surgery? 47. Have you ever heard of prehabilitation? What do you think about that? Do you think it would make sense for your loved one? 48. Has your loved one been offered prehabilitation or rehabilitation? 49. Have you assisted your loved one in a prehabilitation program/or would you have been able to assist your loved one if he/she had been offered this before the surgery? 50. Did you need support during this period?

Table 1. Continued

MOTIVATION	51. Do you think it is useful (for your loved one) to perform physical exercise training prior to the surgery? Did you support your loved one to become more physically active or participate in physical exercise training? How did you do that? Do you think there is a role for the informal caregiver in a patient's preparation for surgery? 52. Do you think it is useful (for your loved one) to follow a protein-rich diet before surgery? Did you support your loved one to eat differently? Do you see a role for yourself here? *For informal caregivers of patients who smoke:* 53. Do you think it was useful (for your loved one) to stop smoking before his/her surgery? Do you see a role for yourself here? Did you help your loved one to stop smoking? If so, how? 54. Do you think it is useful (for your loved one) to receive support from a psychologist prior to the surgery? Do you see a role for yourself here?
CAPABILITY	55. Do you feel you are able to support your loved one in the preparation for surgery in terms of physical exercise training and dietary adjustments? *For informal caregivers of patients who smoke:* 56. Do you feel able to support your loved one to quit smoking? 57. Were you able to help your loved one to stop smoking before the operation?
OPPORTUNITY	58. Did you have enough opportunities (e.g., time) to support your loved one in his/her preparation for surgery? 59. Could you change something in the environment to make it easier for your loved one to be more physically active?

Data analysis

Data was collected according to the standards for reporting qualitative research checklist (22). All interviews were recorded and transcribed verbatim. These transcripts were fragmented and open coded in ATLAS.ti version 9 (ATLAS.ti Scientific Software Development GmbH) (23, 24). The open codes were divided into subthemes and themes using thematic analysis (24). The first three interviews of each study population were independently fragmented, coded, and thematized by two researchers (MV and EB). Themes were discussed until consensus was reached. These themes were used as a base for coding the other transcripts.

Results

Recruitment and sampling

A total of 45 interviews were conducted with twelve healthcare professionals, seventeen patients, and sixteen informal caregivers. Healthcare professionals involved in the treatment process of patients with NSCLC were two rehabilitation physicians, two pulmonologists, one surgeon, one psychologist, two dieticians, two physical therapists, and two case managers (Table 3). The median age of the healthcare professionals was 44 (range 24-64) years. Most healthcare professionals had more than five years of experience in the treatment of lung cancer, but some healthcare professionals mainly treated patients in general pulmonary rehabilitation. All patients and informal caregivers were interviewed at their homes. The median age of the patients was 65 (range 51-85) years, the median time between diagnosis and surgery was six (range 1-24) weeks, and the median length of hospital stay was four (range 2-11) days. Postoperative complications occurred in 69% of the interviewed patients, of which 64% were Clavien-Dindo grade I, 18% were Clavien-Dindo grade II, and 12% were Clavien-Dindo grade IIIa and IV complications. Median age of the informal caregivers was 62 (range 21-84) years. The relationships of the informal caregivers with the patient were spouse (94%) or son (6%). All participant characteristics are summarized in Table 2. Final themes concerning prehabilitation were described and summarized on a code tree (Table 3) The themes from the interviews are summarized in the text below and in Table 4.

Table 2. Characteristics of participating healthcare professionals, patients, and informal caregivers.

Parameters[a]	**Healthcare professionals (n=12)**	**Patients (n=17)**	**Informal caregivers (n=16)**
Sex n (%)			
Male	3 (25%)	9 (56%)	7 (47%)
Female	9 (75%)	7 (44%)	8 (53%)
Age n (%)	44 (24-63)	65 (51-85)	62 (21-84)
21-30 years	1 (8%)	-	1 (6)
31-40 years	3 (25%)	-	-
41-50 years	4 (33%)	1 (6%)	-
51-60 years	3 (25%)	5 (29%)	1 (6%)
61-70 years	1 (8%)	8 (47%)	8 (50%)
71-80 years	-	2 (12%)	5 (31%)
>80 years	-	1 (6%)	1 (6%)
Interview duration in minutes (range)	25 (24-50)	34 (22-57)	23 (7-35)
BMI in kg/m² (range)	-	25 (21-36)	-
FEV_1 as % of predicted (range)	-	78 (41-131)	-
DLCO as % of predicted (range)	-	75 (42-110)	-
Smoking n (%)			
Current	-	4 (24%)	2 (12%)
Former	-	13 (76%)	7 (44%)
Non-smoker	-	0 (0%)	7 (44%)
Work n (%)			
Employed when diagnosed	-	7 (47%)	7 (44%)
Retired	-	10 (59%)	6 (37%)
Not employed	-	0 (0%)	3 (19%)
Weeks between diagnosis and surgery (range)	-	6 (1-24)	-
Length of hospital stay in days (range)	-	4 (2-11)	-
Type of surgery n (%)			
Lobectomy	-	12 (70%)	-
Pneumonectomy	-	3 (18%)	-
Wedge resection	-	2 (12%)	-
Neoadjuvant chemotherapy	-	1 (6%)	-
Clavien-Dindo classification n (%)			
0-1	-	12 (71%)	-
II	-	3 (18%)	-
III	-	1 (6%)	-
IV	-	1 (6%)	-

Table 2. Continued

Parameters[a]	**Healthcare professionals (n=12)**	**Patients (n=17)**	**Informal caregivers (n=16)**
Charlson comorbidity index n (%)			
0-3	-	2 (12%)	-
≥4	-	15 (88%)	-
Relation with patient n (%)			
Spouse	-	-	15 (94%)
Son	-	-	1 (6%)
Function n (%)			
Rehabilitation physician	2 (17%)	-	-
Pulmonologist	2 (17%)	-	-
Surgeon	1 (8%)	-	-
Psychologist	1 (8%)	-	-
Dietician	2 (17%)	-	-
Physical therapist	2 (17%)	-	-
Case manager	2 (17%)	-	-

[a] Age, interview duration, BMI, FEV_1, DLCO, weeks between diagnosis and surgery, and length of hospital stay are presented as median (range).
Abbreviations: BMI=body mass index, FEV_1=forced expiratory volume in one second, DLCO=carbon monoxide lung diffusion capacity.

Table 3. Code tree

Open codes	Subthemes	Themes
Smoking-cessation	Multidisciplinary interventions	Content of prehabilitation and referral
Focus on postoperative period		
Improving aerobic fitness		
Group or individual physical exercise training		
Improving nutritional status		
Coaching/guidance		
Involved disciplines		
Customized prehabilitation components on indication	Referral	
Screening		
Role case manager		
Better prepared for surgery		
Who benefits?	Reasons to refer	
Inclusion		
Decrease postoperative complications (risk)		
Improving postoperative recovery		
Improving survival		
Short period between diagnosis and surgery	Delay surgery for prehabilitation	Organizational factors
Delay surgery not preferred		
Delay surgery is possible		
Prehabilitation so that surgery is possible.		
Planning of appointments	Planning	
Quick referral for multimodal prehabilitation		
Schedule		
Multidisciplinary collaboration	Communication	
Communication with patients		
Developing an application		
Knowledge of healthcare professionals		
Knowledge of patients and informal caregiver		
Digital support		
Involving caregivers in prehabilitation		
Home-based physical exercise training	Location	
Hospital-based physical exercise training		
Physical therapy practice		
Primary care		
Lifestyle clinic		
Patient specific prehabilitation program		
Distance		

Table 3. Continued

Open codes	Subthemes	Themes
Self-confidence	Mental and physical status	Personal factors for participation
Physical fitness		
Stressful period for patients and informal caregivers		
Accepting help		
Capable of surgery		
Concerns about their health and surgery		
Status before surgery		
Willingness to participate	Intrinsic motivational	
Awareness		
Motivation		
Self-management		
Self-discipline		
Preparation for surgery		
Financial barrier	External factors	Environmental factors
Financial facilitator		
Time		
Cultural differences		
Concerns of caregiver	Social support	
Support of caregiver		
Understanding social environment		

Table 4. Summary of main results of expectations, barriers, and facilitators for prehabilitation before lung cancer surgery for each group of stakeholders

Healthcare professionals
Beliefs – It is positive to include all patients, but especially patients with a poor preoperative physical fitness and/or nutritional status – Prehabilitation is cost-saving when length of hospital stay decreases – Multiple professionals within and between primary and secondary care should be involved in organizing prehabilitation – Prehabilitation can best take place in a hospital because of short lines between involved healthcare professionals – A longer time period before surgery is possible **Facilitators** – Clear reasons for referral: a decrease in the risk of postoperative complications, improve postoperative recovery and survival – Providing information to patients on how they can positively influence their health and functioning – Accessible information about prehabilitation in different languages – The case manager screens, refers, and coordinates – Need for agreements for collaboration with involved healthcare professionals in primary and secondary care – Making weekly timeslots available for practitioners to be able to schedule patients quickly for prehabilitation – Quick referral, start within one week after diagnosis – Pulmonologist/surgeon discusses the possibility about a longer time period before surgery with the patient – Adequate skills and knowledge about prehabilitation in primary care is essential for feasibility and effectiveness? – Involving informal caregivers should be involved to motivate and help patients to adhere **Barriers** – There are no cut-off values to identify patients who benefit most from prehabilitation – The short time period between diagnosis and surgery – Prehabilitation is not yet reimbursed by healthcare insurance companies

Patients	Informal caregivers
Beliefs – Consider themselves already sufficiently fit for surgery, having a healthy and varied diet – Prehabilitation makes no difference in the risk of postoperative complications – A better preoperative physical fitness and nutritional status facilitate postoperative recovery – Positive attitude to participate in a preoperative physical exercise training program if this was recommended by a physician. – No need for nutritional support – Many hospital appointments should be no barrier for prehabilitation **Facilitators** – Receiving information about preparing for surgery and the surgical procedure itself, and about a healthy lifestyle before surgery – Being capable to perform physical exercise training such as endurance training (e.g., walking, cycling, swimming) and resistance training – Guidance during the prehabilitation program by a physical therapist – Face-to-face contact with a physical therapist, contact with a dietician by phone or video consultation – Being capable to make time to perform physical exercise training one to three times weekly – Short lines of communication between the patient and healthcare professional during prehabilitation – Prehabilitation organized in their own living context – Physical exercise training in a group or having an experienced training buddy – Support of their loved ones – Motivation to do something in preparation for surgery, such as being more physically active to improve their health status – In order to deal with their perceived level of stress, some patients prefer counseling by a psychologist – Education during the prehabilitation program about the advice/ expectations during the postoperative period **Barriers** – Interference by many visits of friends and family due to their cancer diagnosis – Prehabilitation organized far from home – Unsupervised physical exercise training at home – Negative beliefs about a longer waiting time for surgery – An increase in the perceived level of stress (makes it especially hard to quit smoking)	**Beliefs** – Consider their loved ones to be adequately fit for surgery – Smoking-cessation is more successful when initiated by the loved one – They are accessible to the patient to talk about worries and stress **Facilitators** – Supporting smoking cessation of their loved one – Prehabilitation in the patient's living context or in primary care to provide optimal support – Capable to support their loved one when prehabilitation has to take place: doing physical exercise training together, trying to motivate, logistical support – Good physical condition of their loved one in order to perform physical exercise training together – A positive attitude of themselves and willing to change their diet – Having the opportunity to make extra time to support their loved one **Barriers** – Perceived level of stress/anxiety to lose their loved one in case of a longer time period before surgery

Healthcare professionals

Healthcare professionals mentioned a need for consensus on a cut-off value for including or excluding patients with lung cancer for prehabilitation, as well as regarding the cost-effectiveness of prehabilitation. Healthcare professionals preferred that case managers screen patients on preoperative modifiable risk factors. They expected that prehabilitation would be most effective in patients with a poor preoperative physical fitness and/or a poor nutritional status.

> *"I would prefer that a case manager screens the patient, connecting patients with healthcare professionals, designing treatment plans, and making sure it all gets done on time." Healthcare professional 3*

According to all healthcare professionals, patients should be informed on how they can positively influence their health and functioning preoperatively. They mentioned the importance of providing similar and unambiguous information about a healthy lifestyle before surgery to patients, taking into account different cultures, beliefs, or language barriers. Healthcare professionals mentioned the short period between diagnosis and surgery as a barrier for prehabilitation, which might be too short to initiate an effective prehabilitation program. Nevertheless, most healthcare professionals reported that surgery could be delayed safely when the pulmonologist or surgeon decides that a delay of surgery is possible. They mentioned that referring patients to prehabilitation might be facilitated when multiple professionals within and between primary and secondary healthcare are involved in prehabilitation and have weekly time slots available to schedule patients quickly. Most healthcare professionals prefer prehabilitation to take place at the hospital because communication between healthcare professionals within the hospital is easier. Healthcare professionals share an electronic patient file which gives the opportunity for quick referrals to prehabilitation. Furthermore, they expressed more trust in the knowledge of physical therapists working in their own hospital.

> *"I have doubts about the knowledge and skills regarding prehabilitation by physical therapists in primary care. So, my preference is to offer prehabilitation in the hospital." Healthcare professional 3*

Healthcare professionals encouraged informal caregivers to be involved in prehabilitation as they can stimulate their loved ones and know how to motivate them. A barrier is that, currently, patients must pay the costs associated with

preoperative preventive interventions themselves. Prehabilitation is not yet reimbursed by Dutch healthcare insurance companies.

> *"If patients become more fit preoperatively due to prehabilitation, there will be a faster recovery after surgery and therefore a shorter length of hospital stay. While prehabilitation is not yet standard care and is not reimbursed by the by Dutch healthcare insurance companies, I think this is very effective in lowering healthcare costs." Healthcare professional 9*

Patients

Most patients considered themselves sufficiently fit for surgery; they reported a healthy diet and felt no need for a prehabilitation program.

> *"My condition was sufficient because I cycled to work every day before the diagnosis. In addition, during the test (cardiopulmonary exercise test) before surgery, I did not have to make an effort to reach the level required to be operated on." Patient 2*

> *"I didn't need to get fit before surgery. I think the pulmonologist thought I was fit enough, because in that lung test (forced expiratory volume in one second) it turned out that I could miss a lung." Patient 6*

Patients did not know that a better preoperative physical fitness and nutritional status reduces the risk of postoperative complications. When the pulmonologist concluded that their physical fitness, according to the preoperative lung function tests, was sufficient to undergo surgery, patients indicated that they felt no need to prepare for surgery. When the patients received information about prehabilitation, they believed it facilitated postoperative recovery and mentioned that they would participate in prehabilitation if their physician recommended it. Patients said they would prefer to receive information about preparation for surgery, the surgery itself, and a healthy lifestyle before surgery and during the postoperative period.

> *"During the consultation at which I was diagnosed with lung cancer, the pulmonologist said that I needed to see a physical therapist to increase my endurance capacity. I was fine with it, but I was never referred and never heard from it again." Patient 3*

> *"The doctor asked what activities I did on a regular day. I replied: all household activities, cleaning, and grocery shopping. Hereafter she concluded: well, in that case preoperative physical exercise training is not necessary." Patient 8*

Patients indicated that they want to know what physical exercises would be practical for them and that an expert, such as a physical therapist or sports instructor, is the one to decide. A preoperative physical exercise training program, such as endurance training (e.g., walking, cycling, swimming) and resistance training, was most frequently mentioned as an intervention that patients would prefer. In contrast, patients felt no need for nutritional support from a dietician.

> *"A physical therapist is the best person to advise me what kind of exercises I should do; after all, he has learned for it." Patient 1*

Patients reported that they would prefer face-to-face guidance of a physical therapist or personal trainer to improve their preoperative physical fitness. Guidance of a dietician could be done by phone or via video-consulting. If a physician recommended prehabilitation, all patients reported that they felt capable to execute a physical exercise training session one to three times weekly and would change their diet when necessary. Most patients had enough time to participate and otherwise would have made time for prehabilitation. Patients indicated that they had many hospital appointments and medical examinations but that was not seen as a barrier to take part in a prehabilitation program. Some patients stated that they had a busy preoperative period because friends and family visited them at home, which was experienced as a barrier to take part in prehabilitation.

> *"Normally I walked every day, but in the last week before the operation I had so many visitors that I lost my walking rhythm, and I could not do anything about my fitness anymore." Patient 3*

The opportunity of having a direct communication with a healthcare professional was mentioned as a facilitator for patients to take part in a prehabilitation program. Patients preferred a physical exercise training program organized in primary care, because it fits better within their living context. Group-based exercises or having a training buddy were preferred by most patients, because of contact with other patients and motivational reasons. A long travel distance was seen as a barrier to participate in prehabilitation.

> *"I would have liked to do physical exercises in a group, because it allows you to talk to other patients and it helps to stay motivated." Patient 9*

Unsupervised prehabilitation at home was seen as a barrier for most patients, as they mentioned a lack of self-discipline. Patients felt they needed the support of their loved ones and preferred that they were able to join the appointments in a prehabilitation program. Some patients described that the intense and stressful period before surgery motivated them to be more physically active and to improve their health. Other patients indicated they were worried about the surgery and the outcomes and felt the need for a preoperative consultation by a psychologist, but this was not offered.

> *"I missed psychological support in the entire process. When the doctor said "we found a tumor in your lung", I really would have liked to have a conversation with a psychologist, because your world is falling apart." Patient 15*

Patients would like to receive more information about the postoperative period during a prehabilitation program (e.g., what to expect, how to deal with side effects and complications, medication use, process emotions).

> *"They write in leaflets what you can and cannot do after surgery in case of fever, regarding medication, et cetera, but not about the preparation for surgery in terms of physical exercise training and nutritional support. I would consider that information about physical exercises is being of additional value." Patient 4*

> *"I would have liked information about physical preparation before surgery. I went to the rehabilitation center where I worked until the diagnosis NSCLC and asked if I can do something to improve my physical fitness before the operation, but they mentioned that they did not know what kind of physical exercises were good and safe." Patient 15*

Some patients suggested that smoking-cessation before surgery was difficult because of the stressful period before surgery. Furthermore, patients reported that healthcare professionals recommended that they could quit smoking after surgery to avoid an increase in the perceived level of stress before surgery.

> *"My wife wanted me to stop smoking right away, but the pulmonologist wanted to wait until after surgery to avoid stress before surgery. After surgery I went to the general practitioner myself and asked for help with quitting smoking." Patient 5*

Patients did not feel the need for smoking-cessation interventions during prehabilitation. Most patients mentioned that they could talk to their spouses and family about their feelings and felt supported. Some patients would not like a delay of their surgery in favor of prehabilitation; they indicated that they wanted their tumor to be removed as soon as possible, and postponing surgery would increase their anxiety. However, some patients said they would accept a delay of two to four weeks to improve their physical fitness preoperatively.

Informal caregivers

Most informal caregivers considered their loved ones to be adequately fit for surgery. Informal caregivers said smoking-cessation should be a part of a prehabilitation program merely when initiated by the patient instead of persuading the patient; otherwise, they considered it ineffective. Informal caregivers preferred prehabilitation for their loved ones to be organized in their own living context in primary care in order to be able to provide optimal support. Most informal caregivers indicated they were also willing to participate in a physical exercise training with their loved ones and to offer nutritional support.

> *"I think it is important to provide support. You just do that as a partner. It is... we have been together for so long for a reason." Informal caregiver 4*

Most informal caregivers reported that they wanted the tumor to be resected at the earliest convenience and did not prefer a delay of the surgery in favor of prehabilitation. Most informal caregivers were worried to lose their loved ones due to cancer but tried to remain positive and said they could talk to their loved ones about their feelings and concerns.

Discussion

The aim of this study was to gain insight into beliefs, facilitators, and barriers of 1) healthcare professionals to refer patients to a prehabilitation program, 2) patients to participate in and adhere to a prehabilitation program, and 3)

informal caregivers to support their loved ones in prehabilitation. Healthcare professionals mentioned that the period between diagnosis and surgery might be too short to initiate an effective prehabilitation program. Furthermore, according to healthcare professionals, it is essential to make workable agreements and negotiate with health insurers to include prehabilitation in the basic health insurance.

Patients pointed out that they did not know that prehabilitation would reduce the incidence of postoperative complications; however, they did believe that it would enhance their postoperative recovery. They mentioned that a recommendation from their physician to participate in prehabilitation would facilitate their participation in a prehabilitation program. Furthermore, most patients preferred group-based exercises with supervision of a physical therapist or personal trainer. Informal caregivers said that they would prefer prehabilitation in primary care, in their own living context so they could provide optimal support to their loved ones.

Exercise prehabilitation effectively reduces the occurrence of postoperative complications and reduces length of hospital stay in patients undergoing surgery for NSCLC (13, 14). Patients need to be informed about the benefits of improving their health status before surgery, preferably by a physician (18). Priority should be given to facilitate a physician's involvement in informing patients about the value of physical activity and the need to perform physical exercise training and nutritional support.

The most important barrier for prehabilitation mentioned by healthcare professionals was the short period between diagnosis and surgery. However, previous studies have shown that a two-week prehabilitation program for early-stage NSCLC can already be effective to improve postoperative recovery, as well as that a four-week program can be effective to reduce postoperative complications (12, 25). Furthermore, a delay in surgery of three to four months after diagnosis has been associated with a decreased survival rate for some types of NSCLC compared to receiving surgery within one month, whereas a delay of one month caused no difference in survival (26). In the current study, thirteen out of seventeen patients had to wait at least four weeks for surgery, which means that there had been sufficient time to effectively execute a prehabilitation program.

Healthcare professionals mentioned the need for a consensus on a cut-off value for including or excluding patients in order to select the patients who would benefit the most from prehabilitation. Lower preoperative aerobic fitness has shown to be associated with an increased risk for short-term and long-term postoperative complications in several other surgical populations as well (27-30). There are field exercise tests that predict which patients are at high risk for postoperative complications, but unfortunately there is a lack of accurate test-specific cut-off values for these practical tests, heterogeneity in tests, and used outcome measures (31). In an optimal situation there is a possibility of identifying high-risk patients before starting the treatment, after which the physical performance status might be improved by prehabilitation in order to reduce a patient's risk for complications during and/or after treatment (10, 32).

Most patients considered themselves as adequately fit to undergo surgery and therefore did not need a prehabilitation program. This corresponds with the findings of previous studies amongst patients scheduled for colorectal and gynecological surgery; they also considered themselves fit enough for surgery (18, 33). When standard pulmonary function tests raise concerns about resectability, such as the FEV_1 and carbon monoxide lung diffusion capacity (DLCO), fall below 80% of predicted, a cardiopulmonary exercise test (CPET) is performed for surgical decision-making, by evaluating whether the patient's preoperative aerobic fitness is adequate for surgery (34, 35). If a physician states that a patient is fit enough to undergo surgery, patients mentioned they did not feel the need to do anything in order to prepare for surgery. Another study found that healthcare professionals usually assume that patients understand the plan of care explained because they did not always ask for the patient's opinion. This is partly because the patient did not always express their opinions themselves, and there was no shared decision-making about treatment (36).

Implementation of prehabilitation in usual care

The results from this study provide valuable information to implement a prehabilitation program before lung surgery that considers the facilitators and barriers of healthcare professionals, patients, and informal caregivers. For developing a feasible prehabilitation program for patients to adhere, it is important that content and context is made as optimal as possible. This study shows that there are many facilitators to set up a feasible prehabilitation program. When prehabilitation becomes usual care, it is important that 1) health professionals know when to refer patients to prehabilitation and that

there is a clear application procedure to enroll in a prehabilitation program 2) that patients receive a referral and recommendation for prehabilitation and that patients are adequately informed about the purpose and benefits of prehabilitation (e.g., leaflets, website of the hospital, improving the communication between healthcare professionals and patients). The current study shows that patients were motivated to participate when prehabilitation is recommended by a physician. Knowing the positive effects of prehabilitation before lung resection on postoperative complications, prehabilitation should be considered to become part of usual care.

Patients indicated that they would prefer group training sessions organized in their own living context. A previous study has shown that group-based postoperative physical exercise training for operable lung cancer had social benefits in addition to improved physical fitness in addition to improving exercise adherence, like good social relations with other patients and learning from each other's experiences (37). Thereby, patients prefer a prehabilitation program supervised by a specialized healthcare professional with the possibility that their loved ones could interact as well. Contrary to the patients, most healthcare professionals preferred prehabilitation to take place in the hospital, because communication with other involved healthcare professionals is easier for them. Furthermore, multiple professionals within and between primary and secondary healthcare should be involved in the context of prehabilitation. However, the Dutch government recommends that 50% of care must take place in the living environment of the patient instead of in a healthcare institution by 2030 (38).

Strengths and limitations

The present study provides detailed qualitative data on beliefs, preferences, barriers, and facilitators of prehabilitation from the perspective of healthcare professionals, patients with operable NSCLC, and informal caregivers. Ascertaining what is meaningful to patients in the perioperative period in order to participate in a prehabilitation program may be challenging, but is fundamental to clinical patient care (39), as engagement of patients in their care has been associated with improved clinical outcomes and care experience (40). Limitations of the study should also be acknowledged. First, recruitment for healthcare professionals and scheduling interviews was difficult due to hectic periods in pulmonology departments in the medical centers because of the coronavirus disease 2019 pandemic. As such, not all healthcare professionals had extensive experience in the treatment of patients with lung cancer, but they

did have experience in treatment of patients with other lung diseases. Second, both pulmonologists interviewed for this study were employed in the same medical center, with the same organization of care and information provision. This might have resulted in reduced richness of the data. Third, patients who participated in this study had not been offered to participate in a prehabilitation program. This means that future studies are needed to evaluate experiences with a prehabilitation program that can be developed with the results from the current study.

In order to facilitate healthcare professionals to refer patients to a prehabilitation program directly after the diagnosis of NSCLC, agreements about the preoperative screening, assessment, and enrollment in prehabilitation is needed. With sufficient time between diagnosis and surgery, prehabilitation could be organized in primary care and it is therefore essential to make workable agreements between healthcare professionals and negotiate with health insurance companies to reimburse prehabilitation. Furthermore, it is recommended to focus on the inclusion of high-risk patients with NSCLC prehabilitation as part of usual care because of the positive effects of prehabilitation on surgical outcomes (41).

Conclusion

In order to be able to start a prehabilitation program as soon as possible after the diagnosis of lung cancer, agreement of preoperative screening and assessment is needed to ensure adequate patient selection, and multidisciplinary collaboration of healthcare professionals within primary and secondary care in referring patients to prehabilitation seems vital. The first step is to inform patients about the purpose and effects of prehabilitation in a one-to-one conversation by the pulmonologist and/or case manager. The next step is to consider patient preferences in organizing an individual or group-based program in their own living context under the supervision of a trained physical therapist. Patients report that the support of their loved ones in their own living context is essential for their adherence to a prehabilitation program. Therefore, it would be wise to involve informal caregivers into the program.

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'I was really thrown back by the chemotherapy, but I was relieved to be able to discuss this with the physiotherapist as he reassured me and contacted the case manager about my physical decline.'
-Patient who underwent chemoradiotherapy for NSCLC-

Chapter 9

Feasibility of rehabilitation during chemoradiotherapy among patients with stage III non-small cell lung cancer: a proof-of-concept study

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Abstract: Rehabilitation during chemoradiotherapy (CHRT) might (partly) prevent reduction in physical fitness and nutritional status and could improve treatment tolerance in patients with stage III non-small cell lung cancer (NSCLC). The aim of this proof-of-concept study was to investigate the feasibility of a multimodal program for rehabilitation during CHRT. A home-based multimodal rehabilitation program (partly supervised moderate-intensity physical exercise training and nutritional support) during CHRT was developed in collaboration with patients with stage III NSCLC and specialized healthcare professionals. A predetermined number of six patients with stage III NSCLC (aged >50 years) who underwent CHRT and participated in this program were monitored in detail to assess its feasibility for further development and optimization of the program. The patient's level of physical functioning (e.g., cardiopulmonary exercise test, six-minute walking test, handgrip strength, body mass index, fat free mass index, energy and protein intake) was evaluated in order to provide personalized advice regarding physical exercise training and nutrition. The program appeared feasible and well-tolerated. All six included patients managed to perform the assessments. Exercise session adherence was high in five patients and low in one patient. The performed exercise intensity was lower than prescribed for all patients. Patients were motivated to complete the home-based rehabilitation program during CHRT. Preliminary effects on physical and nutritional parameters revealed relatively stable values throughout CHRT, with inter-individual variation. Supervised and personalized rehabilitation in patients with stage III NSCLC undergoing CHRT seems feasible when the intensity of the physical exercise training was adjusted to the possibilities and preferences of the patients. Future research should investigate the feasibility of a supervised and personalized rehabilitation program during CHRT with a low-to-moderate exercise intensity with the aim to prevent physical decline during CHRT.

Introduction

Lung cancer is the leading cause of cancer-related death all over the world (1), accounting for 18.4% of all cancer-related deaths in 2018 (2). Approximately 85% to 90% of the patients with lung cancer suffer from non-small cell lung cancer (NSCLC) (1). Stage III disease constitutes around 20% of all NSCLC cases (3). Standard treatment for patients with stage III NSCLC is concurrent or sequential chemoradiotherapy (CHRT) (4). Patients with stage III NSCLC often have characteristics that increase the risk for treatment complications, such as a higher age (≥50% is aged over 70 years), smoking-related comorbidity, and poor physical performance status (5-8). Furthermore, frailty, long-term physical inactivity, and malnutrition are often present (9), which can decrease treatment tolerance, survival, and quality of life (6, 10). Rehabilitation during CHRT might be effective to improve treatment tolerance, quality of life, and survival during intensive treatment with CHRT (11-13).

Although patients with lung cancer perceive physical activity as being important for recovery during and after treatment, most patients are insufficiently active; previous studies in patients with NSCLC show that the willingness and ability to participate in a prehabilitation program (between 28% and 56% (14, 15)) is low and that program adherence is only moderate (between 53% and 73% (14, 16)). Among dropout reasons, cancer-related side effects and, mostly, lack of interest and motivation represent key contributors (17). Nevertheless, high adherence of patients to rehabilitation during CHRT is crucial to reduce treatment complications (18). Understanding what amount of training volume is feasible, thereby including patient preferences, is important to ensure that rehabilitation during CHRT is personalized and that patients and their informal caregivers are both able and willing to participate and adhere to the program.

Studies including patients with lung cancer have shown that intramural or extramural physical exercise before, during, and after treatment might counteract adherence because of commuting problems, accessibility of services, comorbidity, and vulnerability (11, 19). Self-monitoring might increase motivation for exercise continuation, as insights regarding improvements can be gained quickly (with a pedometer or with low complexity walk and stair climbing tests), as has been shown in patients with rectal cancer (19, 20). Furthermore, peer support, and involvement of close relatives increases adherence rates in patients who undergo surgery (21, 22). A personalized supervised program that is home-based and takes into

account preferences and experiences of patients, might improve motivation and adherence in patients with stage III NSCLC undergoing CHRT.

Unfortunately, evidence on the feasibility of multimodal rehabilitation during CHRT among patients with stage III NSCLC is lacking. Therefore, the aim of this study was to investigate whether a multimodal program for rehabilitation during CHRT, constructed in collaboration with patients and healthcare professionals, was feasible with respect to adherence to the rehabilitation program during CHRT, motivation, patients' preferences and experiences, dropout rate, adverse events, and logistic planning.

Methods

Patients

In this single-group prospective proof-of-concept study, a predefined number of six patients participated. Patients were checked for eligibility by their treating pulmonologist at VieCuri Medical Centre between February 2019 and March 2021. These patients were diagnosed with stage III NSCLC according to the 8th edition of the TNM guidelines and were referred for and underwent CHRT (either concurrent CHRT or sequential CHRT). Patients were eligible when they were aged ≥50 years and provided written informed consent. Patients unable to perform a moderate-intensity physical exercise program, a diagnosis of previous cancer in the past three years, or psychological or somatic constraints that might limit their ability to cooperate with study procedures were excluded. The Medical Research Ethics Committee of Maastricht UMC+ decided that this study met the ethical policies and regulations of the Dutch government (non-WMO statement 2017-0154).

Cancer treatment

Patients enrolled in this study received standard treatment including at least thirteen weeks of concurrent CHRT or eighteen weeks of sequential CHRT. Regimens for chemotherapy consisted of two or three concurrent cisplatin or carboplatin-based doublet cycles or three to four sequential cisplatin or gemcitabine doublet cycles. Radiotherapy was delivered with an arc technique and delivered using 6-10 MV photons. Gross tumour volume included the primary tumour and pathologic lymph nodes as identified on the fluorodeoxyglucose-positron emission tomography scan. Volume constraints for the oesophagus have not been performed; the maximum point dose in the oesophagus is 76 Gy

(biologically equivalent dose in 2 Gy fractions). The clinical target volume had an extra margin to include regions at risk of microscopic extension. Planning target volume encompassed a margin for inter- and intrafraction patient and organ motion. Schedules were 33 × 2 Gy (once daily), 24 × 2.75 Gy (once daily), and radiotherapy according to an individualized prescribed maximal tolerated dose protocol (once or twice daily).

Content and assessment of the multimodal rehabilitation program during CHRT

After informed consent was obtained, baseline data including demographics sex, age, World Health Organization (WHO) performance status, and Charlson comorbidity index (23) were collected from the electronic patient file. The schedule of enrolment, interventions, and assessments for patients who underwent rehabilitation during CHRT is shown in table 1.

The aim of the pretreatment baseline assessment (T0) was to evaluate the patient's level of physical functioning (e.g., physical functioning parameters, nutritional parameters) in order to provide personalized advice regarding physical exercise training and nutrition. To monitor changes and subsequently adjust the program, baseline assessments, excluding the cardiopulmonary exercise test (CPET), were repeated between the first and second course of chemotherapy (T1) and after the last session of radiotherapy (T2). Three months after treatment (T3), all assessments, including the CPET, were repeated again. Preliminary effects of the program were evaluated by changes in physical and nutritional parameters during assessments T0, T1, T2, and T3. A blueprint of the rehabilitation program during CHRT was developed and discussed in the multimodal and transmural project team, as well as with patients (representatives). The rehabilitation program during CHRT, which was incorporated into the patient's cancer treatment schedule, consisted of physical exercise training, a nutritional support module, and smoking cessation. The length of rehabilitation during CHRT depended on the duration of treatment, including treatment delay.

Table 1. Schedule of enrolment, interventions, and assessments for patients who underwent rehabilitation during chemoradiotherapy.

Assessments		T0		T1	T2	T3
Concurrent CHRT (cCHRT)	Week 0	Week 1	Week 2	Week 5	Week 13	Week 22
Sequential CHRT (sCHRT)	Week 0	Week 1	Week 2	Week 5	Week 19	Week 28
ENROLMENT:						
Informed consent	•					
Informed about smoking	•					
CANCER TREATMENT:						
Consultation with pulmonologist		•			•	
Intake by case manager		•				
Chemotherapy			Start			
Radiotherapy			For cCHRT: start during CT; for sCHRT: start after CT			
MULTIMODAL REHABILITATION DURING CHRT:						
Physical counseling[a]		•	•	•	•	
Dietary counseling[b]		•	•	•	•	
Case manager[c]	•	•	•	•	•	•
ASSESSMENTS:						
CPET		•				•
6MWT		•		•	•	•
HGS		•		•	•	•
BMI		•		•	•	•
FFMI		•		•	•	•
Energy and protein intake		•		•	•	•
Pedometer			•	•	•	•
FEASBILITY:						
Adherence and dropouts						•
Smoking		•		•	•	•
0-10 VAS score for motivation			•	•	•	

Abbreviations: 6MWY=six-minute walking test; BMI=body mass index; CHRT=chemoradiotherapy; cCHRT= concurrent chemoradiotherapy; CPET=cardiopulmonary exercise test; CT=chemotherapy; FFMI=fat free mass index; HGS=handgrip strength; NSCLC=non-small cell lung cancer; sCHRT=sequential chemoradiotherapy ; VAS=visual analogue scale. [a]:once every two weeks: supervision of the exercise program at the patient's home or a visit during treatment with chemotherapy.[b]:Telephone consultation every three weeks during chemotherapy and every week during radiotherapy.[c]:Every three weeks by telephone.

Physical exercise training

The blueprint of the physical exercise training program was developed according to the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) scale and is presented in Table 2.

Emphasis was put on the preferences of the patient by personalization of functional exercises that were of relevance and meaningful to a patient. The thirteen- or eighteen-week physical exercise training program was carried out in the patient's living environment. Once every two weeks, a training session was supervised by a physical therapist specialized in oncology. Training frequency was five times a week and started at a duration of at least fifteen minutes, which was progressively increased to 45 minutes. Training intensity for the home-based sessions was tailored using the 6-20 Borg scale for rating of perceived exertion, aiming at a moderate intensity with a Borg score of 13-15 (24). Aerobic training consisted of a patient's preferred activities involving large muscle groups (e.g., walking, cycling, climbing stairs, swimming). Peripheral resistance exercises of the large muscle groups of the lower and upper extremities using functional open and closed kinetic chain exercises (e.g., stair climbing, sit-to-stand exercises, a Thera band, filled 0.5-liter bottles) were designed for each individual according to the relevant training zones (6-20 Borg score of 13-15). For inspiratory muscle training (IMT), patients performed two daily sessions of 30 breaths using an inspiratory muscle trainer (Threshold IMT, Philips Respironics, Murrysville, PA, USA) at the highest tolerable intensity (25). The initial resistance (cm H_2O) was set and increased using the 6-20 Borg scale (13-15), which was also based on the patient's symptoms of fatigue, dyspnoea, or pain.

Nutritional support

Nutritional counselling was performed based on the standard protocol for patients with cancer in the general (26) and elderly population (27). Individualized counselling aimed to educate patients on how to modify their usual meals by making them adhere to individual energy, protein, and other macronutrient requirements. The dietary advice aimed to specify the type and amount of food, the number of meals, and calorie or protein amounts to achieve on a daily base or dietary recommendation as part of standard care. Advice by a dietician was personalized to a patient's eating pattern and preferences.

Table 2. Blueprint of the physical exercise training program according to the i-CONTENT scale.

Patient selection	Patients aged ≥50 years diagnosed with stage III NSCLC according to the 8th edition of the TNM guidelines undergoing CHRT (either concurrent CHRT or sequential CHRT)
Type and dosage of the rehabilitation program during CHRT(F: Frequency, I: intensity, T: Time, T: Type)	**Aerobic exercises**: **F:** 5 times/week 30 min, **I:** 6-20 Borg score 13-15, **T:** 30-60 min**, T**: Functional exercises involving large muscle groups (e.g., walking, cycling, climbing stairs, and swimming) **Resistance exercises**: **F:** 3 times/week, **I:** 6-20 Borg score 13-15, **T**: 3 × 15-20 repetitions, **T:** Peripheral resistance training of the large muscle groups of the lower and upper extremities using open and closed kinetic chain exercises (e.g., stair climbing, sit-to stand exercises, a Thera band, filled 0.5-liter bottles) **Breathing exercises**: **F:** 2/day, **I:** highest tolerable intensity, **T:** 30 breaths, **T:** Inspiratory muscle training
Qualified supervisor (if applicable)	The physical exercise training program was carried out in the patient's living environment, every two weeks supervised by a physical therapist specialized in oncology
Type and timing of outcome assessment	Type: feasibility of the multimodal rehabilitation program during CHRT was measured by the patient's preferences and experiences, patient dropout, and adverse events during rehabilitation, adherence to the rehabilitation program, motivation, and problems concerning logistic planning Timing: before the start of CHRT (T0), between the first and second chemotherapy (T1), after the last session of radiotherapy (T2), three months after the last treatment (T3)
Safety of the exercise program	Patient dropout and adverse events to rehabilitation during CHRT were registered by the healthcare professionals during contact moments as part of usual care
Adherence to the exercise program	Adherence was monitored with a diary and weekly feedback from the patients. Successful exercise session adherence was defined as achieving >80% of the prescribed duration, intensity, and frequency of the training sessions during the physical exercise training program

Abbreviations: CHRT=chemoradiotherapy; i-CONTENT=international consensus on therapeutic exercise and training; NSCLC=non-small cell lung cancer.

Smoking cessation

Patients who smoked were encouraged to quit. When applicable, patients were referred to their general practitioner for a smoking-cessation program (according to Dutch guidelines) (28). During contact moments with the healthcare professionals, patients were motivated to persevere smoking-cessation.

Physical assessments

The pulmonologist referred patients to the sports physician for a CPET to examine the patient's aerobic fitness and provided personalized advice regarding the content of the physical exercise program. An incremental CPET was performed on an electronically braked cycle ergometer (Monark LC6 novo, Exercise AB, Vansbro, Sweden) according to ATS/ERS standards (29) with respiratory gas analysis measurements. CPET interpretation was performed by a sports physician. Absolute oxygen uptake (VO_2) at peak exercise (VO_{2peak}) was calculated as the average value over the last 30 seconds prior to termination of the test. Peak heart rate was defined as the highest heart rate achieved during the CPET (30). In order to personalize rehabilitation during CHRT, the physical therapist aimed to evaluate the level of physical functioning using performance-based tests to estimate functional walking distance (six-minute walk test (6MWT)), muscle strength (handgrip strength (HGS)), and daily physical activity level (pedometer). Functional walking distance was assessed by the 6MWT according to the ATS guideline (31). After the test, patients were asked to rate their individually perceived exertion using the 6-20 Borg scale for rating of perceived exertion (24). Maximal handgrip strength was assessed with a Jamar hydraulic hand dynamometer (J.A. Preston Corporation, Jackson, MI, USA). The highest value of three attempts for the dominant hand was registered (32). Daily physical activity level was assessed by a pedometer (HiTrax Walk pedometer, TFA Dostmann, Wertheim, Germany).

Nutritional assessment

In order to provide tailored nutritional advice, the dietician aimed to evaluate a patient's nutritional status with the body mass index (BMI), fat free mass index (FFMI), and energy requirement. In addition, the dietician provided insight into the protein requirement, which was estimated using the formula of Gallagher (33). Body height was measured in standing position without shoes. Body mass was measured without shoes and coat. Body composition assessment (e.g., FFMI) was performed by direct segmental multi-frequency bioelectrical impedance analysis (Seca Medical Body Composition Analyzer

515, Hamburg, Germany). The estimates obtained are from the manufacturer's proprietary algorithms with patients standing.

Feasibility of the performed assessments and the rehabilitation program during CHRT

Feasibility of performing the assessments and the rehabilitation program during CHRT was measured by adherence to the rehabilitation program during CHRT, motivation, patient preferences and experiences, patient dropout and adverse events during rehabilitation, as well as by logistical planning of the inclusion of patients and communication in this multimodal setting. Adherence to the rehabilitation program was monitored with an exercise diary and weekly feedback from the patients. A high exercise session adherence was defined as achieving ≥80% of the prescribed training session frequency and duration throughout the training program. Motivation was measured after each supervised physical exercise training session by asking patients to rate their motivation of performing the rehabilitation program, with help of a visible analogue scale (VAS) from 0-10, in which 10 meant excellent motivation. Involvement of an (in)formal caregiver was encouraged to promote motivation. Patient preferences and experiences (e.g., beneficial effects, deficiencies, impediments, (transmural) logistical problems) regarding the performance of physical and nutritional assessments, physical exercises, nutritional approach, willingness to quit smoking, supervision, and social support were recorded via usual care appointments with the healthcare professionals every two to three weeks. Patient dropout and adverse events from treatment or rehabilitation were collected by the healthcare professionals during contact moments as part of usual care. Logistical planning was discussed every six months with healthcare professionals from the three involved healthcare organizations (hospital, radiation centre, and rehabilitation centre within the hospital).

Statistical analyses

Data were analysed by using IBM SPSS Statistics version 24.0. Detailed descriptive analyses were performed to describe feasibility of the rehabilitation program during CHRT at each time point. Statistical significance was not determined as the included patient group was too small for any kind of valid statistical testing.

Results

Patient and treatment characteristics

Seven patients were invited to participate in this proof-of-concept study. One patient refused participation, because of being vulnerable and having a very limited social network. Six patients completed the rehabilitation program during CHRT. Patient characteristics, treatment schedule, physical and nutritional parameters, and feasibility of rehabilitation during CHRT are presented in Table 3. All patients in this study started chemotherapy within four days after baseline assessments. Four patients received concurrent CHRT and two patients received sequential CHRT. The chemotherapy regimens for NSCLC patients were docetaxel, vinorelbine, and pemetrexed in one patient, and cisplatin + gemcitabine in five patients. Radiotherapy was followed as prescribed (33 × 2 Gy or 24 × 2.75 Gy) once daily in all patients. Adverse events that were judged to be related to chemotherapy were anaemia (2 patients, 33%) and hypoalbuminemia (4 patients, 67%).

The multimodal rehabilitation program during CHRT

To improve aerobic fitness, five patients chose to walk, and one patient choose to cycle and swim at least five times a week. All patients lived in a single-family home; as such, stairs, a chair, bench, and table could be used to perform resistance exercises. All patients received nutritional advice that supported physical exercise training by ensuring sufficient protein intake. All patients reported a history of smoking and current smokers (n=4) were advised to quit smoking with the guidance of the general practitioner. Two patients had stopped smoking two years before the diagnosis of lung cancer.

Table 3. Patient characteristics, treatment schedule, physical and nutritional parameters, and feasibility of rehabilitation during CHRT in patients with stage III NSCLC.

	Patient 1				**Patient 2**			
Age	57				60			
Sex	Male				Male			
Stage	IIIB				IIIB			
Comorbidities	None				None			
Time of assessment	**T0**	**T1**	**T2**	**T3**	**T0**	**T1**	**T2**	**T3**
Treatment schedule								
Type of CHRT	Concurrent				Concurrent			
Treatment time of CT	8 weeks				9 weeks			
Treatment time of RT	6 weeks				4 weeks			
Physical parameters								
CPET VO_{2peak} (mL/kg/min)	17.7	-	-	17.8	27.1	-	-	22.1
CPET VO_2 at the VAT (mL/kg/min)	9.3	-	-	8.9	16.6	-	-	12.2
CPET RER_{peak}	1.02	-	-	1.02	1.21	-	-	1.19
6MWT (m)	460	500	430	535	465	548	480	487
6MWT 6-20 Borg score	11	11	12	11	10	12	10	11
HGS dominant hand (kg)	46	48	48	52	37	NM	30	25
Nutritional parameters								
Body mass (kg)	74.0	75.3	74.8	77.1	62.9	66.3	69.5	72.9
BMI (kg/m^2)	23.4	23.7	23.6	24.3	21.2	21.9	23.0	24.1
FFMI (kg/m^2)	16.6	16.5	16.9	16.7	16.7	17.4	17.3	17.2
Energy intake (% of recommended)	93	113	90	85	95	116	102	99
Protein intake (% of recommended)	98	78	100	94	80	112	107	81
Feasibility								
Adherence to rehabilitation	100%				80%			
6-20 Borg score during exercises	13	12	11	13	11	10	10	11
Smoking	yes	no	no	yes	yes	no	no	yes
0-10 VAS for motivation to perform rehabilitation	10	10	10	9	7	8	8	9

Abbreviations: 6MWT=six-minute walk test; BMI=body mass index; CABG=coronary artery bypass graft; CHRT=chemoradiotherapy; CPET=cardiopulmonary exercise test; CT=chemotherapy; FFMI=fat free mass index; HGS=handgrip strength; NSCLC=non-small cell lung cancer; RA=rheumatoid arthritis; RER_{peak}=respiratory exchange ratio at peak exercise; RT=radiotherapy; VAS=visual analogue scale; VAT=ventilatory anaerobic threshold; VO_{2peak}=oxygen uptake at peak exercise.
[a]: not assessed due to COVID-19 restrictions.

	Patient 3				**Patient 4**				**Patient 5**				**Patient 6**			
	74				58				70				69			
	Male				Female				Male				Male			
	IIIA				IIIA				IIIA				IIIA			
	CABG (2017)				Depression (since 1995)				Osteopenia (since 2017)				RA (since 2010)			
	T0	**T1**	**T2**	**T3**	**T0**	**T1**	**T2**	**T3**	**T0**	**T1**	**T2**	**T3**	**T0**	**T1**	**T2**	**T3**
	Sequential				Concurrent				Concurrent				Sequential			
	16 weeks				8 weeks				10 weeks				19 weeks			
	6 weeks				5 weeks				4 weeks				5 weeks			
	13.8	-	-	11.7	15.0	-	-	13.3	14.3	-	-	16.6	19.2	-	-	18.3
	8.7	-	-	7.0	9.0	-	-	10.9	12.0	-	-	10.0	11.1	-	-	14.1
	1.07	-	-	1.04	1.04	-	-	1.02	1.21	-	-	1.36	1.06	-	-	1.03
	265	250	323	310	470	396	-[a]	445	482	480	500	505	441	455	400	400
	13	14	13	12	12	12	-[a]	12	12	11	11	13	12	12	13	13
	31	26	28	25	29	30	-[a]	32	30	38	38	35	26	28	25	29
	63.0	62.6	66.4	67.3	79.9	81.2	77.0	81.8	77.6	77.8	79.2	79.5	99.4	96.3	94.1	89.5
	22.6	22.5	23.8	24.1	29.0	28.7	27.6	29.3	24.6	24.5	25.0	25.1	31.4	30.4	29.7	28.3
	15.3	14.9	16.9	15.6	17.2	17.4	-[a]	17.4	17.8	18.5	18.3	18.9	19.2	17.8	17.5	17.6
	53	92	90	99	69	88	92	87	81	112	115	113	60	86	100	64
	56	88	82	98	61	77	76	76	56	85	92	88	75	92	100	83
	48%				80%				100%				80%			
	10	10	10	10	11	12	10	12	11	11	11	11	13	12	10	12
	yes	yes	yes	yes	yes	no	no	Yes	No	No	No	No	No	No	No	No
	7	8	9	10	8	7	8	8	9	9	8	8	7	8	6	9

Feasibility

Feasibility of the rehabilitation program during CHRT

Outcomes of patient characteristics, physical and nutrition assessments, and adherence to the multimodal rehabilitation program during CHRT are shown in Table 3. Adherence to the rehabilitation program was high in five patients as they completed ≥80% of the prescribed sessions and increased session time of aerobic and resistance exercises from 15 to 45 minutes. Adherence was low (48%) in one patient due to fatigue and decreased mood. None of the patients were able to increase the resistance of the IMT during the cancer treatment; five patients were able to maintain the same IMT resistance and to maintain the IMT daily exercise frequency. One patient failed to exercise with the IMT device due to anxiety and shortness of breath. Alternative resistance exercises for the respiratory muscles (e.g., shoulder press, lateral raises, dumbbell press) were offered to this patient. All patients completed the exercise diary adequately; however, merely three patients reported occasionally the daily number of steps taken with the pedometer. Patients who did not adequately fill out the exercise diary reported that they forgot this and found it difficult to keep thinking about it, especially due to the long period of CHRT. All patients performed functional, resistance, and IMT training with a Borg score of 11-12 as perceived training intensity. Hence, none of the patients achieved the advised training intensity of 13-15 on the 6-20 Borg scale during these exercises. Four patients had mild swallowing irritation of the trachea during radiotherapy. These patients received adapted nutritional advice to improve the safety and comfort of eating, aiming to maintain an adequate nutritional intake. The intensity of physical exercise training had to be adjusted due to side effects of CHRT such as fatigue, shortness of breath, and pain in all patients. There were no dropouts or adverse events as a result of the rehabilitation program. Regarding patient preferences and experiences, patients experienced their cancer treatment as an intense period in which many appointments took place, especially during radiotherapy. Patients reported feeling comfortable and safe because of the short lines between healthcare professionals as there was direct coordination between them when questions or uncertainties were posed by the patient. It was notable that patients needed and preferred intensive coaching during the first two weeks, and patients indicated that processing the situation (e.g., diagnosis, treatment, being concerned about their future) was stressful. Three patients (50%) indicated that the physical exercise training could be executed well, also during CHRT. One of the main reasons for being able to persevere was that the physical exercises and daily activities were performed together with their informal caregiver. Patients liked to perform the physical exercise

training sessions at home. Regarding motivation, all patients indicated that they were motivated to participate in the study. This motivation remained relatively stable throughout the rehabilitation program. Patients indicated that it was difficult to remain motivated to perform the exercises during the weeks of chemotherapy and radiotherapy due to the many hospital appointments for the chemotherapy and radiotherapy and fatigue. Patients reported that they were better able to adhere to the interventions in the presence of healthcare professionals, but patients had difficulties motivating themselves to adhere to the frequency and intensity of the program during the unsupervised sessions. In five patients (83%), informal caregivers were actively involved. These patients indicated that their informal caregivers were a major source of social support and motivated them to continue the rehabilitation program. The patient with low adherence (48%) did not have an involved caregiver during rehabilitation.

There were problems concerning logistical planning in the multimodal setting. The inclusion of patients took a long time (25 months); however, 6 of the 7 patients who were eligible and asked to participate in the study period immediately agreed to participate. The main reasons for the long inclusion period were a lack of attention for the study by the referring pulmonologists, the high work pressure at the outpatient clinic, and the COVID-19 pandemic. Communication between case managers, pulmonologists, and healthcare professionals was good; however, it was experienced that it was difficult to keep each other informed about changes in treatment programs. Working at different healthcare organizations (hospital, rehabilitation centre, and radiation clinic) with different electronic patient files was experienced as a barrier by healthcare professionals.

Feasibility of performing assessments

One patient was unable to perform a part of the T2 assessments because of the lockdown due to the COVID-19 pandemic. Two patients experienced the CPET as very intense and were reluctant to perform it on forehand; however, they were able to complete the CPETs. Patients were able to visit the hospital during all assessments. One patient had completed the 6MWT with a Borg score of 13-15. The other patients completed the 6MWT with a Borg score ≤12. The physical therapist observed that these patients were not short of breath or tired, but the patients indicated that they had walked as many meters as possible. The other physical and nutritional parameters were performed by all patients at all assessments.

Preliminary effects on physical and nutritional parameters

Preliminary changes in physical and nutritional assessments are shown in table 3 and figure 1.

Physical parameters

Regarding aerobic fitness, three patients (50%) deteriorated in VO_{2peak} between T0 and T3 and one patient (17%) improved between T0 and T3. In one patient, a 19% decrease in VO_{2peak} could be partly explained by a significant weight gain (62.9 kg at T0 versus 72.9 kg at T3). Mean VO_2 at the VAT at T0 was 11.1 mL/kg/min and at T3 10.5 mL/kg/min). Distance on the 6MWT between T0 and T3 had improved with a mean percentage of 4.3%. HGS remained stable between T0 and T3.

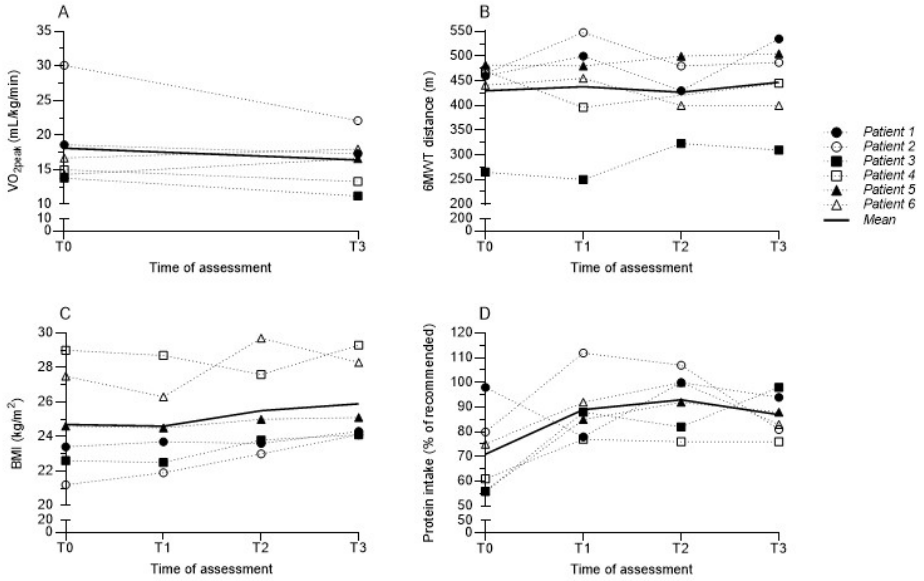

Figure 1. Preliminary changes in physical and nutritional assessments at T0, T1, T2, and T3. Graphs represent individual outcomes of the CPET (A), 6MWT (B), BMI (C), and protein intake (D). The thick solid line represents mean values. Abbreviations: 6MWT=six-minute walk test; BMI=body mass index; CPET=cardiopulmonary exercise test; VO_{2peak}=oxygen uptake at peak exercise.

Nutritional parameters

BMI and FFMI increased slightly in all patients during treatment; however, FFMI had reduced in one patient between T0 and T3. All patients improved their protein and energy intake during treatment (T1 and T2) with a small decrease at T3. In three patients (50%), protein intake at T0 was too low (<80% of required). In two patients (33%), energy intake was too low at T0 (<80% of

required). In three patients (33%), energy and protein intake improved after the first consultation and remained relatively stable during treatment. In the other three patients (33%), energy and protein intake decreased again at T3.

Discussion

In this proof-of-concept study, it was aimed to investigate whether multimodal rehabilitation during CHRT was feasible in patients with stage III NSCLC. Patients showed good training session adherence and adhered to the nutritional advice during multimodal rehabilitation. However, patients were unable to adhere to the prescribed training intensity. Although supervision of healthcare professionals and the involvement of an informal caregiver led to better motivation, adherence to physical exercise training and dietary advice during CHRT was reported to be challenging as a consequence of fatigue and decreased mood. At group level, physical and nutritional parameters remained relatively stable during CHRT; however, large variety existed in response to rehabilitation, as some patients showed large improvements in physical and nutritional outcome measures, whereas others showed no progression or even deteriorated.

Patients indicated to have difficulties to adhere to rehabilitation during the intensive treatment with CHRT, which might be due to the fact that patients with NSCLC often suffer from smoking-related comorbidity, physical inactivity, and frailty (6, 34), making adherence particularly challenging.

The proposed physical exercise training intervention in the current study aimed for a moderate training intensity (Borg score 13-15). Exercise session adherence was high (≥80%) in five patients with the prescribed session time, and low (48%) in one patient. Adhering to moderate intensity exercises was not feasible for the patients. In a guideline from the American Cancer Society (33), it is reported that patients receiving chemotherapy and/or radiation therapy may need to exercise at a lower intensity and/or for a shorter duration during their treatment to maintain strength, which might help to counteract fatigue and depression. It has been hypothesized that home-based low-intensity physical exercise training programs may be easier for patients to complete during chemotherapy (35), whereas higher intensity, supervised exercise programs that incorporate resistance training and aerobic exercise may be most effective to improve physical fitness (36). It could be questioned whether training at these low intensities provides sufficient overload to improve physical fitness.

However, the aim of rehabilitation during CHRT should not be to improve, but to preserve physical fitness.

Although no randomized clinical trial on rehabilitation during CHRT in patients with NSCLC has yet been conducted, it was hypothesized for this study that rehabilitation during CHRT prevents the expected decline in physical fitness and reduces treatment complications. In a previous study in patients with NSCLC (37), lower physical activity levels during chemotherapy and radiotherapy were associated with complications during and after treatment. Preliminary results of the current study showed no noticeable decline in physical activity levels. The absence of decline can be perceived as a gain for this group who would otherwise have been expected to deteriorate (37). In studies including patients with rectal cancer (20, 38), supervised physical exercise training during CHRT has also demonstrated promising results to minimize physical decline and prevent the often observed decline in physical fitness during chemoradiotherapy.

In this proof-of-concept study, patients reported positive experiences with the support and guidance of the multidisciplinary team. Patients felt that it was easy to adhere to the prescribed exercises and nutritional advice, because they were home-based and personalized to their preferences and tailored to individual needs. The perceived importance of personalised interventions is in accordance with a previous retrospective study (39), in which patients indicated that a walking intervention after treatment for lung cancer was accessible, as walking was experienced as a familiar and enjoyable form of exercise and was therefore easy to adhere to. Furthermore, another benefit of home-based exercise is that it potentially increases long-term adoption and maintenance of physical activity as part of the patient's daily routine (40, 41). In the current study, patients particularly noted the added value of guidance by a physical therapist as training volume could be adjusted in times of increased fatigue and decreased mood. Adding supervision to the home-based program might facilitate personalization of the physical exercise training program, which can improve adherence and motivation to the home-based program.

Patients in this study indicated that their informal caregivers were a major source of social support that motivated them to continue the rehabilitation program. In the patient with low adherence, there was no involvement of an informal caregiver. Among patients with cancer, social support is recognized as a positive determinant of adherence to a prehabilitation program (42). Informal

caregivers are a major source of social support and may influence patient's physical activity adoption and maintenance by serving as role models and motivators (43, 44). A previous study reported that supervision of healthcare professionals played an important role in the completion of prehabilitation in patients with cancer, as the patients needed to be pressured, monitored, and controlled (45). Supervision as part of our intervention, along with increased social support at home, may have resulted in better adherence to the intervention. A tool to improve adherence could be the use of tele-monitoring (46). In patients performing cardiac rehabilitation, technologies such as tele-monitoring can improve motivation and adherence, as coaching and encouragement are perceived as positive and supervision and adjustment of training intensity can help promote adherence through tele-monitoring while conducting their home-based physical exercise training sessions (46, 47).

Strengths and limitations

The present study provides detailed qualitative and quantitative data on the feasibility of a multimodal rehabilitation program during CHRT. This allowed patients to explain themselves how, why, or what they thought, felt and experienced at a certain time or during CHRT. This combination of qualitative and quantitative data provides deeper insights into real-world problems and aggregates patient experiences, preferences, and facilitators alongside quantitative data. However, there were also some limitations. First, program adherence was mainly assessed using the patient's diary, potentially posing a risk of bias on reliability that might over- or underestimate actual training frequency, intensity, and duration despite regular contact with healthcare professionals. Patients undergoing CHRT experience disease-related and treatment-related impairments, for which a diary could be supportive. Second, although it was not the primary aim of the study, it was not possible to measure whether there was actually a significant improvement in physical performance due to the small sample size. Alternatively, demonstrating the feasibility of the program as well as preliminary effects of the training on relevant end points is a necessary first step to generate qualitative and detailed information regarding the feasibility and experiences before the initiation of randomized controlled trials.

Implications and future research

Rehabilitation programs during CHRT can improve overall health and lifestyle in multiple areas, such as physical exercise training, nutritional support, smoking-cessation, especially with supervision of healthcare professionals (48, 49). In

patients with NSCLC undergoing CHRT, low-intensity training during CHRT seems recommended with regard to feasibility. To possibly achieve a similar training volume as moderate- to high-intensity training, it is recommended to use the results of this rehabilitation program to design a supervised and personalized rehabilitation program during CHRT with a low-to-moderate training intensity and a longer training session duration. Improving treatment outcomes in a joint coalition with patients with cancer, supported by multimodal rehabilitation during CHRT, is an emerging therapeutic area. Future research should attempt to optimize the adherence of the exercise training intensity of rehabilitation during CHRT, for example through a combination of physically guided and/or tele-monitored supervision. Moreover, a larger prospective observational study could be designed to evaluate effectiveness on aerobic fitness and treatment outcomes of rehabilitation when different interventions (e.g., supervised, partly supervised, home-based, tele-monitoring) of multimodal prehabilitation are performed by patients.

Conclusion

Supervised and personalized rehabilitation in patients with stage III NSCLC undergoing CHRT seems feasible when the intensity of the physical exercise training program and nutritional advice are adjusted to the possibilities and preferences of the patients. Furthermore, a large variety existed in response to rehabilitation as some patients showed large improvements in preliminary effects on physical and nutritional outcome measures, whereas others showed no progression or deteriorated. It is therefore recommended to use the results of this proof-of-concept study to investigate the feasibility of a supervised and personalized rehabilitation program during CHRT with a low-to-moderate exercise intensity with the aim to prevent physical decline during CHRT.

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'Through the encouragement of my wife by doing the activities of daily living and performing the physical exercises together, I was able to perform the adjusted exercises by the physiotherapist in a modified form and with an appropriate intensity.'

-Patient who underwent chemoradiotherapy for NSCLC-

Chapter 10

The clinical decision-making process of healthcare professionals within a personalized home-based rehabilitation program during sequential chemoradiotherapy for stage III non-small cell lung cancer: a case study

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Abstract

Introduction The purpose of this case study was to demonstrate the clinical decision-making process of healthcare professionals within a rehabilitation program during chemoradiotherapy (CHRT) for a high-risk patient diagnosed with stage III non-small cell lung cancer (NSCLC). The course of CHRT and patient's preferences, facilitators, and barriers were considered.

Case-description The patient was a 69-year-old man with a history of rheumatoid arthritis diagnosed with stage III NSCLC.

Intervention A home-based, personalized, and partly supervised rehabilitation program during CHRT, including aerobic, resistance, and breathing exercises, as well as nutritional counselling.

Outcomes The patient suffered from side effects of CHRT, which required adjustments in the context and intensity of the exercises. An important facilitator for the patient was encouraged by his wife in following the home-based rehabilitation program. During home visits, the patient and physiotherapists performed the exercises together to help him to overcome the burden and motivate the patient to adhere to the rehabilitation program.

Conclusion This case study demonstrates that physical exercise training could be performed by adjusting training intensity and the way in which the physical exercise training was delivered, while the patient experienced side effects from CHRT. In addition, the involvement and support of (in)formal caregivers seems essential for adherence to rehabilitation.

Introduction

Non-small cell lung cancer (NSCLC) constitutes the majority of lung cancer cases with a prevalence of approximately 85% to 90% (1). Stage III disease accounts for around 20% of all NSCLC cases (2). The main treatment for a patient with a good performance status is chemoradiotherapy (CHRT). CHRT could be delivered either concurrently or sequentially with chemotherapy preceding radiotherapy (3). Patients with stage III NSCLC often have characteristics that increase the risk for treatment complications, such as a higher age (≥50% is aged over 70 years), smoking-related comorbidity (e.g., chronic obstructive pulmonary disease (COPD), hypertension, cardiovascular disease), and poor physical performance status (4-7). Furthermore, frailty, long-term physical inactivity, and malnutrition are often present (8), which can decrease treatment tolerance, survival and quality of life (5, 9). Common consequences of treatment complications are unplanned hospitalizations (9), dose reduction (10),functional decline (11), and premature discontinuation of CHRT (10). Rehabilitation that includes physical exercise training, nutritional support, and smoking-cessation can potentially be very effective to improve treatment tolerance, quality of life, and survival in high-risk patients, especially for those receiving intensive treatment such as CHRT (12-15).

To achieve an optimal effect of rehabilitation, high adherence of patients to the rehabilitation program during CHRT is crucial to reduce treatment complications (side effects from CHRT), as well as to limit the reduction in, or even maintain, physical fitness. A recently completed feasibility study has shown that ensuring a patient's perspective, motivation, and training session and intensity adherence was challenging in patients with stage III NSCLC during CHRT (16). This feasibility study showed that understanding what amount of training volume is feasible is important. Additional understanding of the impact and process of CHRT, and barriers and facilitators experienced by patients to participate in a rehabilitation program is lacking. Therefore, it is important to understand what support patients need to adhere to a rehabilitation program (16). Especially since rehabilitation during CHRT is not yet standard care, the challenge remains to develop a rehabilitation program during CHRT with the right content and delivered in the right context to ensure that patients are able to benefit from the program and that health professionals are able to implement the program in their regular care (12).

Considering the importance of rehabilitation during CHRT in relation to treatment tolerance, the purpose of this case study was to demonstrate the clinical decision-making process of healthcare professionals in prescribing and administering a rehabilitation program during CHRT in a high-risk patient diagnosed with stage III NSCLC. The course of CHRT treatment and patient's preferences, facilitators, and barriers were taken into account.

Evidence for rehabilitation during CHRT

There is growing evidence that physical exercise training is of added value in patients with NSCLC, not only to improve treatment tolerance, but also to maintain or improve physical fitness (17). Exercises of moderate intensity, such as walking, running, swimming, or cycling, two to three times a week for 30 to 60 minutes should be offered to patients if possible (17). Challenges to exercise due to bouts of fatigue and decreased mood, decreased motivation, unplanned hospitalizations, and demanding treatment schedules should be considered (32). Support and guidance is needed, especially when daily physical exercise increases or when exercise decreases during times of side effects of CHRT (18, 19). Low-intensity home-based programs are easier than home-based high-intensity exercises for patients to follow during CHRT (20), but higher-intensity exercise programs, which include aerobic and resistance training, are the most effective for improvements in physical fitness (21). Furthermore, malnutrition is common in patients with lung cancer (22). Patients receiving CHRT for stage III lung cancer are at high risk of esophagitis and irritation of the trachea resulting in inadequate nutritional intake (23). This is further exacerbated by the cancer itself and treatment-induced catabolism, anorexia, nausea, abdominal discomfort, fatigue, pain, anxiety, depression, and other psychosocial distress. This means that adequate nutritional support and weight control are necessary (23).

The clinical decision-making process

The role of the physiotherapist, who is part of the interdisciplinary team (e.g., physiotherapist, dietician, case manager, pulmonologist), in managing care for the patient during his treatment with CHRT for stage III NSCLC was described with the application of the hypothesis-combined algorithm for clinicians II (HOAC II) for clinical reasoning. Case report guidelines (CARE) were followed (24).

Several steps throughout the algorithm highlight consulting with specialists as needed as an integral part of the decision-making process (25). The HOAC II and the recently revised World Health Organization (WHO) framework of

the international classification of functioning (ICF) were used to structure and organize the patient's medical history and clinical status, as well as to develop hypotheses prior to the pretreatment examination and development of the plan of care. The step of the HOAC II expanded with the ICF framework is shown in Figure 1.

Figure 1. The steps of the hypothesis-oriented-algorithm for clinicians II expanded with the international classification of functioning framework.

Collected initial data:	**Patient data**: 69-year-old man; married, 3 children, 7 grandchildren; ADL independent. **Medical history:** melanoma (2001); hypertension; rheumatoid arthritis. **ICF components: body function and structure:** joints (s710), hypertension (b4200), structure of the respiratory system (s430). **Medical diagnosis and treatment options:** NSCLC stage IIIB, sequential chemoradiotherapy.
	↓
Patient identified problems	Coughing, cycling, carrying household. **ICF components activities and participation:** cycling (d4700); performing household (d640).
	↓
Examination strategy	Physical functioning; nutritional assessment; quality of life and fatigue; feasibility of rehabilitation during CHRT. **ICF components body function and structure:** exercise tolerance (b455); muscle power function (b730), cardiovascular system (b410), respiratory function (b440), nutritional status, cognitive status.
	↓
Conduct examination	**Patient characteristic**: WHO performance status. **Physical parameters**: CPET; 6MWT; HGS. **Nutritional parameters**: BMI; FFMI; energy and protein intake. **Quality of life and fatigue**: MFI-20; EORTC QLQ-C30; EQ5D. **ICF components body function and structure:** exercise tolerance (b455); muscle power function (b730), cardiovascular system (b410), respiratory function (b440), nutritional status, cognitive status.
	↓
Non-patient-identified problems	**Comorbidity**: hypertension and rheumatoid arthritis. **Outcomes of examination**: low HGS, and impaired nutritional intake. **ICF components risk factors:** exercise tolerance (b455); muscle power function (b730); cardiovascular system (b410); respiratory function (b440); nutritional status; cognitive status.
	↓
Generate hypothesis	Reduction in the patient's physical fitness and nutritional status during CHRT and thereby decreased functional recovery and quality of life after treatment.

Figure 1. Continued

	↓
Identify rationale to plan of care	Through partial supervision and taking into account the patient's preferences and expectations allowing for adjustment of physical activities and nutritional intake, rehabilitation during CHRT optimizes treatment tolerance, functional recovery, and quality of life.
	↓
Establish goals	**Patient level:** performing household activities; cycling to the shopping center; care for his wife. **Therapeutic level:** optimize/ maintaining aerobic capacity level; optimize/ maintain muscle strength; optimize/maintain functional mobility.
	↓
Identify and manage anticipated problems	**Measurements during CHRT:** physical functioning; nutritional assessment; quality of life, and fatigue. **CHRT and its side effects:** adjustments in content and/or intensity of exercise rehabilitation. **Motivation and adherence:** taking preferences, facilitators, and barriers into account. **Social support:** involving informal caregiver (his wife).

Abbreviations: 6MWT=six-minute walk test; ADL=activities of daily living; BMI=body mass index; CHRT=chemoradiotherapy; CPET=cardiopulmonary exercise test; EORTC QLQ-C30=European organization for research and treatment of cancer quality of life questionnaire; HGS=handgrip strength; ICF=international classification of functioning, disability and health; FFMI=fat-free mass index; MFI=multidimensional fatigue index; NSCLC=non-small cell lung cancer VAS=visual analogue scale; WHO=World Health Organization.

Case Description: HOAC II–Part 1, Initial Data Collection

While conducting the aforementioned feasibility study (16), the importance of demonstrating the clinical decision-making process within a rehabilitation program during CHRT for a patient diagnosed with stage III NSCLC who underwent CHRT was deemed important. This case study provides insight into how optimal adherence to the rehabilitation program during CHRT can be achieved to reduce treatment complications, as well as to limit the reduction in, or even maintain, physical fitness, thereby considering patient's preferences, facilitators, and barriers. The patient selected for this case study was the next patient to be included in the feasibility study and was a 69-year-old man with a history of rheumatoid arthritis, hypertension, and melanoma (2001), living in a single-family home and able to perform his activities of daily living independently. He retired three years ago. His wife had COPD and she had

undergone surgery for colon cancer at the end of 2020. Her recovery process had stagnated, and she still suffered from abdominal complaints and shortness of breath on a regular basis. As a result, household and daily activities were mainly performed by the patient. They have three children and seven grandchildren. His exercise activities were daily cycling for one to two hours with a low to moderate intensity and supervised aqua fitness for two times a week of one hour at a moderate to high intensity. In January 2021, he consulted the general practitioner because of coughing and was referred to the nearest general hospital for an X-ray. He was diagnosed with pneumonia and despite treatment, his cough persisted. He was referred to a pulmonologist for further investigation. A positron emission tomography computed tomography (PET-CT) was performed. The PET-CT scan showed a probable carcinoma in the lung with metastases to the lymph nodes. In addition, an endobronchial ultrasound (EBUS) and magnetic resonance imaging (MRI) cerebrum examination were performed. After three weeks, the patient was diagnosed with stage IIIB NSCLC and discussed his treatment options with the pulmonologist. In Table 1, the patient journey is presented in a timeline, starting at the time he first developed physical complaints.

Plan of primary cancer treatment

During the multidisciplinary team meeting with the pulmonologist specialized in oncology, radiologist, lung surgeon, pathologist, and clinical nurse specialist, results of the diagnostics tests (e.g., PET-CT-scan and MRI-scan) and treatment options for the patient were discussed. The multidisciplinary team concluded that the diagnosis was NSCLC (stage: cT2aN3M0; histology: squamous cell carcinoma) and, taken the existing hypertension, rheumatoid arthritis, the localization and the size of the irradiation area into account, the patient was scheduled for sequential CHRT. After the multidisciplinary team meeting, the patient received an EBUS to determine the irradiation field, where mediastinal lymph nodes and cervical lymph node metastasis were found positive for squamous cell carcinoma. The patient had agreed to the proposed primary treatment with sequential CHRT. The planned chemotherapy was cisplatin 75 mg/m^2 and gemcitabine 1250 mg/m^2. Radiotherapy had to be administered in Maastro Clinic in Maastricht, because of the cervical lymph node metastasis for which radiation with a mask was necessary.

Table 1. The patient journey presented in a timeline, starting at the time he first developed physical complaints.

	Planned care	
Living context	**Primary care + planning rehabilitation interventions and assessments**	**Hospital**
• 69-year-old man • 3 children • 7 grandchildren • Living in a single-family home • Married • Activities: 1/day cycling and 2/week swimming		
	• 1 month before treatment: appointment with the general practitioner with referral to the pulmonologist	X-ray thorax
	• 3 weeks before CHRT: PET-CT thorax • 2 weeks before CHRT: consultation pulmonologist for diagnosis • 1 week before CHRT: multidisciplinary team meeting: discussed that sequential CHRT is the best treatment option; consultation pulmonologist: treatment plan discussed with the patient including the option for rehabilitation during CHRT	
	Sports physician: • Baseline assessment[a] Physiotherapist: • Baseline assessments[a] • 1/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based exercises during a hospital visit for CT Dietician: • Baseline assessments[a] • Hospital visit for CT with nutritional advice Research nurse: • EQ-5D-L and EORTC QLQ-C30	CT with cisplatin (158 mg) and gemcitabine (2630 mg)
	Physiotherapist: • Home visit to evaluate and instruct physical exercises Dietician: • Phone call to evaluate and coach nutritional intake	Last infusion of CT to complete course 1

	Timeline	Outcomes	
		Clinical decision-making process	Patient's barriers and facilitators
	<------Diagnostic process------>		Complaints: • Dyspnea for one month • Coughing for one month • Pneumonia
	T0 Week 1	Training was performed with a 6-20 Borg RPE score of 13	• Difficulty physical exercises: VAS[b] 4 • Complaints: none • Facilitators: making barriers and facilitators discussable by the physiotherapist to create a safe atmosphere and discuss the expectations of the patient and his wife towards each other, doing the home-based exercises together by the physiotherapist and his wife • VAS for motivation physical exercises: 9
	week 2	Training intensity was adjusted to a 6-20 Borg RPE score of 11-12 because of increasing fatigue; the patient pays extra attention to nutrition with proteins	• Difficulty physical exercises: VAS 4-5 • Barrier: moderate fatigue • Facilitators: feeling safe by the support of the dietician and his wife doing the home-based exercises together, beliefs about the effects of exercise and his desire to perform activities independently as much as possible

Table 1. Continued

Planned care		
Living context	**Primary care + planning rehabilitation interventions and assessments**	**Hospital**
	Physiotherapist: • 2/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	
	Physiotherapist: • 2/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	
	Physiotherapist: • Assessment[a] • 1/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises by a hospital visit during CT Dietician: • Assessment[a] • Hospital visit during CT • Research nurse: • EQ-5D-L and EORTC QLQ-C30	• CT with cisplatin (123 mg) and gemcitabine (2050 mg) with 25% dose reduction due to slow recovery of the leukocytes • Injection of pegfilgrastim
	Physiotherapist: • 1/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	Last infusion of CT to complete course 2
	Physiotherapist: • 2/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	

Timeline	Outcomes	
	Clinical decision-making process	Patient's barriers and facilitators
Week 3	Training intensity was adjusted to a 6-20 Borg RPE score of 11-12 because of fatigue	• Difficulty physical exercises: VAS 6-7 • Barriers: shortness of breath, skin pain on the head • Facilitator: the support of his wife doing the home-based exercises together
Week 4	Training intensity was adjusted to a 6-20 Borg RPE score of 11-12 because of fatigue	• Difficulty physical exercises: VAS 5 • Barriers: bleeding from the nose by blowing, inflammation of the nose • Facilitator: the support of his wife doing the home-based exercises together • Comments: CT postponed due to poor blood values, bad mood
T1 Week 5	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue	• Difficulty physical exercises: VAS 5 • Barriers: none • Facilitators: the support of his wife doing the home-based exercises together, intensive coaching from the physiotherapist to master the aerobic and resistance exercises, and inspiratory muscle trainer, share emotions and frustrations with the physiotherapist regarding fatigue and pain and the intensity of chemotherapy • VAS for motivation physical exercises: 9
Week 6	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue, and pain in bones and muscles	• Difficulty physical exercises: VAS 7 • Barriers: pain in bones and muscles due to the injection of pegfilgrastim, less appetite • Facilitators: his daughter by giving the injection with pegfilgrastim, motivation by the support of his wife doing the home-based exercises together
Week 7	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue, and pain in bones and muscles	• Difficulty physical exercises: VAS 8 • Barriers: pain in bones and muscles due to the injection • Facilitator: better appetite, positive communication and feedback from his children and grandchildren, motivation by the support of his wife doing the home-based exercises together

Table 1. Continued

Planned care		
Living context	**Primary care + planning rehabilitation interventions and assessments**	**Hospital**
	Physiotherapist: • 1/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	• X-ray thorax and consultation pulmonologist • CT with cisplatin (165 mg) and gemcitabine (2750 mg) • Injection of pegfilgrastim
	Physiotherapist: • 2/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	Last infusion of CT to complete course 3
	Physiotherapist: • 2/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	
	Physiotherapist: • 1/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	• Consulta-tion pulmo-nologist • CT with cisplatin (165 mg) and gemcitabine (2750 mg)
	Physiotherapist: • 1/week supervised swimming at the rehabilitation department in the hospital, home-based visit • Coaching in home-based physical exercises	Last infusion of CT to complete course 4

Timeline	Outcomes	
	Clinical decision-making process	Patient's barriers and facilitators
Week 8	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue, and pain in bones and muscles	• Difficulty physical exercises: VAS 6 • Barriers: fatigue, pain in bones and muscles • Facilitators: the support of his wife doing the home-based exercises together, share emotions and frustrations with the physiotherapist regarding fatigue and pain and the intensity of chemotherapy • Comments: positive feeling, tumor shrunk
Week 9	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue, and pain in bones and muscles	• Difficulty physical exercises: VAS 8 • Barrier: pain in bones and muscles due to the injection • Facilitator: the support of his wife doing the home-based exercises together
Week 10	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue, and pain in bones and muscles	• Difficulty physical exercises: VAS 6 • Barriers: fatigue, pain in bones and muscles • Facilitator: the support of his wife doing the home-based exercises together
Week 11	Training intensity was adjusted to a 6-20 Borg RPE score of 11 because of fatigue	• Difficulty physical exercises: VAS 7 • Barrier: moderate fatigue • Facilitator: the support of his wife doing the home-based exercises together
Week 12	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue, and pain in bones and muscles	• Difficulty physical exercises: VAS 6 • Barrier: none • Facilitator: the support of his wife doing the home-based exercises together • Comments: glad the last CT is over

Table 1. Continued

Planned care		
Living context	**Primary care + planning rehabilitation interventions and assessments**	**Hospital**
	Physiotherapist: • Assessment[a] • Coaching in home-based physical exercises • Dietician: • Assessment[a] • Research nurse • EQ-5D-L and EORTC QLQ-C30	• PET-CT thorax • Consultation pulmonologist for results scan and discuss further treatment plan • Packed cell transfusion due to low platelets and anemia
	Physiotherapist: • Coaching in home-based physical exercises by a phone call	
	Physiotherapist: • Coaching in home-based physical exercises by a phone call	• CT-scan Maastro Clinic Maastricht before radiotherapy
		• CT-scan Maastro Clinic Maastricht • First radiotherapy session
	Physiotherapist: • Coaching in home-based physical exercises by a phone call Dietician: • Phone call[c]	Radiotherapy sessions

	Timeline	Outcomes	
		Clinical decision-making process	Patient's barriers and facilitators
	T2 Week 13	Training intensity was adjusted to a 6-20 Borg RPE score of 10-11 because of fatigue and poor blood values	• Difficulty physical exercises: VAS 9 • Barrier: fatigue • Facilitator: adequate action by the physiotherapist by contacting the case manager motivation by the support of his wife doing the home-based exercises together • VAS for motivation physical exercises: 9
	Week 14	Training intensity was adjusted to a 6-20 Borg RPE score of 11-12 because of fatigue	• Difficulty physical exercises: VAS 9 • Barrier: fatigue • Facilitator: the support of his wife doing the home-based exercises together
	Week 15	Training intensity was adjusted to a 6-20 Borg RPE score of 11-12 because of fatigue	• Difficulty physical exercises: VAS 8 • Barrier: moderate fatigue • Facilitator: the support of his wife doing the home-based exercises together • Comments: failed CT-scan because puncture failed
	Week 16	Training intensity was adjusted to a 6-20 Borg RPE score of 12 because of fatigue	• Difficulty physical exercises: VAS 6 • Barrier: serious fatigue • Facilitator: the support of his wife doing the home-based exercises together • Comments: glad that the CT-scan was successful, making a radiotherapy mask was an emotional moment
	Week 17	Training intensity was adjusted to a 6-20 Borg RPE score of 10 because of fatigue	• Difficulty physical exercises: VAS 8 • Barriers: serious fatigue, daily afternoon nap • Facilitators: the support of his wife doing the home-based exercises together and activities of daily living together, creating a new daily routine with the physiotherapist

Table 1. Continued

	Planned care	
Living context	**Primary care + planning rehabilitation interventions and assessments**	**Hospital**
	Physiotherapist: • Coaching in home-based physical exercises by a phone call Dietician: • Phone call[c]	Radiotherapy sessions
	Physiotherapist: • Coaching in home-based physical exercises by a phone call Dietician: • Phone call[c]	Radiotherapy sessions
	Physiotherapist: • Coaching in home-based physical exercises by a phone call Dietician: • Phone call[c]	Radiotherapy sessions
	Physiotherapist: • Coaching in home-based physical exercises by a phone call Dietician: • Phone call[c]	Last radiotherapy session
	Physiotherapist: • Coaching in home-based physical exercises by a phone call Dietician: • Phone call[c]	• X-ray • Consultation pulmonologist

Timeline	Outcomes	
	Clinical decision-making process	Patient's barriers and facilitators
Week 18	Training intensity was adjusted to a 6-20 Borg RPE score of 10 because of fatigue and irritation of the trachea during radiotherapy; the patient received adapted nutritional advice to improve the safety and comfort of eating and to maintain nutritional intake	• Difficulty physical exercises: VAS 8 • Barriers: serious fatigue, daily afternoon nap, burnt skin in the neck on both sides, a black tongue, a dry mouth, irritation of the trachea • Facilitator: the support of his wife doing the home-based exercises and activities of daily living together
Week 19	Training intensity was adjusted to a 6-20 Borg RPE score of 10 because of fatigue	• Difficulty physical exercises: VAS 8 • Barriers: serious fatigue, daily afternoon nap, burnt skin in the neck on both sides, a black tongue, and a dry mouth • Facilitator: the support of his wife doing the home-based exercises and activities of daily living together
Week 20	Training intensity was adjusted to a 6-20 Borg RPE score of 10 because of fatigue	• Difficulty physical exercises: VAS 8 • Barriers: serious fatigue, daily afternoon nap, burnt skin in the neck on both sides, a black tongue, and a dry mouth • Facilitator: the support of his wife doing the home-based exercises together
Week 21	Training intensity was adjusted to a 6-20 Borg RPE score of 10 because of fatigue	• Difficulty physical exercises: VAS 8 • Barriers: serious fatigue, daily afternoon nap, burnt skin in the neck on both sides, a black tongue, and a dry mouth • Facilitator: the support of his wife doing the home-based exercises together
Week 22	Training intensity was adjusted to a 6-20 Borg RPE score of 10 because of fatigue	• Difficulty physical exercises: VAS 8 • Barriers: serious fatigue, daily afternoon nap, burnt skin in the neck on both sides, a black tongue, and a dry mouth • Facilitator: the support of his wife doing the home-based exercises together • Comments: tumor has shrunk, cautiously positive

Table 1. Continued

Planned care		
Living context	**Primary care + planning rehabilitation interventions and assessments**	**Hospital**
Start swimming in own environment	Physiotherapist: • Coaching in home-based physical exercises by a phone call	CT-scan
	Physiotherapist: • Assessment Dietician: • Assessment Research nurse: • EQ-5D-L and EORTC QLQ-C30	

[a]: Assessments: CPET by the sport physician; 6MWT, HGS, and MFI-20 by the physiotherapist; BMI, FFMI, energy and protein intake by the dietician; EORTC and EQ-5D-L by the research nurse.
[b]: 0-10 VAS scale: 0=very easy; 10=very hard.
[c]: As the patient receives radiotherapy in the Maastro Clinic in Maastricht, the weekly regular consultation has been changed to a telephone consultation.
Abbreviations: 6MWT=six-minute walk test; ADL=activities of daily living; BMI=body mass index; CHRT=chemoradiotherapy; CPET=cardiopulmonary exercise test; CT=chemotherapy; EORTC QLQ-C30=European organization for research and treatment of cancer quality of life questionnaire; EQ-5D-L=European quality of life five dimension; HGS=handgrip strength; FFMI=fat free mass index; MFI=multidimensional fatigue index; PET-CT=positron emissive tomography computed tomography; RPE=rating of perceived exertion; VAS=visual analogue scale.

	Timeline	Outcomes	
		Clinical decision-making process	Patient's barriers and facilitators
	Week 27	Training intensity was adjusted to a 6-20 Borg RPE score of 11-12 because of fatigue	• Difficulty physical exercises: VAS 4 • Barriers: burnt skin in the neck on both sides, a black tongue, and a dry mouth • Facilitator: less fatigue, the support of his wife doing the home-based exercises together • Comments: tumor seems to have disappeared, positive mood
	T3 Week 32	Training intensity was adjusted to a 6-20 Borg RPE score of 12-13 because of fatigue	• Difficulty physical exercises: VAS 4 • Barriers: a black tongue, and a dry mouth • Facilitator: less fatigue, the support of his wife doing the home-based exercises together • VAS for motivation exercises: 9

Examination strategy

The clinical impression was that this patient had several risk factors which were associated with complications during and after treatment (e.g., age, comorbidity). Because of these patient characteristics, this patient was eligible for participation in the aforementioned feasibility study. The patient received information about the study while discussing the treatment plan with the pulmonologist (Table 1). Three days later, the case manager (nurse specialized in lung oncology) contacted the patient by telephone to inquire about the possibility of participating in the study. The patient was educated about the possibilities of optimizing physical functioning to reduce the risk of intolerance of CHRT and to improve treatment outcomes. After the patient agreed to participate, the case manager informed the study team and appointments with the physiotherapist, sports physician, and dietician were scheduled. The rehabilitation program during CHRT consisted of multiple collaborative disciplines to optimize and maintain the patient's physical fitness, nutritional status, and the patient's journey. Assessments for the study and personal appointments with healthcare professionals were combined as much as possible with standard hospital visits.

Plan of pretreatment examination

Baseline parameters (demography, WHO performance status, patient's preferences, facilitators, and barriers for rehabilitation during CHRT, physical fitness, nutritional status, and quality of life) were assessed before the start of CHRT (T0). The aim of this pretreatment baseline assessment was to evaluate the patient's physical status (e.g., physical functioning parameters, nutritional parameters), to provide personalized advice regarding physical exercise training and nutrition, and to deliver the treatment in the most facilitative context.

The pulmonologist referred the patient to the sports physician for a cardiopulmonary exercise test (CPET) to examine the patient's aerobic fitness and set personalized training zones for the start of physical exercise training. An incremental CPET (12 W/min) was performed until exhaustion on an electronically braked cycle ergometer (Monark, LC6 novo, Vansbro, Sweden) according to ATS/ERS standards (26) with respiratory gas analysis measurements. In case of a maximal effort (respiratory exchange ratio (RER) at peak exercise (RER_{peak}) >1.10), absolute oxygen uptake (VO_2) at peak exercise (VO_{2peak}) was calculated as the average value over the last 30 seconds prior to termination of the test. In order to personalize the content and intensity

of the rehabilitation during CHRT, the physiotherapist evaluated the level of physical functioning by using performance-based tests to estimate functional walking distance (six-minute walk test (6MWT)), muscle strength (handgrip strength (HGS)), and daily physical activity level (pedometer). Functional walking distance was assessed by the 6MWT according to the ATS guideline (27). After the 6MWT, the patient was asked to rate his individually perceived exertion using the 6-20 Borg rating of perceived exertion (RPE) scale (28). To evaluate muscle strength, HGS was assessed with a Jamar hydraulic hand dynamometer (J.A. Preston Corporation, Jackson, MI, USA). The highest value of three attempts for the dominant hand was registered (29) and compared with norm values (the UK Biobank reference values, taking sex, age, and body height into account (30)). Fatigue was measured with the multidimensional fatigue index-20 (MFI). In addition, the physiotherapist evaluated the preferences, facilitators, and barriers with respect to the rehabilitation program before and during CHRT in order to offer a tailor-made rehabilitation program to optimize treatment adherence while considering the side effects of CHRT.

To provide tailored nutritional advice, the dietician evaluated the patient's nutritional status by body mass index (BMI), fat free mass index (FFMI), waist circumference, and daily energy requirement compared to the protein requirement of 1.5 g/kg. In addition, the dietician provided insight into the minimal daily energy requirement, which was estimated using the formula Harris & Benedict with surcharge 30-50% (31). Body height was measured in standing position without shoes. Body mass was measured without shoes and coat. Body composition assessment (e.g., FFMI) was performed by direct segmental multi-frequency bioelectrical impedance analysis (Esca Medical Body Composition Analyser 515, Hamburg, Germany). The estimates obtained are from the manufacturer's proprietary algorithms with the patient standing.

The research nurse evaluated the health-related quality of life (HRQoL) with the following validated questionnaires: European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30) and European quality of life five dimension (EQ-5D-5L) (32).

Results of pretreatment examination

Results of the pretreatment examination are presented in Table 2 and Figure 2 and the most important outcomes are described below. The pulmonologist independently classified the patient with a WHO performance status of I which indicates a good level of physical function (33). The patient scored a VAS 9 for

motivation to follow the rehabilitation program during CHRT. The patient had a VO_{2peak} of 19.2 mL/kg/min at the baseline CPET with a RER_{peak} of 1.06. The maximal HGS score was 26 kg (57% of the norm value). Nutritional assessment revealed a BMI of 31.4 kg/m^2, a FFMI of 19.2 kg/m^2, a waist circumference of 120 cm, and a current deficiency of energy and protein (60% and 75% of the recommended amount). The patient indicated that he was satisfied with his current physical activity level and that he would like to continue swimming. He also stated: "*I need my wife to stay motivated, as she stimulates me to adequately follow the rehabilitation program.*" The global quality of life score on the EORTC QLQ-C30 was 75%.

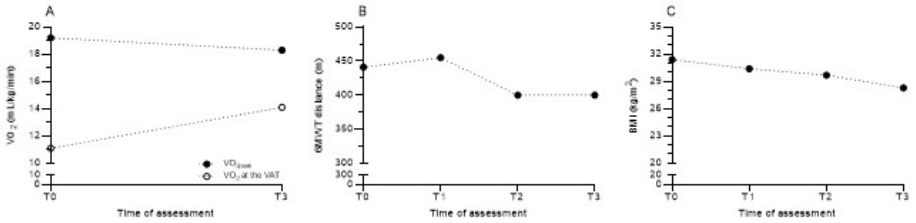

Figure 2. Changes in physical and nutritional parameters at T0, T1, T2, and T3. Graphs represent outcomes of the VO_{2peak} mL/kg/min and VO_2 at the VAT at the CPET (A), distance at the 6MWT (B), and BMI kg/m^2 (C).
Abbreviations: 6MWT=six-minute walk test; BMI=body mass index; CPET=cardiopulmonary exercise test; VAT=ventilatory anaerobic threshold; VO_2=oxygen uptake; VO_{2peak}=oxygen uptake at peak exercise.

Evaluation

Quantitative clinical impression II

The examination supported the clinical impression that this patient had several risk factors that might be associated with complications during and after treatment. According to previous studies, his advanced age, comorbidities, no maximal effort on the CPET, low HGS, and his impaired nutritional intake at baseline (Table 2) are all independently associated with a high risk for treatment complications (33, 34). To prevent the patient from intolerance of CHRT which might lead to a delayed treatment, decline in physical functioning, complications, and an impaired recovery of physical functioning after treatment, it is recommended to support the patient to maintain or even improve his physical fitness and nutritional status during CHRT.

Table 2. Patient characteristics and outcomes of physical and nutritional parameters.

Age (years)	69			
Sex	Male			
NSCLC stage	IIIA			
Comorbidities	Melanoma 2001, rheumatoid arthritis since 2010			
	T0[a]	**T1**	**T2**	**T3**
WHO performance status	I	I	I	I
Smoking	No	No	No	No
VAS for motivation	9	9	9	9
Physical parameters				
CPET VO_{2peak} (mL/kg/min)	19.2	-	-	18.3
CPET VO_2 at the VAT (mL/kg/min)	11.1	-	-	14.1
CPET RER_{peak}[b]	1.06	-	-	1.03
6MWT distance (m)	441	455	400	400
6MWT 6-20 Borg RPE score	12	12	13	13
HGS (kg) (%[c])	26 (57%)	28 (62%)	25 (55%)	29 (64%)
Nutritional parameters				
BMI (kg/m^2)	31.4	30.4	29.7	28.3
FFMI (kg/m^2)	19.2	17.8	17.5	17.6
Waist circumference (cm)	120	116	116	113
Energy intake (%)	60	86	100	64
Protein intake (%)	75	92	100	83
MFI-20				
General fatigue	15	12	16	16
Physical fatigue	12	10	16	13
Activity	12	12	14	13
Motivation	12	11	13	13
Mental fatigue	12	11	13	9
EORTC QLQ-C30				
Global health (%)	50	67	67	83
EQ 5D				
Health today (%)	75	75	75	83

Abbreviations: 6MWT=six-minute walk test; BMI=body mass index; CPET=cardiopulmonary exercise test; EORTC QLQ-C30=European organization for research and treatment of cancer quality of life questionnaire; HGS=handgrip strength; FFMI=fat free mass index; MFI=multidimensional fatigue index; RER_{peak}=respiratory exchange ratio at peak exercise; RPE=rating of perceived exertion; VAS=visual analogue scale; VAT=ventilatory anaerobic threshold; VO_{2peak}=oxygen uptake at peak exercise; WHO=World Health Organization.

[a]Timing of the outcome assessment: before the start of CHRT (T0), between the first and second chemotherapy (T1), after the last session of radiotherapy (T2), three months after the last treatment (T3).

[b]maximal effort was achieved at a RER_{peak} >1.10.

[c]compared with norm values (the UK Biobank reference values, taking sex, age, and body height into account (10).

Plan of rehabilitation during CHRT

The blueprint of the physical exercise training program was developed according to the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool (35) and training frequency, intensity, time, and type are presented in Table 3. The physical exercise training program was carried out in the patient's living environment. Once every two weeks, the program was supervised by a physiotherapist specialized in oncology from the rehabilitation department of the hospital. To improve aerobic fitness, the advice was to do aerobic exercises at least five times a week with an intensity using the 6-20 Borg RPE scale 13-15. The patient chose to cycle at least five times a week outside in his own neighborhood, and to swim two times a week at the rehabilitation department in the hospital under supervision of the physiotherapist. Exercises using stairs and furniture such as chair, bench, and table were used to improve muscle strength and endurance. A Thera-band and filled 0.5-liter bottles were used for additional resistance. For improving pulmonary function, the patient performed inspiratory muscle training consisting of two daily sessions of 30 breaths using an inspiratory muscle trainer (Threshold IMT, Philips Respironics, Murrysville, PA, USA) at the highest tolerable intensity (36). The initial resistance (cm H_2O) was set and the initial resistance using the 6-20 Borg RPE scale 13-15. At the first home-based visit of the physiotherapist, the patient's wife was involved and her role in the rehabilitation program was discussed. The patient and his wife expected that the rehabilitation program would be challenging, and that encouragement would be needed. The patient indicated that support and encouragement of his wife was important and could motivate and help him to persist in following the rehabilitation program. Especially performing exercises together would encourage him. Daily physical activity level was assessed by a pedometer (Hyrax Walk pedometer, TFA Dostmann, Wertheim, Germany). The physiotherapist also invited the patient's wife to participate in the swimming exercises, because she indicated that she would like this, and it would motivate her husband.

Nutritional counselling was performed based on the standard protocol for patients with cancer in the general (23) and elderly population (37). Individualized counselling was used to educate the patient on how to modify his usual meals by making them adhere to individual energy, protein, and other macronutrient requirements. The dietary advice focused on specifying the type and amount of food, the number of meals, and calorie or protein amounts to achieve a daily base or dietary recommendation as part of standard care. Advice was personalized to the patient's eating pattern and preferences by the dietician.

Table 3. Blueprint of the physical exercise training program according to the i-CONTENT tool.

Patient selection	Patients aged ≥50 years diagnosed with stage III NSCLC according to the 8th edition of the TNM guidelines undergoing CHRT (either concurrent CHRT or sequential CHRT).
Type and dosage of the rehabilitation program during CHRT (F: Frequency, I: intensity, T: Time, T: Type)	**Aerobic exercises**: **F:** 5 times/week, **I:** 6-20 Borg RPE score 13-15, **T:** 30-60 min**, T**: functional exercises involving large muscle groups (e.g., walking, cycling, climbing stairs, swimming). **Resistance exercises**: **F:** 3 times/week, **I:** 6-20 Borg RPE score 13-15, **T**: 3 × 15-20 repetitions, **T:** peripheral resistance training of the large muscle groups of the lower and upper extremities using open and closed kinetic chain exercises (e.g., stair climbing, sit-to-stand exercises, Thera band exercises, exercises using filled 0.5-liter bottles). **Breathing exercises**: **F:** 2 times/day, **I:** highest tolerable intensity, **T:** 30 breaths, **T:** inspiratory muscle training.
Qualified supervisor (if applicable)	The physical exercise training program was carried out in the patient's living environment, once every two weeks supervised by a physiotherapist specialized in oncology.
Type and timing of outcome assessment	Type: the preferences, facilitators, barriers, and adverse events with respect to the rehabilitation program were evaluated before and during CHRT. Physical fitness was measured with the CPET, 6MWT, and HGS. Timing: before the start of CHRT (T0), between the first and second chemotherapy (T1), after the last session of radiotherapy (T2), and three months after the last treatment (T3).
Safety of the exercise program	Patient dropout and adverse events to rehabilitation during CHRT were registered by the healthcare professionals during contact moments as part of usual care.
Adherence to the exercise program	Adherence was monitored with a diary and weekly feedback from patients: successful exercise session adherence was defined as achieving >80% of the prescribed duration, intensity, and frequency of the training sessions during the physical exercise training program.

Abbreviations: 6MWT=six-minute walk test; CHRT=chemoradiotherapy; CPET=cardiopulmonary exercise test; HGS=handgrip strength; i-CONTENT=international consensus on therapeutic exercise and training; NSCLC=non-small cell lung cancer; RPE=rating of perceived exertion.

Patient's preferences, experiences, facilitators, and barriers regarding physical exercise training, supervision, dietary advice, and social support (his wife) were recorded via usual care appointments with the physiotherapist, dietician, and case manager every two to three weeks. During these appointments it was evaluated how the rehabilitation program was experienced. In a short interview with the physiotherapist several items were discussed to gain insight into the patient's view (see Table 4). Social support was given by the healthcare professionals during the entire rehabilitation program to, for example, perform the exercises together and encourage and support the patient. The case

manager contacted the patient by telephone at least every two to three weeks as part of usual care and evaluated with the patient his compliance and his experiences with the program. Motivation was measured after each supervised physical exercise training session by asking the patient to rate his motivation to adhere to the personalized pretreatment rehabilitation plan, with help of a visible analogue scale (VAS) from 0-10, in which 10 meant excellent motivation.

To monitor changes in functioning and motivation, and subsequently adjust the program, baseline assessments, except for the CPET, were repeated between the first and second course of chemotherapy (T1) and after the last session of radiotherapy (T2). Three months after treatment (T3), all assessments, including the CPET, were repeated. The patient kept a daily diary to monitor whether the rehabilitation program during CHRT was followed or not. The patient journey is presented in a timeline in Table 1, starting at the time he first developed physical complaints.

Table 4. Questions to the patient about the experiences, preferences, barriers, and needs of the rehabilitation program.

1. What do you think the rehabilitation program during CHRT can bring you?
2. How active are you on this moment? Can you give a number for the current activity with the VAS 0-10? Not active 0 1 2 3 4 5 6 7 8 9 10 active
3. Would you like to become even more active during CHRT?
4. Do you plan to continue following the rehabilitation program?
5. Do you think you can adhere the rehabilitation program?
6. To what extent you can maintain this?
7. What helps you to adhere the rehabilitation program?
8. Can informal caregivers help you to adhere to the program?
8a. How should they do that? 8b. Is it nice if someone comes along? 8c. Why do you need that?
9. To what extent did you succeed in following the rehabilitation program?
9a. What made it work? 9b. What made it fail?

Abbreviations: CHRT=chemoradiotherapy; VAS=visual analogue scale.

Tailoring of the rehabilitation program during CHRT

Ten days after the consultation with the pulmonologist in which the treatment plan with CHRT and participation in the rehabilitation program during CHRT was discussed, the first chemotherapy was administered. The patient indicated: *"I had only a little time to think about treatment and rehabilitation choices, because the first chemotherapy was provided as soon as possible".*

At the first home-based visit by the physiotherapist, a safe atmosphere was needed to discuss the importance of managing his physical activity and nutrition intake to achieve optimal benefits from rehabilitation during CHRT. The patient indicated that he preferred to carry out daily activities, such as cooking and cleaning, as independently as possible.

Rehabilitation during chemotherapy

The patient received the first course of cisplatin (158 mg) and gemcitabine (2630 mg). The patient had to spend the night in the hospital for prehydration so that he could receive chemotherapy the following day. One week after admission, the patient received an additional intravenous dose of gemcitabine to complete the course. The first course of chemotherapy resulted in mild complaints on the 10th day with fatigue and a few days of constipation which was treated with Movicolon. The patient was able to perform his weekly physical exercise training with a Borg RPE score between 11-13. Facilitators of adherence to the rehabilitation program were his beliefs about the positive effects of exercise and good nutrition, his desire to perform activities independently as much as possible. Furthermore, the patient indicated that he needed the support of his wife to persevere his exercise program: *"I occasionally need a kick in the ass from my wife to complete my exercises, but it is especially encouraging when she says she is proud of how I am handling the situation."* The patient's wife accompanied the patient to all hospital appointments and often participated in physical exercises during home-based visits by the physiotherapist. The patient prepared the meals together with his wife, taking the nutritional advice of the dietitian into account. After the first course of chemotherapy, the physical and nutritional tests took place (T1). The patient improved his 6MWT distance with 3% and HGS with 5% in comparison with T0. BMI, FFMI, and waist circumference decreased slightly (3.2%, 7.3%, and 4.0 cm), but energy and protein intake had improved with 43% and 23%. The score on de MFI-20 decreased with 11%. The score on HRQoL remained stable. It was notable that intensive coaching from the physiotherapist for the first two weeks facilitated the patient to master the aerobic and resistance exercises, as well as the inspiratory muscle training. During all courses of chemotherapy, the same training intensity was maintained during inspiratory muscle training.

Because of febrile neutropenia, the second course of chemotherapy was delayed for a week and was given with a 25% dose reduction (123 mg cisplatin and 2050 mg gemcitabine). The third course of chemotherapy was given with the scheduled dose (cisplatin 165 mg and gemcitabine 2750 mg). For the

febrile neutropenia, the patient received an injection of pegfilgrastim after the second and third course. There were severe side effects of this injection with pegfilgrastim, such as fatigue and pain (0-10 visual analogue scale (VAS) score of 8) in bones and muscles. Acetaminophen relieved this pain a little bit. In this situation, particularly his daughter supported her father by giving him the injection with pegfilgrastim at home, thereby normalizing the side effects of CHRT which reassured him. A weekly telephone consultation with the physiotherapist was scheduled to adjust the program when needed and to motivate the patient. During these consultations the side effects fatigue and pain were discussed which helped to put these symptoms in the right perspective. The physiotherapist advised to continue the physical exercise training at a lower training intensity, according to the evidence that patients receiving chemotherapy and/or radiation therapy may need to exercise at a lower intensity and/or shorter duration during their treatment (33). While doing exercises in the water, there was an opportunity to share emotions and frustrations with the physiotherapist regarding fatigue, pain, and the intensity of chemotherapy. This helped the patient to feel comfortable, which, according to the patient, also improved exercise adherence. The home-based visits were experienced as motivating to complete the exercises because they were performed together with the physiotherapist. The patient was able to maintain exercise and swimming at a lower intensity (Borg RPE score of 10-11), primarily with the encouragement and awareness of the benefits by the physiotherapist. Despite this, the patient experienced setbacks from the primary cancer treatment and his mood was sometimes depressed. In order to remain as physically active as possible, it was discussed with the patient how to continue the physical exercises and to optimize his energy and protein intake. The patient indicated that he liked to cycle outside, and it was agreed that he would cycle to a grocery store every day (30 minutes with a Borg RPE score of 12). The patient's wife motivated the patient to adhere to the dietary recommendations as good as possible by letting him choose the meals that best tasted him. It helped the patient to choose his own meals and he tried to adhere to the nutritional advice; however, he could not eat the advised amounts due to decreased appetite. Positive communication and feedback from his children and grandchildren were important for admission, but also as a facilitator to remain physically active so that family activities important for the patient (e.g., barbequing) could continue. The physiotherapist called the patient every week so that the patient could tell his story and adjustments could be made in the rehabilitation program. The patient liked the phone calls, because it felt like encouragement and motivated him to stay as physically active as possible.

The last course of chemotherapy (165 mg cisplatin and 2750 mg gemcitabine) was completed without major complications; however, the patient experienced severe fatigue which increased in the four weeks after chemotherapy. The patient's physical activity level decreased, and he reported not feeling well on a regular basis. He felt tired and out of breath, and his wife tried to motivate him to carry out daily activities (e.g., cycling to the grocery store) by doing these activities together as much as possible. Swimming felt like a very big effort. He stated: *"I was really thrown back by the chemotherapy, but I was relieved to be able to discuss this with the physiotherapist as she reassured me and contacted the case manager about my physical decline".* A blood test showed that his platelets were too low, and a packed cell transfusion was necessary.

During the last course of chemotherapy and the start of radiotherapy, the physiotherapist advised to continue exercising as much as possible and motivated the patient with the information to use the time between chemotherapy and radiotherapy to optimize his physical fitness. The patient regained his body mass and was able to perform his physical exercises with the same intensity as at the start of the rehabilitation program during CHRT.

Rehabilitation during radiotherapy

Three weeks after the last chemotherapy, radiotherapy with an arc technique using 6–10 MV photons was started. The schedule included 25 × 2.75 Gy (once daily). The dose was specified at 100% in the international commission on radiation units and measurements reference point. The dose gradient was 95-115%. In addition, the cervical lymph node metastasis had to be irradiated, for which a radiation mask had to be fitted. As a result, the patient received radiotherapy in the Maastro Clinic in Maastricht (more than one-hour travel time). It was of great support for the patient that he travelled together with his wife during each radiotherapy session. Together with the psychical therapist, a daily routine was developed to perform his daily activities and physical exercises, but also considering radiotherapy and the associated travel time.

There was no delay in treatment time during radiotherapy and there were no unplanned hospital admissions. The patient had mild irritation of the trachea during radiotherapy for which he received adapted nutritional advice to improve the safety and comfort of eating and to maintain nutritional intake. In addition, in the third week of radiotherapy, the patient suffered from burnt skin in the neck on both sides, a black hairy tongue, and a dry mouth. The patient was very tired, so the intensity of the physical exercise training had to be adjusted in

consultation with the physiotherapist to a level that the patient could sustain for at least 20 minutes and with a Borg RPE score between 10 and 12. The breathing exercises could not be performed due to fatigue and irritation of the trachea. In addition, his wife developed serious intestinal problems, which required additional hospital visits with examinations.

The physical and nutritional tests were all repeated after radiotherapy (T2) and compared with T1. There was a reduction of 12% in 6MWT distance and 7% on HGS. There was a slight decrease in BMI and FFMI (3.3% and 2.7%), but waist circumference remained stable, while energy and protein intake were 100%. The score on the MFI-20 also increased fatigue with 29%. The patient was encouraged to continue doing daily activities as much as possible and to take regular rest periods. The patient indicated: *"My wife facilitates me to carry out my daily activities as much as possible by going to the grocery store, cooking, and doing the household together."*

Three-month follow-up (T3)

Three months after completing radiotherapy, the side effects of the radiotherapy had disappeared, except for a cough and a black hairy tongue. In particular, the black hairy tongue he experienced as mentally very bothersome. The last physical and nutritional assessments took place (T3) and showed a VO_{2peak} of 18.3 ml/kg/min (95% compared with T0) with a RER_{peak} of 1.03 and an 6MWT distance equal to T2 (see Table 2 and Figure 2). BMI and waist circumference decreased slightly again (4.8% and 3 cm) compared with T2, while FFMI remained stable. Food intake was strongly reduced with a relative energy intake of 64% and a protein intake of 83%. MFI-20 score had positively improved by 10% between T2 and T3 and HRQoL improved with 8%. The patient indicated that he was able to resume physical activities at the same level as before the cancer treatment. The patient indicated: *"I was able to slowly build up the activities to the starting level by taking my daily routine with fixed moments of rest into account. Through the encouragement of my wife by doing the activities of daily living and performing the physical exercises together, I was able to perform the adjusted exercises by the physiotherapist in a modified form and with an appropriate intensity."* Four weeks after the last session of radiotherapy, the patient started swimming again in his own environment with a group of people with rheumatoid arthritis.

Discussion

The purpose of this case study was to demonstrate the clinical decision-making process of healthcare professionals within a rehabilitation program during CHRT for a patient diagnosed with stage III NSCLC, taking the course of treatment with CHRT and patient's preferences, facilitators, and barriers into account. The course of this clinical decision-making process within rehabilitation provided two important clinical considerations by using the HOAC II. First, rehabilitation during CHRT was possible when adjustments in CHRT and associated side effects of CHRT were considered. The rehabilitation program had to be regularly adjusted due to the side effects of CHRT, especially in terms of the intensity of physical exercise training and nutritional advice. Second, to adhere to the nutritional advice and the home-based physical exercise training and its side effects required intensive social support of his wife, supervision and emotional support of the physiotherapist.

In this case study, a personalized and supervised rehabilitation program during CHRT was of added value to prevent physical decline and reduce treatment complications when it was adapted to the patient's capabilities. Support and guidance was needed particularly when training volume was progressed and also when training volume needed to be reduced during times of increased symptoms of fatigue and decreased mood. Besides, a supervised program facilitates personalization of the physical exercise training such as turning functional activities into physical exercise, which can improve adherence and motivation (38). While some studies have examined physical exercise training in patients with lung cancer, there is a lack of evidence specifically in patients receiving CHRT, let alone how to deal with adjustments in the treatment schedule. Only two studies were identified in the setting of rehabilitation during radical treatment with CHRT for patients with lung cancer (39, 40). In these studies, muscle strength decreased significantly in most patients during radical treatment despite rehabilitation (11%) compared with usual care (12%), but increased twelve weeks after CHRT with 28% in the rehabilitation group compared to 10% in the usual care group. In addition, physical exercise training during CHRT potentially increases long-term adoption and maintenance of physical activity as part of the patient's daily routine (18, 19), which appears to have positive effects in reducing complications and facilitating recovery after each treatment of chemotherapy and radiotherapy. Furthermore, in previous studies (41, 42) in patients with rectal cancer, supervised physical exercise training during CHRT also showed promising results to minimize physical deterioration and seemed able to prevent an often-seen decline in

physical fitness during CHRT. The patient in the current case study indicated that he could have completed CHRT reasonably fit by participating in the physical exercise training. In addition, there was no marked worsening in functional scores during and after chemoradiotherapy which represents a potential benefit of the rehabilitation program.

The most notable item mentioned by the patient to maintain CHRT and perform rehabilitation during CHRT was the need of support throughout the whole period. The involvement of the physiotherapist and his wife in the rehabilitation program and participation during the physical exercise training during both hospital-based visits and home-based visits was a strong facilitator of physical activity and implementing nutritional advice in his daily meals. Informal caregivers are a major source of social support, and play a significant role in the care of patients with cancer during treatment and rehabilitation (43). Informal caregivers may influence patient physical activity adoption and maintenance by serving as role models and motivators (44). Furthermore, support by healthcare professionals in managing complications of CHRT during exercise is important such as reassuring the patient or referring the patient to the case manager in case of side effects of CHRT, given previous reports that symptoms and fear of triggering symptoms (e.g., shortness of breath, fatigue) are major barriers to participate in rehabilitation (45, 46). Therefore, intensive supervision as part of the intervention, along with social and emotional support at home, is important for an optimal adherence to rehabilitation and give the patient confidence to perform the exercises. Patients, their relatives, and their (in)formal caregivers should be sufficiently educated about the significance of physical activity and physical fitness during CHRT.

Strengths and limitations

The in-depth analysis of the course of the rehabilitation during treatment with CHRT provides professionals and researchers with detailed information on how all diagnostic and therapeutic interventions are performed and how the patient's physical and nutritional status, and quality of life developed in clinical practice during CHRT. In addition, the rehabilitation program was tailored to keep it feasible for the patient so that he could remain as physically active as possible, perform the exercises, and adhere to the nutritional advice. With the use of the HOAC II for clinical reasoning and the i-CONTENT tool, an effort has been made to increase internal validity and options for replicating the study, as well as critically evaluating cause-effect considerations.

As a limitation of this case study, it is difficult to generalize this information one-to-one to daily practice. This case study shows that it is important to implement a rehabilitation program during CHRT as suggested in the blueprint, but in which it is possible to tailor the rehabilitation program because of inter-individual variation in preferences, needs, and side effects during CHRT. Furthermore, case studies are known for their scarce external validity (47) and should therefore be replicated in order to draw conclusions for the population covered in the study. By combining several separate case studies, the variability of the responses of patients undergoing CHRT to a particular intervention (e.g., nutritional counseling, physical exercises, smoking cessation) can be examined for clinical or real variability influenced by, among other things, environmental factors, presence of social support, patient characteristics, comorbidities, and side effects of CHRT.

Implications

Information from this case study can support clinical decision-making in a physiotherapist's daily practice for a patient who receives CHRT. Due to variation in patient and treatment characteristics, inter-individual complaints, and symptoms occurring during CHRT, a standard protocol for rehabilitation seems desirable during CHRT, with the possibility to tailor it to content and context. This case study, together with the literature used to develop the content and context of rehabilitation, makes clear that rehabilitation during CHRT should focus on personalization of the content, thereby taking training principles and nutritional advice into account. In addition, side effects that may occur during CHRT must be considered, requiring adjustment and continuous tailoring of the rehabilitation program. Supervision by healthcare professionals and social and emotional support is highly recommended in order to facilitate and motivate patients to adhere to the program. This case study provides insight into which side effects and expected adjustments in the rehabilitation program must be considered and what patient's preferences, facilitators, and barriers can be during CHRT and rehabilitation. As such, this case study might assist in the development of a randomized clinical trial to assess and improve the effects of rehabilitation on physical fitness and the associated risk of complications during CHRT.

In conclusion, this case study demonstrates how clinical decision-making of rehabilitation during CHRT can support the adherence of physical activities in a patient with a higher risk for treatment intolerance, thereby considering the course of treatment with CHRT and its side effects and patient’s preferences,

facilitators, and barriers. By adjusting training intensity and the content of physical exercise training, physical exercise training could still be performed while the patient was experiencing side effects from CHRT. In addition, the involvement and support of the physiotherapist and (in)formal caregivers seems essential for adhering to rehabilitation.

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Part III

Discussion and summary

'Referring patients to prehabilitation could be facilitated if multiple professionals within and between primary and secondary healthcare are involved in prehabilitation and have time available weekly to schedule patients quickly.'
-Healthcare professional-

Chapter 11

General discussion

General discussion

The overall aim of this thesis was to optimize pretreatment risk assessment for patients requiring treatment for non-small cell lung cancer (NSCLC), as well as to gather information that can be used to develop an effective and feasible (p)rehabilitation program before surgery and during other curative treatment of NSCLC in order to improve treatment tolerance. In this development, the opinion and view of stakeholders (e.g., patients, informal caregivers, healthcare professionals) plays an important role as it has proven to be most valuable for the content of this thesis (see figure 1). Knowledge from this thesis contributes to identifying patients with an increased risk of treatment complications, delayed recovery, and worse survival. Timely recognizing high-risk patients can contribute to an optimal treatment choice for the individual patient and to possibly select patients for a feasible (p)rehabilitation program to improve resilience. Ultimately, this will lead to less treatment complications, improved quality of recovery, better survival, and a better quality of life.

Why resilience of patients with non-small cell lung cancer needs to be improved

Despite the improvements in the treatment of NSCLC, treatment remains intensive and is often associated with complications, delayed recovery or even impaired recovery of physical functioning and deterioration in health-related quality of life (HRQoL). Lung cancer is predominantly a disease of older people, with half of all newly diagnosed patients being ≥70 years of age (1). A low performance status, malnutrition, smoking-related comorbidities, and an inactive lifestyle are common in patients with poor treatment-related outcomes (2, 3). Additionally, geriatric issues such as low mobility and dependence, vulnerability or frailty, living alone, and functional disability could negatively affect treatment outcomes (4, 5). Improving a patient's lifestyle leads to improved resilience, which reduces the risk of complications, accelerates and improves the quality of recovery, and increases HRQoL.

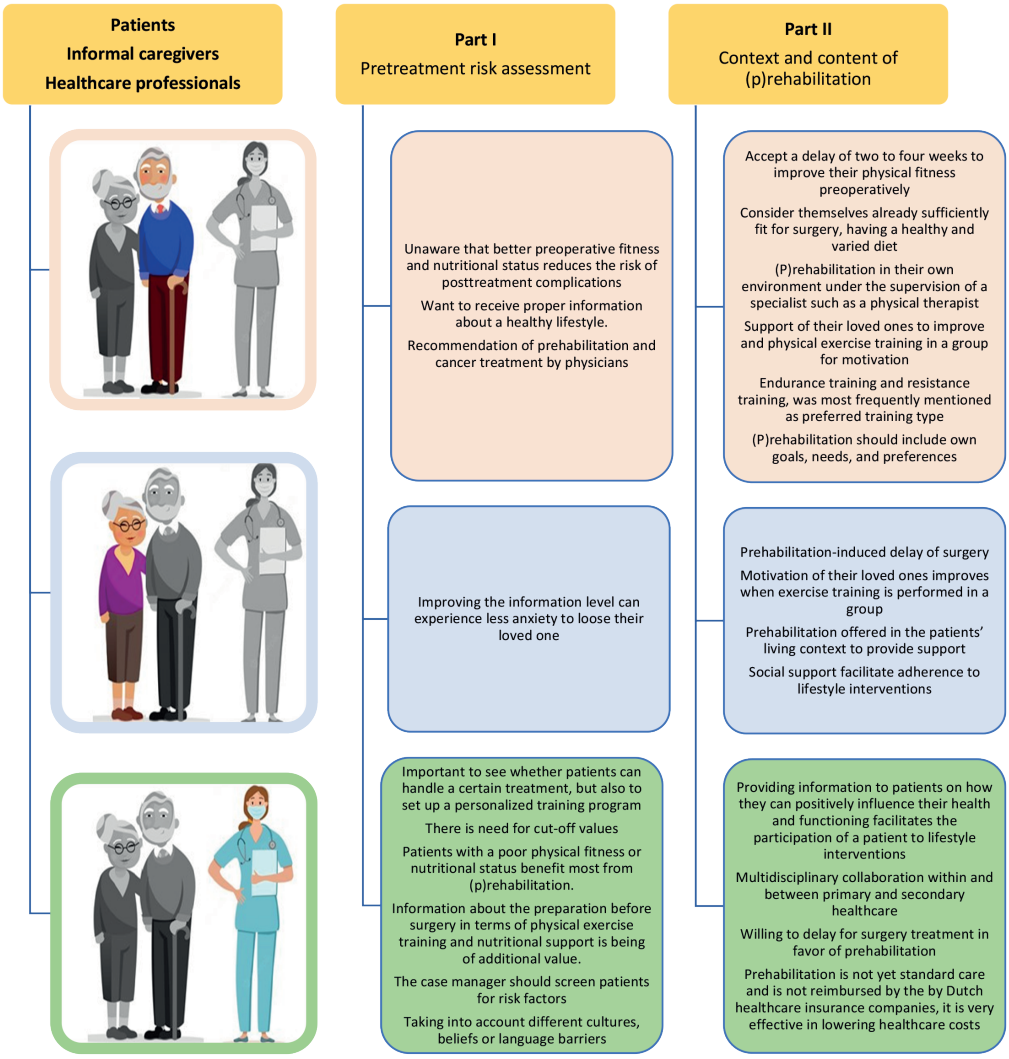

Figure 1. Thoughts and beliefs of patients with non-small cell lung cancer, their informal caregivers and healthcare professionals (**chapter 8**).

PART I

Pretreatment risk assessment

In our qualitative interview study among stakeholders in **chapter 8**, patients who underwent surgery for NSCLC and their informal caregivers reported to be unaware that a better pretreatment physical fitness and nutritional

status reduce the risk of posttreatment complications. In addition, healthcare professionals considered a pretreatment risk assessment to be very important to verify whether patients can cope with a certain treatment, but also to set up personalized preventive interventions if necessary. Two systematic reviews and two retrospective studies have been performed in this thesis that provide evidence regarding the associations between poorer physical fitness, nutritional status and geriatric parameters on the one hand and the risk of treatment complications, longer length of hospital stay, and worse survival on the other hand (**chapters 2-5**).

> *"I do not think that a better physical condition reduces the risk of complications, I think that a better physical condition can recover faster after surgery." (Patient who underwent surgery for NSCLC)*

The results from the systematic review in **chapter 2**, in which almost all patients in the included studies underwent surgery, demonstrate that a wide variety of outcome variables of different preoperative exercise tests seem to be associated with postoperative complications and/or postoperative mortality. These results were confirmed in our study using real-world data, in which a short physical performance battery (SPPB) score ≤9 and short nutritional assessment questionnaire score >1 were associated with a higher risk for postoperative complications in patients who undergo surgery, whereas only a forced expiratory volume in one second <80% of predicted was related with a higher risk for intolerance of stereotactic ablative radiotherapy (SABR) (**chapter 4**). Aerobic fitness assessed by a cardiopulmonary exercise test (CPET), which is already performed in patients with low lung function to verify operability, seems to be the best predictor to objectively estimate the risk for posttreatment complications (**chapter 2**). The CPET is the gold standard for evaluating aerobic fitness, but the CPET is not always feasible or heavy for frail patients. As such, accurate preoperative individual baseline values from for example the incremental shuttle walk test, stair-climb test, and 6-minute walk test (**chapter 2**) the timed-up and go test (**chapter 4**), and as recommendation the (modified) steep ramp test in surgical oncology (6) are easy to administer and promising variables in risk assessment (7). These exercise tests might also be used to timely identify high-risk lung cancer patients who might benefit from lifestyle interventions before and during cancer treatment (8). Therefore, it is recommended that further research should aim at determining the extent to which practical tests such as the steep ramp test, the incremental shuttle walk test, the timed up-and-go test, or the SPPB can contribute in selecting high-

risk patients, including accurate cut-off points. Despite the fact that research has mainly been carried out on pretreatment risk assessment in patients undergoing surgery, it was demonstrated in **chapter 5** of this thesis that poor World Health Organization (WHO) performance status, body mass index (BMI) <18.5 kg/m^2, fat free mass index, and handgrip strength were associated with poor outcomes following concurrent CHRT (cCHRT); however, the strength of the associations differed between males and females and between younger and older patients. Until now, there is a lack in research concerning the predictive value of physical fitness assessments and tolerance of CHRT.

Nutritional status, the presence or absence of malnutrition, is inextricably linked to physical status and can also provide information about the vulnerability of patients. The results of the systematic review presented in **chapter 3** show that several nutritional assessments are predictive of the occurrence of complications in patients undergoing surgery for lung cancer. Since a computed tomography (CT) scan is standard care for diagnosing NSCLC (9), it can be easily applied to measure sarcopenia for predicting treatment complications in this patient group. The psoas muscle mass index, thoracic skeletal muscle area, bone-free midarm muscle area, subscapular skinfold thickness, and triceps skinfold thickness can be used to measure sarcopenia (**chapter 3**). Despite this fact, the assessment of sarcopenia requires specific knowledge and the definition of sarcopenia is not yet fully understood (10). Easy-to-administer nutritional tests to identify patients with NSCLC who are at high risk for treatment complications are useful in daily practice (11, 12). Furthermore, the SPPB demonstrated moderate value in diagnosing sarcopenia, and a cut-off point of ≤8 points in SPPB performance resulted in high sensitivity (82-100%) (13).

In the Netherlands, geriatric screening is used in some hospitals for patients aged ≥70 years. First of all, it is important to provide a general impression of the frailty status of patients aged 70 years or older in order to make an optimal shared treatment decision. The G8 screening tool consists of an 8-item questionnaire (14). An observational study using real-world data in this thesis shows that the G8 score is predictive for the risk of postoperative complications in patients with NSCLC patients who underwent surgery (**chapter 4**). Recent research shows that the G8 score with two cut-off values (low (<11) and intertermediate (11-14)) can predict functional status, tolerance of chemotherapy, and postoperative prognosis in elderly patients with lung cancer (15).

Since several physical, nutritional, and/or geriatric tests can be used to timely identify patients who are at high risk for treatment complications and mortality, consideration should be given to which tests are easy-to-use to identify patients who are at high-risk for complications to ensure that implementation of assessments in everyday practice are feasible (16). It is advisable to use assessment tools that are already used in the diagnostic process or that are already used in daily practice. An important limitation for the implementation of practical field tests is the lack of evidence for accurate treatment-specific cut-off values (**chapters 2 and 3**). Therefore, international consensus is critical to standardize pretreatment physical, nutritional and geriatric screening and to obtain accurate cut-off values for pretreatment risk assessment.

The abovementioned evidence shows that better pretreatment physical fitness and nutritional status reduce the risk of treatment complications. Since patients with early-stage NSCLC undergoing lung surgery reported to be unaware about the fact that their preoperative physical status influences the development of complications (chapter 8), they need to be informed properly about the existing evidence. In **chapter 8**, it was also shown that many patients consider themselves already sufficiently fit for surgery, as well as having a healthy and varied diet. This means that patients need to become aware of their lifestyle and modifiable risk factors, in which a pretreatment risk assessment provides insight to the patient. In addition, patients indicated that they need information about preparing for surgery of NSCLC (**chapter 8**). Patients and their informal caregivers should therefore be sufficiently educated about the significance of physical activity, a healthy and protein-rich diet, and physical fitness (17, 18).

> *"I didn't need to get fit before surgery. I think the pulmonologist thought I was fit enough, because in that lung test (forced expiratory volume in one second) it turned out that I could miss a lung." (Patient who underwent surgery for NSCLC)*

> *"I would consider that information about the preparation for surgery in terms of physical exercise training and nutritional support is being of additional value." (Patient who underwent surgery for NSCLC)*

Also healthcare professionals believe that patients should be informed about how to optimize their health and functioning, taking into account different cultures, beliefs, and language barriers (**chapter 8**). Some patients lack the

right knowledge and information, and the skills to obtain, understand, and apply information to their own situation. Limited health literacy seems to be particularly prevalent among patients with a low level of education, migrants, and the elderly (19). Particularly, patients with a lower socio-economic status have the highest risk of developing lung cancer and, moreover, report their symptoms late (20, 21), and thus already appear to be at high risk.

According to healthcare professionals, providing information to patients on how they can positively influence their health and functioning stimulates the participation of a patient in lifestyle interventions (**chapter 8**). Lifestyle advice given by healthcare professionals makes an important contribution to changing the patient's lifestyle. Healthcare professionals mainly provide lifestyle advice to patients who are at high risk or who already have symptoms of certain diseases (22). According to previous research, there still seems to be room for improvement in both the frequency and the quality of lifestyle advice given (23). Common barriers for general practitioners to provide lifestyle advice include a lack of confidence in its effectiveness, as well as a lack of time and financial incentive (23).

To summarize part 1, identifying specific impairments in several physical, nutritional, and geriatric domains helps to generate an individual risk profile for each patient who has to undergo treatment for NSCLC. Age ≥70 years, low aerobic fitness, malnutrition, and tobacco-related comorbidity are common among patients with NSCLC. This often leads to treatment complications and a decreased HRQoL. Therefore, it is important to select high-risk patients who might benefit from (p)rehabilitation. Outcomes of preoperative physical, nutritional, and geriatric tests (many of which seem easy-to-use or already used in the diagnostic process) are associated with postoperative complications , especially in patients who undergo surgery. However, there is barely any evidence on the potential of physical, nutritional, and geriatric tests to predict treatment complications in patients with NSCLC who undergo other intensive treatments, such as CHRT and radical radiotherapy. Furthermore, consensus on the most clinically relevant cut-off values of physical, nutritional and geriatric tests is lacking. High-risk patients in particular may benefit from (p)rehabilitation, thereby improving posttreatment outcomes. Better informing patients and their informal caregivers about the purpose and effect of (p) rehabilitation is therefore important.

PART II

Context and content of (p)rehabilitation

Since research has shown that poor physical or nutritional status are associated with an increased risk for treatment complications and a longer recovery (Part I), lifestyle interventions before, during, and after surgery, SABR, or CHRT are important to increase the resilience of vulnerable NSCLC patients to improve treatment tolerance as result. A systematic review (**chapter 6**) has shown that prehabilitation results in a reduction of postoperative pulmonary complications, severe postoperative complications, and postoperative length of hospital stay in patients who underwent surgery. Although prehabilitation seems effective, it remains unclear how an optimally effective exercise prehabilitation program should be designed (**chapter 6**).

> *"I would accept a delay of two to four weeks to improve my physical fitness preoperatively." (Patient who underwent surgery for NSCLC)*

The period between cancer diagnosis and surgery is often time constrained due to current treatment guidelines (24). Therefore, the timeframe for surgical prehabilitation is relatively short. This means that a prehabilitation program that is effective in a short time period, as well as patient adherence to prehabilitation, are needed. A longer time period for prehabilitation should be preferred for improving resilience in high-risk patients. A previous systematic review that included studies with median time intervals of 6-121 days from diagnosis to treatment and 4-19.5 days from primary care to a specialist visit found that in 35% of the time intervals studied there was no association between mean or median waiting times and poor postoperative outcomes, while 37.5% had a better prognosis (25). In two other systematic reviews (26, 27), 37.5% of the included studies even found a better prognosis for survival with longer waiting times and 27.5% found a better prognosis for survival with shorter waiting times. Shorter waiting times have positive consequences in terms of anxiety, mental health, HRQoL and patient satisfaction, and lead to lower treatment costs (28, 29). In our qualitative stakeholder analysis (**chapter 8**), some patients mentioned they would accept a delay of two to four weeks to improve their physical fitness preoperatively, and healthcare professionals are willing to delay treatment in favor of prehabilitation. Although it is emphasized that the period between diagnosis and surgery should be as short as possible, the median number of weeks between diagnosis and surgery in our study was six, which was apparently everyday clinical practice, indicating that

there is an opportunity to offer prehabilitation, specifically for high-risk patients (**chapter 8**).

Setting up a (p)rehabilitation program can be described in two parts. Firstly, the context in which (p)rehabilitation should take place, such as facilitating factors that ensure optimal feasibility of (p)rehabilitation. Secondly, the content of (p)rehabilitation, which refers to the parameters a program has to contain in order to achieve the best possible effects.

Referral of patients with NSCLC who can benefit from a preoperative lifestyle intervention to a physical therapist, sports physician, psychologist, or geriatrician requires substantial changes in organizational structure. It is important to have one coordinator who has the overview and who appoints an accessible contact point for patients who undergo surgery (**chapter 8**). Collaboration between the various departments involved in lung cancer care (surgeon, anesthesiologist, oncologist, case manager, sports physician, physical therapist, dietician, geriatrician, psychologist) and between medical centers will be even more challenging, as each center relies on its own protocols and preferences.

> *"I would prefer that a case manager screens the patient, connecting patients with healthcare professionals, designing treatment plans, and making sure it all gets done on time." (Healthcare professional)*

Patients indicate that they would like to actively do something about their health themselves instead of waiting for surgery (**chapter 8**). Dutch citizens and patients are increasingly expected to take an active role in caring for their own health and illness and that of their loved ones (30). Patients who underwent surgery and CHRT reported that they would prefer face-to-face guidance of a physical therapist or personal trainer to improve their preoperative physical fitness (**chapters 8 and 10**). Guidance of a dietician could be done by phone or via video-consulting. Unsupervised prehabilitation at home was seen as a barrier for most patients who underwent surgery, as they mentioned a lack of self-discipline (**chapter 8**).

> *"A physical therapist is the best person to advise me what kind of exercises I should do; after all, he has learned for it." (Patient who underwent surgery for NSCLC)*

> *"I would have liked to do physical exercises in a group, because it allows you to talk to other patients and it helps to stay motivated." (Patient who underwent surgery for NSCLC)*

Patients who underwent surgery or CHRT felt they needed the support of their loved ones and preferred that they were able to join the appointments in a (p)rehabilitation program (**chapters 8 and 10**). In patients with stage III NSCLC, a personalized and supervised rehabilitation program during CHRT can be of added value to prevent physical decline and reduce treatment complications when it is adapted to the patient's capabilities (**chapters 9 and 10**). A supervised program facilitates personalization of the physical exercise training such as turning functional activities into physical exercise, which can improve adherence and motivation (31). For both surgery and CHRT, patients indicated that the support of a caregiver was an added value as motivation (**chapters 8 and 10**). Informal caregivers indicated that they were willing to participate in physical activity and nutritional optimization with their loved ones to facilitate prehabilitation (**chapter 8**). Informal caregivers and/or fellow sufferers have been found to be an important source of social support and play an important role in caring for patients with cancer during treatment and (p)rehabilitation (32, 33). It is therefore recommended to establish close involvement of informal caregivers from the start of treatment, as this may influence the patient's acceptance and maintenance of physical activity by serving as a motivator.

Unfortunately, prehabilitation and rehabilitation during treatment is not yet reimbursed by Dutch healthcare insurance companies. This means that patients must pay the costs associated with preoperative preventive interventions themselves. However, prehabilitation appears to be a cost-saving method in for example patients with ovarian cancer (34) and undergoing major abdominal surgery (35) due to lower complication rates and decreased care facility requirements. The cost-benefit ratio of providing (p)rehabilitation to patients with lung cancer is being conducted (36). The Integral Care Agreement (IZA) that is offered by the Department of Health and Sports in the Netherlands states that attention must be paid to qualified, accessible, and affordable care (37). This is important for health and well-being, so that patients with NSCLC are and remain as healthy as possible before, during, and after their cancer treatment. According to healthcare professionals, patients must be encouraged to lead a healthy lifestyle, with extra attention for patients to stop smoking and drinking, and have a healthy weight, to prevent them from developing more complaints

(**chapter 8**). These preventive strategies for gaining a healthy lifestyle should focus on how to organize this within primary and secondary care.

> *"While prehabilitation is not yet standard care and is not reimbursed by the by Dutch healthcare insurance companies, it is very effective in lowering healthcare costs." (Healthcare professional)*

Characteristics of the content of a physical exercise training program should be specified using the training frequency, training intensity, training time, training type, training volume, and training progression principles (FITT-VP) (38, 39) so that all items required to complete a training program to be set up are well described and reproducible. In two systematic reviews (**chapters 6 and 7**), the correct description of the exercise prehabilitation program was missing in the included studies, which was assessed with the i-CONTENT tool (40). As this is such important data, we discuss these items using the FITT-VP principle for rehabilitation before, during, and after treatment of NSCLC.

Training can be optimally arranged with a duration of an exercise program of at least two to four weeks to improve aerobic fitness and a patient's performance of activities of daily living, to reduce cancer-related fatigue, and to improve HRQoL (41). If a physician recommended prehabilitation, all patients reported that they felt capable of executing a physical exercise training program before surgery with a training *frequency* of one to three times weekly (**chapter 8**). It seems most optimal, whether it involves (p)rehabilitation before surgery or during treatment with CHRT, when patients exercise with a minimum of three to five times per week to improve their aerobic fitness, muscle strength, and respiratory muscle function (42).

Although aerobic fitness can be improved through moderate-*intensity* exercise, high-*intensity* interval training can improve aerobic fitness faster and more time-efficiently (43). According to the relevant training zones, training intensity can be optimally arranged with a 6-20 Borg score of 13-15 for a moderate-intensity exercise training program and >15 for a high-intensity interval training program [24]. High-intensity interval training needs to be supervised and seems feasible and effective to improve aerobic fitness in the short period before surgery (**chapter 6**); however, moderate- or high-intensity training seems not feasible for patients undergoing CHRT (**chapters 9 and 10**). Patients receiving chemotherapy and/or radiation therapy may need to exercise at a lower intensity and/or for a shorter duration

during their treatment to maintain aerobic fitness and muscle strength (**chapter 9**). Therefore, low-intensity physical exercise training may be easier during chemotherapy, which seems able to preserve physical fitness throughout treatment [35]. Low-intensity training can be performed at the patients home and might not need supervision.

Training *time* in the included studies in **chapter 6** varied between 15-120 minutes per session with varying types of training and number of sessions per week. This makes it difficult to interpret training time, which means that we still do not know the best duration per session and best training time per week to perform physical training. Most patients indicated that they want to know what exercises would be relevant and practical for them and that an expert, such as a physical therapist or sports instructor, is the one to decide (**chapter 8**). A preoperative physical exercise training program, such as endurance training (e.g., walking, cycling, swimming) and resistance training, was most frequently mentioned as a training *type* that patients would prefer (**chapters 8 and 9**). Even for the general population, making major lifestyle changes such as exercise is a challenge (44). Since prehabilitation takes place at a very stressful time for a patient with cancer, it should be emphasized that, next to targeting their individual modifiable risk factors, their own goals, needs, and preferences should be reflected in their program prescription (**chapter 8**). Individual barriers need to be identified and strategically addressed to maximize adherence (45).

> *"I would prefer walking, swimming and resistance training if I need to do preoperative exercises." (patient who underwent surgery for NSCLC)*

Training *volume* is usually expressed as the energy (in Kilojoules of Kilocalories) that is expended during an entire training program episode. Due to improvements in aerobic fitness as a result of training adaptations, training volume should be increased (by either increasing training frequency, intensity, and/or training time) to make sure an adequate overload is maintained throughout the complete program. This is known as personalization, as well as adequate training progression (46). As sufficient progress in aerobic fitness should be the main outcome parameter of exercise prehabilitation and was missed in the description of the content of prehabilitation programs in the included studies (**chapter 6**), progression of training should frequently be assessed (referred to as "titration" (47)), preferably on a (bi)weekly base using a formal performance test (48).

Given recent developments in favor of prehabilitation, we urge that, in the near future, the next experimental steps required to implement multimodal prehabilitation and rehabilitation during treatment as part of standard of care are carefully but swiftly performed. Implementation of such (p)rehabilitation programs still requires research into the optimal (and feasible) method (maximum effect) to simultaneously improve multiple risk factors (multimodal (p)rehabilitation programs).

In short, in order to start a prehabilitation program as soon as possible after the diagnosis NSCLC, agreements for preoperative screening, assessment, and preventive interventions between participating healthcare professionals are needed, and multidisciplinary collaboration of healthcare professionals within primary and secondary care in referring patients to prehabilitation seems vital. It would be wise to involve informal caregivers into the program to improve adherence to cancer treatment and the lifestyle intervention as well as the support of other patients (fellow sufferers). Exercise (p)rehabilitation seems to decrease postoperative complications and improve HRQoL, despite the fact that therapeutic quality of exercise (p)rehabilitation programs measured with the i-CONTENT scale was limited. Future research should focus on the quality, reporting, and standardization of (p)rehabilitation programs, which is expected to improve postoperative outcomes through exercise prehabilitation with higher certainty. Physical training during CHRT could be performed by adjusting the exercise intensity and the way the physical training was delivered, while patients experienced side effects of CHRT.

Strengths and limitations

This thesis provides detailed quantitative and qualitative data about pretreatment risk assessment and concerning the context and content of multimodal lifestyle interventions before surgery, during SABR and during CHRT. This combination of qualitative and quantitative data provides a deeper insight into feasibility and effectiveness and aggregates qualitative data of patient beliefs, preferences, barriers, and facilitators alongside quantitative data of pretreatment risk assessment tools and the content of (p)rehabilitation. The quantitative data collected for this thesis have shown that there are many possibilities of pretreatment physical, nutritional, and geriatric assessment to select patients at high risk for poor treatment outcomes. Furthermore, it is especially valuable that much of the data from the diagnostic assessment is already being used and can now also be used as a risk assessment to predict poor treatment outcomes in patients undergoing treatment for NSCLC on the one

hand. On the other hand, it is also difficult to make a good choice for an optimal pretreatment risk assessment because of the many associated instruments, depending on each treatment option and different strengths in association. The qualitative data provides insight into what the stakeholders consider important so that the quantitative data can be adapted according to the preferences and beliefs of patients, informal caregivers, and healthcare professionals.

However, there were also some limitations. After the systematic review in which we evaluated which outcome variables and cut-off values of pretreatment exercise tests are associated with treatment complications (**chapter 2**), we continued to search for parameters in the domain of nutrition to create an optimal pretreatment risk screening and risk assessment (**chapter 3**). First, available studies in literature lacked easy-to-administer nutritional screening questionnaires useful in daily practice (11, 12). Second, in the included studies hardly any attention was paid to patients with NSCLC who underwent another treatment than surgery. As a result, there is still much uncertainty regarding a pretreatment risk assessment for physical fitness and nutritional status in patients undergoing SABR or CHRT. Third, the large heterogeneity of included studies in the systematic reviews (**chapters 2, 3, and 7**) with respect to various types and stages of cancer, differences in anticancer therapy (chemotherapy and/or surgery), differences in outcome measurements, the risk of bias regarding HRQoL and fatigue, and across the items of the i-CONTENT tool, meta-analyses could not be performed. Fourth, conducting retrospective studies for evaluating the associations between a pretreatment risk assessment and treatment outcomes may not have been the best study design, because the results depend on data already collected, the number of patients included was small and there were many missing data (**chapters 4 and 5**). Future prospective studies are needed, in which easy-to-use physical and nutritional tests can be performed in patients who undergo not only surgery but also other intensive curative treatment options for NSCLC. Fifth, although our proof-of-concept study and case study provided very relevant detailed information on the context of rehabilitation in patients undergoing CHRT, we still lack information about the optimal content of such rehabilitation programs.

In conclusion, there is a wide variety of user-friendly screening tests to design a pretreatment assessment to identify specific disorders in different physical, nutritional and geriatric domains, although there is a lack of consensus on cut-off values. Most studies have focused on patients undergoing surgery and barely on patients with NSCLC undergoing other intensive treatments, such as CHRT

and radical radiotherapy. Through a pretreatment risk assessment, patients can be better identified if they may benefit from (p)rehabilitation, which improves the results after treatment. Research shows that (p)rehabilitation appears to reduce treatment complications and allows for faster recovery. This (p)rehabilitation programs must be optimally organized through good cooperation between healthcare professionals and healthcare organizations, properly informing patients and their loved ones about the benefits of (p) rehabilitation, and an optimal content of the (p)rehabilitation program.

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'Surgery could be delayed safely when the pulmonologist or surgeon decides that a delay of surgery is possible.'
-Healthcare professional-

Summary

Summary

Lung cancer is the fourth most commonly diagnosed cancer and the most common cause of death in the United States and Europe. Non-small cell lung cancer (NSCLC) accounts for 85% of all types of lung cancer. For fit patients with early stage I, II, or -in some cases- IIIa NSCLC, lung resection is recommended according to European guidelines. For patients with early-stage disease (stage I and II) who are considered inoperable, stereotactic radiotherapy is the preferred treatment. For fit patients with locally advanced NSCLC (stage III), chemoradiotherapy (CHRT) is the standard treatment with the option of adjuvant immunotherapy after non-progression. NSCLC is primarily a disease that occurs in the elderly, as half of all newly diagnosed patients are aged ≥70 years. Patients with a higher risk for treatment complications are often characterized as aged ≥70 years, having tobacco-related comorbidity and/or cognitive impairment, being physically inactive and/or malnourished, and especially as having a low physiological reserve capacity (low aerobic fitness). Pretreatment screening and assessment of risk factors can help to timely identify patients who are at increased or high risk for treatment complications and functional decline. Pretreatment risk assessment is essential for clinical reasoning and shared decision-making for the choice of treatment interventions, but also to determine who might benefit from a lifestyle intervention such as (p)rehabilitation for improving physical fitness and nutritional status. **Chapter 1** introduces the objective of this thesis forthcoming out of the abovementioned rationale to optimize risk assessment for patients requiring treatment for NSCLC and to gather information what can be used to develop an effective and feasible prehabilitation program before and rehabilitation program during and after curative treatment options for NSCLC aiming to improve treatment outcomes in which the patient's view plays an important role.

The first part of the thesis focuses on the identification of pretreatment risk factors for treatment tolerance and survival (**chapters 2 to 5**). A systematic review of the literature review has shown that a better performance on physical parameters such as preoperative exercise testing, particularly better aerobic fitness as measured by the cardiopulmonary exercise test (CPET), was associated with a lower risk of postoperative complications in patients with NSCLC (**chapter 2**). Since the CPET is relatively expensive, time-consuming and requires trained personnel for adequate interpretation of results, this thesis also focused on physical exercise tests that are easy to administer,

practical, cheap and time efficient. A lower number of steps during the stair-climb test, a lower walking speed and walking distance on the six-minute walk test and the incremental shuttle walk test were also associated with a higher risk of postoperative complications. Another systematic review of the literature has shown that a poorer score on nutrition tests such as body mass index, sarcopenia, albumin, controlling nutritional status, prognostic nutrition index, nutrition risk score and the (geriatric) nutrition risk index before treatment were also associated with a higher risk of treatment complications and mortality, especially in patients who had to undergo surgery (**chapter 3**). In a retrospective study of patients aged 70 years and older with early-stage NSCLC, a lower level of functioning on the short physical performance battery and poorer nutritional status appeared to be associated with a higher risk of postoperative complications (**chapter 4**). Reduced lung capacity measured by the forced expiratory volume in one second was related to a higher risk of intolerance of stereotactic radiotherapy. A retrospective observational study has shown that several physical parameters were associated with complications after concurrent CHRT (**chapter 5**). In particular, a low World Health Organization performance status, low body mass index, low fat-free mass, and low handgrip strength were predictive of complications after concurrent CHRT.

Despite these findings of the predictive value of easy-to-administer and manageable measurement tools, there was little consensus on standardizing physical, geriatric, and nutritional tests to determine accurate cut-off values in pretreatment risk stratification (**chapters 2 to 5**). For clinical reasoning and shared treatment decision-making with patients, pretreatment risk assessment can be used to identify patients who are expected to be at high risk for treatment complications, poor survival, and/or a reduced quality of life. This information can subsequently be used for identification of patients who can benefit from prehabilitation and rehabilitation to improve treatment tolerance.

The second part of this thesis focuses on the content and context of prehabilitation and rehabilitation. A systematic review of the literature demonstrated that prehabilitation by physical exercise interventions reduces postoperative complications and length of hospital stay in patients with operable NSCLC, but no studies were found that systematically described and evaluated the quality and content of prehabilitation of physical exercise interventions using clear and predefined criteria, which contributed to a score of a high risk of ineffectiveness of the interventions (**chapter 6**).

Exercise prehabilitation reduced the occurrence of postoperative pulmonary complications, postoperative Clavien-Dindo grade II-IV complications, and length of hospital stay. Nevertheless, the evidence about the effect of prehabilitation on postoperative mortality is very weak. In another systematic review of the literature, an inconsistent effect of prehabilitation and rehabilitation on health-related quality of life in patients with NSCLC undergoing surgery was found (**chapter 7**), whereas prehabilitation and rehabilitation seemed to have no effect on fatigue in patients undergoing surgery for early-stage NSCLC. Because of the high risk of ineffectiveness of exercise interventions, it is not possible to provide a definitive conclusion regarding the best form of exercises to improve HRQoL and to reduce fatigue. The high risk of ineffectiveness of exercise interventions in the studies of the systematic reviews (**chapters 6 and 7**) was often due to the fact that there was no adequate selection of patients at increased risk for poor treatment outcomes or due to the fact that there was a lack of monitoring adherence. In addition to these systematic reviews of the literature, which explored the optimal content of prehabilitation, a qualitative stakeholder analysis was performed (**chapter 8**). This qualitative stakeholder analysis explored the thoughts and preferences of patients, informal caregivers, and healthcare professionals with regard to prehabilitation. In this qualitative stakeholder analyses, patients and their loved ones mentioned that they did not receive adequate information about prehabilitation and patients considered themselves already fit to undergo surgery and therefore did not see the need for prehabilitation for themselves. In case a physician recommended prehabilitation, they would participate and their informal caregivers would support them. Patients preferred to exercise in a group with supervision from a professional (physical therapist), close to home. Patients also expressed the ability to perform physical exercise training three times a week such as endurance training and strength training. Healthcare professionals see the benefits of prehabilitation to prevent postoperative complications, especially in patients with a high risk for postoperative complications. They also indicated that there is a need to make arrangements for collaboration with involved healthcare professionals in primary and secondary care, and agreements should be made with health insurance companies regarding reimbursement for prehabilitation. The short period between diagnosis and surgery may be a barrier to an effective exercise and nutrition program, but most healthcare professionals mentioned the possibility of delaying surgery for two to four weeks in favor of prehabilitation. A feasibility study in patients with stage III NSCLC gained insight into the feasibility of rehabilitation during CHRT (**chapters 9 and 10**). Rehabilitation

during CHRT with partial supervision by a healthcare professional (physical therapist, dietitian and case manager) seems feasible when the intensity of the physical exercise training program and nutritional advice are adjusted to the possibilities and preferences of the patients (**chapter 9**). In patients with stage III NSCLC, training of low-to-moderate intensity (BORG score 12-13) during CHRT was recommended. Rehabilitation during CHRT should not necessarily improve physical fitness, as preservation of physical fitness is a positive effect as well. Ensuring motivation, adherence, and logistical planning of the physical exercise intervention was found to be challenging. A case study following the feasibility study examined the clinical decision-making process of healthcare professionals in prescribing and administering a rehabilitation program during CHRT (**chapter 10**). This case study showed that the rehabilitation program had to be frequently modified in terms of training intensity and dietary advice because of the side effects of CHRT. Intensive social support of the informal caregiver, as well as supervision and emotional support by the physical therapist were essential to be able to adhere to the nutritional advice and the home-based physical exercise training. Support and guidance was needed particularly when training volume was progressed and also when training volume needed to be reduced during times of increased symptoms of fatigue and decreased mood.

In conclusion, worse outcomes of pretreatment physical, nutritional, and geriatric tests were shown to be associated with a higher risk of treatment complications in patients undergoing curative treatment for NSCLC, especially in patients undergoing surgery. However, there is little evidence on the potential of these pretreatment tests to predict treatment complications in patients receiving CHRT or radical radiotherapy, and consensus on the most clinically relevant cut-off values is lacking. Especially patients with a high risk for treatment complications may benefit from prehabilitation and rehabilitation by improving aerobic fitness, treatment tolerance, and quality of life. To make prehabilitation and rehabilitation feasible, programs should be optimally organized by close collaboration between healthcare professionals and healthcare organizations, and by properly informing patients and their loved ones about the purpose and effect of (p)rehabilitation. Furthermore, it is advised to involve loved ones for improving compliance. Future research should focus on the quality, reporting, and standardization of prehabilitation and rehabilitation programs.

'Surgery could be delayed safely when the pulmonologist or surgeon decides that a delay of surgery is possible.'
-Healthcare professional-

Samenvatting

Samenvatting

Longkanker staat op de vierde plaats van meest voorkomende gediagnosticeerde vormen van kanker in de Verenigde Staten en Europa en is de meest voorkomende doodsoorzaak bij patiënten met kanker. Longkanker bestaat voor 85% uit niet-kleincellige longkanker (NSCLC). Voor fitte patiënten met een vroeg stadium I, II en -in sommige gevallen- IIIa NSCLC wordt in de Europese richtlijnen longresectie aanbevolen. Stereotactische radiotherapie is de aanbevolen behandeling voor een vroeg stadium van longkanker bij patiënten die inoperabel zijn. Voor patiënten met een lokaal-uitgebreide vorm van NSCLC is chemoradiotherapie de standaardbehandeling, met eventueel adjuvante immunotherapie na chemoradiotherapie. NSCLC is een ziekte die vooral bij ouderen voorkomt: de helft van alle nieuw gediagnosticeerde patiënten is ouder dan 70 jaar. Patiënten met een hoger risico op complicaties van behandeling zijn vaak ouder dan 70 jaar, hebben tabaks-gerelateerde co-morbiditeit en/of cognitieve stoornissen, zijn lichamelijk inactief en/of ondervoed en hebben vaak een lage fysiologische reservecapaciteit (lage aerobe fitheid). Het adequaat inschatten van het risico op complicaties is essentieel voor het kiezen van de juiste behandeling (risico-inschatting). Daarnaast is risico-inschatting van belang om vast te stellen wie baat zou kunnen hebben bij een leefstijlinterventie om onder andere de fysieke fitheid en de voedingsstatus te verbeteren vóór aanvang van de behandeling (prevalidatie) en/of tijdens en na de behandeling (revalidatie). Het doel van dit proefschrift, zoals beschreven in **hoofdstuk 1**, is om risico-inschatting te optimaliseren voor patiënten die een behandeling voor NSCLC moeten ondergaan en om informatie te verzamelen die gebruikt kan worden voor het ontwikkelen van effectieve en haalbare (p)revalidatieprogramma's vóór, tijdens en na curatieve behandelopties voor NSCLC. Het ultieme doel is om behandeluitkomsten te verbeteren, waarbij de visie van de patiënt een belangrijke rol speelt.

Het eerste deel van het proefschrift richt zich op het identificeren van (modificeerbare) risicofactoren voor behandeltolerantie en overleving (hoofdstukken 2 tot en met 5). Een systematische literatuurstudie toonde aan dat betere preoperatieve prestaties van patiënten op fysieke fitheidtesten, met name een hogere aerobe fitheid gemeten met de cardiopulmonale inspanningstest (CPET), geassocieerd zijn met een lager risico op postoperatieve complicaties bij patiënten met NSCLC (**hoofdstuk 2**). Gezien de kosten en de tijd die nodig zijn voor een CPET, alsook het vereiste adequaat opgeleid personeel voor een juiste interpretatie van de resultaten, wordt in

dit proefschrift juist ook gekeken naar de voorspellende waarde van fysieke testen die gemakkelijk, praktisch, betaalbaar en breed beschikbaar zijn. De literatuurstudie liet zien dat ook minder gelopen treden tijdens de traplooptest, een tragere loopsnelheid en daarmee kortere loopafstand tijdens de zes-minuten wandeltest en de incremental shuttle walk test geassocieerd zijn met een hoger risico op postoperatieve complicaties. Een andere systematische literatuurstudie toonde aan dat een slechtere score op verschillende voedingstesten vóór de behandeling van NSCLC ook samenhangt met een hoger risico op complicaties van behandeling en sterfte, vooral bij patiënten die een operatie ondergingen (**hoofdstuk 3**). In een retrospectief dossieronderzoek bij patiënten van 70 jaar en ouder met een vroeg stadium NSCLC werd aangetoond dat een lagere preoperatieve score op de geriatrische-8 (G8) en de short physical performance battery en een slechtere voedingsstatus samenhingen met een hoger risico op postoperatieve complicaties (**hoofdstuk 4**). Een verminderde longfunctie gemeten met het geforceerd expiratoire volume in 1 seconde (éénsecondewaarde, FEV_1) hing samen met een hoger risico op het slecht verdragen van stereotactische radiotherapie (**hoofdstuk 4**). Een andere retrospectieve observationele studie bij alle patiënten met stadium III NSCLC toonde aan dat verschillende fysieke parameters geassocieerd waren met complicaties na gelijktijdige chemoradiotherapie (**hoofdstuk 5**). Met name een lage World Health Organization performance status, body mass index (BMI), vetvrije massa en handknijpkracht waren geassocieerd met een hogere kans op complicaties na de behandeling met gelijktijdige chemoradiotherapie.

Ondanks de bevindingen van de voorspellende waarde van eenvoudige en praktische meetinstrumenten, is er geen consensus over de specifieke te gebruiken fysieke testen en voedingstesten, alsook niet over het standaardiseren van de testuitvoering en de fysieke uitkomstmaten. Daarnaast ontbreekt het aan nauwkeurige test-specifieke afkappunten voor risico-inschatting voorafgaand aan de behandeling (**hoofdstukken 2 tot en met 5**). Om weloverwogen beslissingen te nemen met de patiënt over behandelopties en de daaraan gerelateerde risico's, kan een assessment vóór de behandeling worden gebruikt om het risico op complicaties tijdig in te schatten. Hoog-risicopatiënten kunnen vervolgens baat hebben bij prevalidatie en revalidatie om de behandeltolerantie te verbeteren.

In het tweede deel van het proefschrift wordt aandacht besteed aan de inhoud en context van prevalidatie vóór de behandeling en revalidatie tijdens en na de behandeling van NSCLC. In een systematische literatuurstudie bij

patiënten met een operabel NSCLC werd aangetoond dat prevalidatie door middel van fysieke trainingsinterventies postoperatieve uitkomsten verbetert (**hoofdstuk 6**). Er werden echter geen publicaties gevonden die de kwaliteit en inhoud van het prevalidatieprogramma systematisch beschreven en beoordeelden aan de hand van duidelijke en vooraf gedefinieerde criteria. Prevalidatie via fysieke trainingsinterventies bleek het risico op postoperatieve pulmonale complicaties, complicaties graad II-IV volgens het Clavien-Dindo-classificatiesysteem en de duur van het ziekenhuisverblijf te verminderen. Het bewijs voor het effect van prevalidatie op postoperatieve sterfte was echter zeer zwak vanwege de lage zekerheid van het bewijs. Een andere systematische literatuurstudie liet inconsistent bewijs zien voor het effect van prevalidatie en revalidatie op gezondheid-gerelateerde kwaliteit van leven bij patiënten die een operatie ondergingen voor NSCLC (**hoofdstuk 7**). Prevalidatie en revalidatie leken geen effect te hebben op vermoeidheid na operatie. Vanwege de matige kwaliteit en beschrijving van trainingsinterventies (risico op ineffectiviteit), met name bij een korte duur van de interventie, kon geen definitieve conclusie worden getrokken over de optimale inhoud van een preoperatieve trainingsinterventie. Het hoge risico op ineffectiviteit van de trainingsinterventies in de geïncludeerde publicaties was vaak te wijten aan het niet selecteren van patiënten met een verhoogd risico op slechtere behandelresultaten of onvoldoende controle op therapietrouw.

Als aanvulling op de systematische literatuurstudies die de optimale inhoud van prevalidatie onderzochten, is een kwalitatieve stakeholdersanalyse uitgevoerd om de gedachten en voorkeuren van patiënten, hun naasten en zorgverleners met betrekking tot prevalidatie te onderzoeken (**hoofdstuk 8**). Uit deze studie bleek dat patiënten en hun naasten onvoldoende informatie ontvingen over het doel en de mogelijkheden van prevalidatie. Bovendien achtten patiënten zichzelf vaak al fit genoeg om een operatie te ondergaan en zagen ze daarom de noodzaak van prevalidatie voor henzelf niet. Als de behandelend arts prevalidatie echter specifiek zou aanbevelen, dan zouden patiënten bereid zijn om deel te nemen, waarbij naasten dan bereid zouden zijn om hen te ondersteunen. Patiënten gaven de voorkeur aan groepstraining onder toezicht van een zorgverlener, zoals een fysiotherapeut, dicht bij huis. Ze gaven ook aan in staat te zijn om drie keer per week fysieke training uit te voeren, zoals duurtraining en krachttraining.

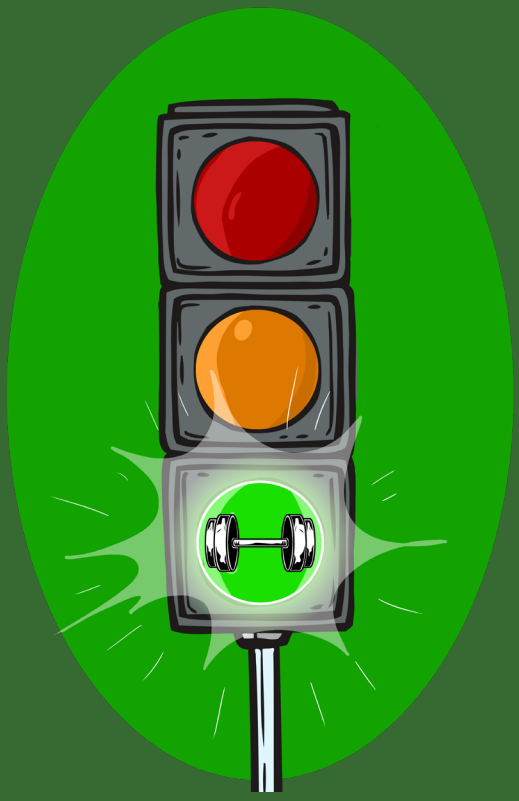
Zorgverleners erkennen de voordelen van prevalidatie om postoperatieve complicaties te voorkómen, met name bij patiënten met een hoog risico

op dergelijke complicaties. Zij benadrukten ook dat er behoefte is aan samenwerkingsafspraken met zorgprofessionals in de eerste en tweede lijn, evenals afspraken met zorgverzekeraars over de vergoeding van prevalidatie. De korte tijdspanne tussen de diagnose van NSCLC en de operatie kan echter een belemmering vormen om een effectief trainings- en voedingsprogramma in zo een korte tijd te kunnen uitvoeren. In het kader hiervan gaven de meeste zorgverleners aan dat het vaak mogelijk en medisch verantwoord is om de operatie twee tot vier weken uit te stellen ten gunste van prevalidatie.

In een pilotstudie bij patiënten met stadium III NSCLC werd inzicht verkregen in de haalbaarheid van revalidatie tijdens chemoradiotherapie (**hoofdstukken 9 en 10**). Revalidatie tijdens chemoradiotherapie met gedeeltelijke supervisie door zorgprofessionals, zoals een fysiotherapeut, diëtist en casemanager, was haalbaar wanneer de intensiteit van het fysieke trainingsprogramma en het voedingsadvies werden aangepast aan de mogelijkheden en voorkeuren van de patiënten (**hoofdstuk 9**). Bij patiënten met stadium III NSCLC bleek voor alle patiënten de uitgevoerde trainingsintensiteit lager dan voorgeschreven door de fysiotherapeut. Revalidatie tijdens chemoradiotherapie leidde niet tot een verbetering van de fysieke fitheid, maar zorgde ervoor dat de meeste patiënten de bestaande fysieke fitheid konden behouden, hetgeen als winst gezien kan worden tijdens zo'n ingrijpende behandeling. Uit de resultaten van het onderzoek bleek ook dat het motiveren van patiënten, de therapietrouw en de logistieke planning van fysieke trainingsinterventies uitdagend waren. Intensieve ondersteuning door de partner, evenals supervisie en emotionele steun door de fysiotherapeut, waren essentieel om patiënten te helpen bij het uitvoeren van de fysieke trainingen in de thuissituatie en bij het naleven van het voedingsadvies. In een casestudie die volgde op de haalbaarheidsstudie, werden de voorkeuren en bevorderende en belemmerende factoren rondom revalidatie tijdens chemoradiotherapie onderzocht (**hoofdstuk 10**). Uit deze casestudie bleek dat het revalidatieprogramma regelmatig moest worden aangepast om de intensiteit van de training te verlagen en voedingsadviezen aan te passen, vanwege de bijwerkingen van chemoradiotherapie.

Op basis van de resultaten uit dit proefschrift kan geconcludeerd worden dat slechtere preoperatieve uitkomsten bij fysieke fitheidstesten, voedingstoestand en geriatrische status samenhangen met een verhoogd risico op complicaties na een operatie voor NSCLC. Er is echter nog nauwelijks bewijs voor het potentieel van deze testen om complicaties van chemoradiotherapie

of radicale radiotherapie te voorspellen. Daarnaast ontbreekt consensus over de te gebruiken testen en zijn er nog geen accurate test-specifieke afkappunten voor een verhoogd risico op complicaties. Met name patiënten met een hoog risico op behandelcomplicaties kunnen profiteren van prevalidatie en revalidatie, omdat dit kan leiden tot verbetering van de aerobe fitheid, en daarmee de behandeltolerantie, herstel en kwaliteit van leven. Om trainingsinterventies optimaal in te richten en te standaardiseren is het essentieel dat toekomstig onderzoek gericht is op de kwaliteit en beschrijving van trainingsinterventies. Om prevalidatie en revalidatie haalbaar te maken, is het belangrijk een gepersonaliseerd en (deels) gesuperviseerd programma aan te bieden welke (tussentijds) aangepast kan worden aan de mogelijkheden van de patiënt en waarbij naasten betrokken worden om therapietrouw te bevorderen. Bovendien is een optimale organisatie van programma's vereist door nauwe samenwerking tussen zorgverleners en zorgorganisaties, evenals een adequate informatieverstrekking aan patiënten en hun naasten over het doel en de effecten van prevalidatie en revalidatie.



'The idea behind (p)rehabilitation is so easy to comprehend that it is hard to image that a patient would not benefit from it.'
-Melissa Voorn-

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Lung cancer is one of the most common cancers worldwide (1). It is predicted there will be 28 million new cancer cases worldwide each year by 2040, assuming that incidence remains stable and population growth and ageing continues in line with recent trends. [1] This is an increase of 54.9% in twenty years, which is expected to be even higher in males (60.6% increase) (2). In the Netherlands, the incidence of lung cancer is predicted to increase to 8,526 diagnoses per year in females and 8,145 in males through 2032 (3). To keep healthcare accessible in the future, the entire healthcare sector faces a major challenge. Representatives of the Dutch healthcare sector made agreements for Dutch healthcare for the next four years with the Integral Care Agreement (IZA) (4). The aim of the IZA is to better manage and absorb the increasing demand for care. As such, healthcare parties are committed to more regional cooperation, strengthening primary care, focusing on prevention and better working conditions for healthcare professionals. By focusing on health and well-being through prevention and support, care needs are prevented or reduced. It is clear from an increasing number of diseases that lifestyle can play an important role in treatment and/or recovery. All the more reason to make lifestyle a standard part of treatment, and where necessary reimbursed. This is very relevant for patients with NSCLC who are often characterized as aged ≥70 years, having tobacco-related comorbidity and/or cognitive impairment, being physically inactive and/or malnourished, and having a low physiological reserve capacity (5). Lifestyle interventions deserve an equal place in curative care, alongside, for example, medication, and medical interventions. This means promoting a healthy lifestyle and strengthening people's self-reliance. Thus, the focus of care is increasingly on the impact of complications after cancer treatment, and promoting faster recovery after treatment. Patients with NSCLC with a high risk for complications, worse recovery, longer hospital stays, and worse survival could benefit from (p)rehabilitation by improving a patient's physical fitness. Adequate risk assessment to decide on the best treatment option is essential, but it also identifies patients who might benefit most from a lifestyle intervention such as (p)rehabilitation. The overall aim of this thesis was to optimize the pretreatment risk assessment for patients requiring treatment for NSCLC, who are generally vulnerable, and to gather information that can be used to develop an effective and feasible (p)rehabilitation program before and after surgery and during other curative treatment options for NSCLC to improve treatment tolerance, in which the patient's view plays an important role.

The research described in this thesis highlights that identifying specific impairments in several physical, nutritional, and geriatric domains helps to generate an individual risk profile for each patient who has to undergo treatment for NSCLC. Better pretreatment physical fitness and nutritional status reduce the risk of treatment complications and improve survival. Objectively assessed aerobic fitness of operable patients during a cardiopulmonary exercise test seemed to be the best predictor for complications after treatment, but also cheap and easy to administer field tests were associated with postoperative complications. The advantage of these tests is that some of them are already routinely used for diagnostic purposes and/or to determine operability, and can therefore easily be used for risk assessment in everyday clinical practice.

Lifestyle interventions before, during, and after intensive treatment for NSCLC are important to increase the resilience of vulnerable NSCLC patients with improved treatment tolerance as a result. We have shown that prehabilitation results in a reduction of postoperative pulmonary complications, severe postoperative complications, and postoperative length of hospital stay in patients who underwent surgery. Although prehabilitation seems effective, it remains unclear how an optimally effective exercise prehabilitation program should be designed. Patients indicate that they would like to actively do something about their health themselves instead of waiting for surgery. A supervised program facilitates personalization of the physical exercise training such as turning functional activities into physical exercise, which can improve adherence and motivation. For both surgery and chemoradiotherapy, patients indicated that the support of an informal caregiver was an added value as motivation to improve adherence.

Relevance

Scientific impact

In addition to the treatment of patients with lung cancer, developments in lifestyle management are important. Lifestyle management is not an alternative to traditional medicine, but additive and should be integrated within current care. Results from this thesis have shown that a variety of physical, nutritional, and geriatric assessments can be used to identify patients who are at high risk for treatment intolerance and who can benefit from lifestyle advice or lifestyle interventions. Since many of these assessments are already used in the diagnostic trajectory, implementation of the use of the outcomes of these assessments to inform the patient and informal caregivers, and to decide

whether or not to participate in (p)rehabilitation. Given the positive results of (p)rehabilitation in reducing postoperative complications and to improve survival in patients undergoing treatment for lung cancer, the next step should be to integrate prehabilitation and rehabilitation (at least consisting of physical training, nutritional advice, and smoking cessation as presented in this thesis) into the standard treatment regimen, focusing on an individual patient's risk factors and ideally organized in the patient's living environment.

Given our results regarding prehabilitation, the function of "waiting time" between diagnosis and initiation of treatment in relation to treatment outcomes has become an important issue. The time before treatment can be converted into a proactive preparation period for treatment by performing preventive interventions (prehabilitation). This seems complicated, because "waiting time" is currently used as one of the performance indicators for quality of hospital care. Recommendations regarding treatment interval vary widely and may even differ within countries due to the lack of fundamental evidence-based guidelines. Scientific evidence from these guidelines currently used for waiting time in patients with lung cancer are more than 10 years old (6). Moreover, there is no evidence that a longer pretreatment period has negative effects on treatment outcomes (7). As a result of these guidelines, healthcare professionals are not always motivated to delay surgery to optimize a patient's health status preoperatively. When hospital logistics are optimized, including optimal cooperation between all disciplines, the currently recommended short "wait time" can be realized as a "preparation period" in most patients. We suggest that optimization of the preoperative physical fitness of high-risk patients is preferred. In addition, new developments such as neoadjuvant immunotherapy in patients who are operable prolong the preoperative period, which might provide additional opportunities to prepare patients for surgery. Currently, neoadjuvant immunotherapy is still only being used in randomized controlled trials, and the possibilities for lifestyle interventions during neoadjuvant immunotherapy need to be further explored.

For compliance and effectiveness of prehabilitation in high-risk patients, we suggest that the exercise component of the prehabilitation program is best performed in the patient's own living environment with (partly) supervision of a physical therapist and involving the patient's informal support system. The benefit of implementing physical exercise training at home is that patients can use activities of daily living as exercises that are relevant and important for the individual patient (e.g., stair climbing, cycling, walking), which also have

a beneficial effect on daily functioning in the elderly. As one of the results of these findings, we considered it important to initiate a project in which we completed focus groups with patients who have had experience with cancer treatment and healthcare professionals to investigate how the help of buddies can be arranged in the home setting to cook healthy meals with patients, go for walks together, and/or provide social support. The output of these focus group discussions led to a targeted plan for a grant application for a qualitative stakeholder analysis within VieCuri Medical Center, Venlo, in the Netherlands.

Social impact

Identifying patients at risk for complications or inadequate recovery after treatment for lung cancer and implementing targeted preventive interventions such as (p)rehabilitation can have a positive impact on patient-related outcomes, the need for healthcare resources, and consequently on costs. The costs associated with preventing complications would likely outweigh the costs of caring for the postoperative complications, and would significantly reduce the physical, mental, and social burden of the patient. We therefore expect that prehabilitation is cost-effective. Future studies should provide evidence for these assumptions. In addition, it has become clear to physical therapists conducting research that it is important to capture "exactly what" we are doing. Due to the lack of research of sufficient quality (methodological and therapeutic quality due to insufficiently clear description of the interventions used), Dutch healthcare insurance companies are questioning treatment of physical therapists with regard to content and quality. This thesis has shown that physical training interventions are not well reported in the literature. To describe the content of physical exercise interventions, the international Consensus on Therapeutic Training aNd Training (i-CONTENT) tool is recommended (8). For example, the i-CONTENT tool is now introduced in the master studies of specialized physical therapy of Avans+ in students working on their thesis. Given the worldwide developments in (p)rehabilitation, there is a lot of attention at Avans+ for (p)rehabilitation programs in patients who have to undergo surgery for cancer.

Target groups and activities

First, the general findings of this thesis are of value to patients and their informal caregivers. Adequate pretreatment risk assessment can help patients and their informal caregivers to understand the risks for an impaired course of treatment with surgery, stereotactic radiotherapy, or chemoradiotherapy. The pretreatment period can be used as a "teachable moment," during which a

patient might be more receptive towards lifestyle advices and more motivated to change their lifestyle than he or she would be in ordinary life. Second, our findings may help healthcare professionals (e.g., physical therapists, surgeons, anesthesiologists, general practitioners) to identify patients who are at risk for poor treatment tolerance. They can offer these patients a targeted preventive interventions to improve their health status such as prehabilitation and/or rehabilitation. Third, scientists can use our findings to further improve the content and implementation (p)rehabilitation programs for appropriately selected low- and high-risk patients. The aforementioned target groups can be involved and informed about the research findings in different ways. First, patients can be individually informed about the study findings during their visit to the outpatient clinic. The results can be used to identify a patient's own (modifiable) risk factor(s) and, if necessary, a personalized (p)rehabilitation program can be offered to the patient. Second, the knowledge of healthcare professionals and scientists gained during the research period of this thesis has been shared with different hospitals and colleagues in (inter)national communities of practice to transfer/share knowledge and experiences. Third, the research results have been and will be presented at (inter)national conferences by scientists.

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Curriculum Vitae

Curriculum Vitae

Melissa Johanna Jacoba Voorn was born on December 15, 1984. After graduation from high school in 2003 (HAVO, Melanchton College, Rotterdam), she completed the bachelor physical therapy at Hogeschool Rotterdam, Rotterdam, the Netherlands, in 2007. After working in a community physical therapy practice, she started working at the Department of Rehabilitation of the VieCuri Medical Center and Adelante Zorggroep, Venlo, the Netherlands, in 2010. From 2010 to 2015, she completed the Master Oncology Physical Therapy at Avans+, Breda, the Netherlands.

In 2019, Melissa commenced her PhD research at VieCuri Medical Center in collaboration with Maastricht University (GROW, School for Oncology and Reproduction). She conducted her research activities at VieCuri Medical Center in Venlo, while simultaneously working as a physical therapist at Adelante Zorggroep in Venlo and teacher at Avans+ in Breda, the Netherlands.

While continuing her work as a physical therapist and teacher, she is currently conducting research activities within the sector plan for health sciences and medicine theme prevention at the Department of Rehabilitation Medicine (CAPHRI, Care and Public Health Research Institute) at Maastricht University, Maastricht, the Netherlands.

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Dankwoord

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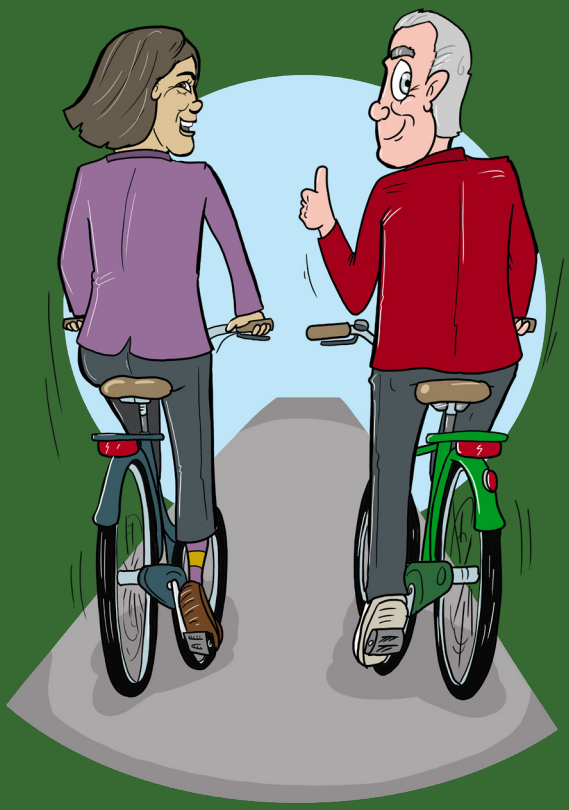

'I think that physical prehabilitation will contribute to a faster recovery after surgery.'
-Patient who underwent surgery for NSCLC-

'Supporting my husband by doing physical training together to motivate him is important.'
-Informal caregiver-

'When prehabilitation is standard care a nd reimbursed by the Dutch healthcare insurance companies, it is very effective in lowering healthcare costs.'
-Healthcare professional-