

Multimodal lifestyle optimization before, during, and after treatment for non-small cell lung cancer

Citation for published version (APA):

Voorn, M. J. J. (2023). *Multimodal lifestyle optimization before, during, and after treatment for non-small cell lung cancer: from pretreatment assessment to (p)rehabilitation for improving treatment tolerance*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20231222mv>

Document status and date:

Published: 01/01/2023

DOI:

[10.26481/dis.20231222mv](https://doi.org/10.26481/dis.20231222mv)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Chapter 12

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.