

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

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## Impact paragraph

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  $\geq 70$  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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