Strength and Endurance Training in the Treatment of Advanced Lung Cancer Patients

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3. Introduction

Lung cancer remains the most common malignancy, with an estimated 1.04 million new cases each year worldwide, which accounts for 12.8% of new cancer cases. Lung cancer is the cause of 921,000 deaths each year worldwide, accounting for 17.8% of cancer-related deaths (Maghfoor, 2005).

The two general types of lung cancer include small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (Walker, 2008). Small cell lung cancers comprise 25% of all lung cancer patients and are generally believed to be a systemic disease. Approximately 80% of patients respond to chemotherapy, which is therefore often the treatment of choice. Unfortunately the majority relapses and only 10% are still alive two years after they have been diagnosed (NICE guideline, 2005).

NSCLC is used as an umbrella term for several types of lung cancers that show similar symptoms and also offer similar treatment options. NSCLC are the most common forms of lung cancer and include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. They comprise about 75% of all lung cancer cases (National Cancer Institute, 2007). Since it metastasizes later in its course, surgery is normally the best choice for treatment. Unluckily only 15% of patients are suitable for resection after being diagnosed. Since most patients suffer from a more advanced stage of the disease, patients often receive a combination of chemotherapy and radiation. Although NSCLC is much less sensitive to chemotherapy, chemotherapy can improve survival and quality of life (NICE guideline, 2005).

More than 90% of lung cancer patients will be symptomatic at diagnosis. Most patients have either non-specific systemic symptoms including anorexia, fatigue and weight loss, or specific symptoms indicating an already more advanced stage at first presentation. Prognosis is often clearly related to presenting symptoms. In case a patient shows atypical or no symptoms his or her prognosis is normally better than for patients showing symptoms directly related to the primary tumour (Beckles et al. 2003).

Central tumours of the lung often cause symptoms such as cough, haemoptysis, dyspnoea, and post obstructive pneumonia. Peripheral tumours frequently have symptoms resulting from infiltration of surrounding tissues. In patients with locally advanced disease, involvement of the pleura, chest wall, vertebrae, and brachial plexus frequently cause pain (Silvestri et al. 2002).

Lung cancer is staged using the International Staging System. The system has two major components; the anatomical staging of the disease (TNM; tumour, nodes, metastasis), and the
cell type (Milroy, 2008). Clinical staging relies on information obtained from imaging studies and biopsies (Silvestri et al. 2003).

In stage IIIB and IV non-small cell lung cancer patients, palliative chemotherapy offers an improvement in survival. For patients with a good performance status, first-line platinum-based chemotherapy regimes are recommended (Syrigos et al. 2006, pp. 273-288). Although side effects are reduced compared to former therapies, patients still experience fatigue, nausea and may develop neutropenic sepsis (Williams, 2006).

Since most lung cancer patients live only for a short time, the need for palliation of symptoms should be first priority. Lung cancer symptoms and the side effects of chemotherapy, reduce the patient’s physical activity level, which makes the patient very dependent on others. According to Kosmidis (1996) quality of life is consequently reduced due to the fact that symptoms have not only an impact on the patient’s physical capacity, but also on the patient’s social status and psychological state.

In quality of life (QOL) studies of lung cancer patients it was emphasized that initial quality of life was the strongest prognostic factor for survival (Montazeri et al. 1998).

In order to improve this factor this protocol was developed, including a physiotherapeutical muscle strength and endurance training. It serves as a set-up for a prospective randomized controlled trial.

This leads us to the following hypothesis of our protocol:

Physiotherapy with a combination of muscle strength and endurance training has a positive impact on the quality of life in NSCLC patients stage IIIB/IV, receiving chemotherapy as palliative treatment. This will be measured using the EORTC QLQ-C30 questionnaire and the Barthel Index and compared to patients receiving usual care during chemotherapy.
4. Clinical Picture

4.1. Pathology
Bronchial carcinomas are normally divided into two major types based on the histology. Physicians make important treatment decisions based on which major type of lung cancer the patient has. The two general types of lung cancer consist of SCLC and NSCLC (Walker, 2008). SCLC comprises 25% of all lung cancer cases and is generally believed to be a systemic disease. Approximately 80% of patients respond to chemotherapy, which is consequently the common treatment of choice. Unfortunately the majority of the patients relapses and only 10% are still alive following two years after diagnosis (NICE, 2005). NSCLC is used as an umbrella term for several types of lung cancers that show similar symptoms and also offer similar treatment options. NSCLC are the most common forms of lung cancer and include squamous cell carcinoma, adenocarcinoma and large cell carcinoma. They comprise about 75% of all lung cancer cases (National Cancer Institute, 2007). Surgery is normally the best treatment choice, since NSCLC metastasizes later in its course. Unluckily only 15% of patients are suitable for resection at diagnosis. Due to the fact patients suffer from a more advanced stage of the disease, patients receive a combination of chemotherapy and radiation. Although NSCLC is much less sensitive to chemotherapy, chemotherapy can induce the tumour’s shrinkage and improve survival and quality of life (Walker, 2008).

4.2. Epidemiology
Routine mortality statistics have confirmed that lung cancer became more frequent during the first half of the 20th century. At the end of the century, the disease had become one of the world’s leading causes of preventable death. In the beginning of that century, lung cancer was a rather rare disease, but exposure to new etiologic agents and an increasing lifespan resulted in an increase of the amount of lung cancer cases reported. The increased number of new lung cancer cases followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung tissue to inhaled carcinogens (Alberg & Samet, 2003).
Although lung cancer is the most commonly diagnosed cancer worldwide its geographic distribution shows marked regional variation (Gilliland & Samet, 2004).
Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America (Parkin et al. 1994). The low rates of lung cancer in Africa are comparable to United States rates in 1930, when rates of lung cancer were under 5 cases per 100,000 for both sexes.
(Gordon et al. 1961). In contrast, African-Americans in the United States, now experience lung cancer incidence rates that are among the highest in the world. The higher risk to developing lung cancer and also a lower chance in survival might be related to a lack of knowledge, a low socioeconomic status, lack of surgery in early disease or noncompliance with treatment (Razaq et al. 2005).

As the lung cancer epidemic begins to subside in the developed countries, it is on the rise in the developing world (Boffetta et al. 1994). Trends in its regional distribution can provide clues about the determinants of lung cancer. In the past, rates tended to be highest in urban areas, which led to conjecture that air pollution might be a cause of the lung cancer epidemic (Stocks & Campbell, 1955).

The epidemiologic evidence and the biological understanding of respiratory carcinogenesis have supported the fact that smoking causes lung cancer. Thus the majority of lung cancer cases are attributable to cigarette smoking. Any action preventing cigarette smoking initiation or being in contact with second-hand smoke, is a step to reducing the risk of lung cancer (Alberg et al. 2007).

Due to historical cigarette smoking patterns, the epidemic of lung cancer started later in women than in men. In contrast to the situation in men, lung cancer incidence rates in women are still increasing. Smoking prevalence has always been lower among women than men, but from the mid-1960s through the mid-1980s, the amount of smoking women increased tremendously and it has remained fairly constant since that time (Alberg & Samet, 2003).

4.3. Risk Factors

A number of factors may increase the risk of developing lung cancer. Some of these factors can be controlled, other factors can not be influenced.

Since the 1950s cigarette smoking, which is the most common cause of lung cancer, has been causally linked to disease’s development (Peto et al. 2000). The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day (Doll & Peto, 1978). Since environmental tobacco smoke has to be considered as a human carcinogen, passive smoking might also increase the risk of developing lung cancer. The National Research Council reviewed the epidemiologic evidence and concluded that non-smoking spouses who were married to cigarette smokers were about 30% more likely to develop lung cancer than non-smoking spouses who were married to non-smokers.
Additionally there are other factors contributing to the individual risk, such as the following (Biesalski et al. 1996):

- Genetic predisposition
- Exposure to radon, asbestos and chemical carcinogens
- Previous lung disease such as chronic obstructive pulmonary disease (COPD)
- Previous tobacco-related cancer
- Low consumption of fruit and vegetables

4.4. Clinical Manifestations and Course

More than 90% of lung cancer patients will be symptomatic at diagnosis. Most patients have either non-specific systemic symptoms including anorexia, fatigue and weight loss, or specific symptoms indicating an already more advanced stage at first presentation. Prognosis is normally clearly related to presenting symptoms (Beckles et al. 2003). The histological type, biological behaviour, and the anatomical location of lung cancer within the thoracic cage determine the type and severity of respiratory symptoms (Kvale et al. 2007). Symptoms and signs related to lung cancer can be classified in four different categories. First of all there are symptoms related to the primary lesion. Additionally there are symptoms related to intrathoracic spread, those related to distant metastasis and those related to paraneoplastic syndromes (Beckles et al. 2003).

Central tumours of the lung often cause symptoms such as cough, haemoptysis, dyspnoea, and post obstructive pneumonia. Peripheral tumours frequently have symptoms resulting from infiltration of surrounding tissues. In patients with locally advanced disease, involvement of the pleura, chest wall, vertebrae, and brachial plexus frequently cause pain (Silvestri et al. 2002).

Since all the above mentioned symptoms have not only an effect on the physical activity level, but also have a psychological impact and influence on the patient’s social status, quality of life (QOL) as a new important clinical end point, might be affected. The concept is particularly relevant to NSCLC patients, for which treatment tends to be palliative (Kosmidis, 1996).

In quality of life studies of lung cancer patients it was stated that initial quality of life was the strongest prognostic factor for survival (Montazeri et al. 1998).

Although patients with poor performance status treated with platinum based chemotherapy have a similar rate of toxicity compared to patients showing a good performance status, their overall survival was lower despite a similar response to chemotherapy (Stinchcombe, 2005).
4.5. Diagnosis/ Staging
Lung cancer is staged using the International Staging System. The system has two major components; the anatomical staging of the disease (TNM; tumour, nodes, metastasis), and the cell type. The TNM staging system for lung cancer provides a consistent reproducible description of the extent of anatomic involvement (Labadebe et al. 1999). Clinical staging relies on information obtained from imaging studies and biopsies. Pathological staging is determined following surgical resection. Stage IV denotes the presence of metastatic disease. Patients with IIIB disease who are not appropriate for combined therapeutical modality approaches, such as those patients with a malignant pleural/ pericardial effusion and certain patients with advanced palpable supraclavicular adenopathy, are typically included with stage IV patients. In both patient groups the benefit of systemic chemotherapy is considered to be the best treatment option (Socinski et al. 2003).

4.6 Chemotherapy Treatment
At present, most patients who receive an initial diagnosis of lung cancer suffer from an advanced stage of the disease and can not be cured with currently available therapies (Bach et al. 2003). In stage IIIB/IV non-small cell lung cancer patients, palliative chemotherapy offers an improvement in survival. For patients with a good performance status, first-line platinum-based chemotherapy regimes are recommended. Although side effects are reduced compared to former therapies, patients still experience fatigue, nausea and may develop neutropeanie sepsis . Current recommendations, based on clinical trials, advise four cycles of chemotherapy, because longer duration of treatment does not improve survival and can lead to increased toxicity. Prolonged treatment is not needed, because the most benefit occur in the first three or four sessions (National Comprehensive Cancer Network, 2007). Since most lung cancer patients live only for a short time, the need for palliation of symptoms should be first priority (Montazeri et al. 1998).

4.7. Side Effects Caused by Chemotherapy
According to Socinski et al. (2003) only 22% of patients would be willing to choose chemotherapy for a survival benefit of three months. However, over half (68%) would choose chemotherapy if it substantially improved QOL.
Most of the side effects are due to the fact that drugs given for chemotherapy do not selectively kill cancer cells but interfere with any rapidly dividing cells. Tissues in the body that normally grow and divide rapidly can be damaged. Although side effects are reduced compared to former therapies, patients still experience fatigue, nausea and may develop neutropenic sepsis (Williams, 2006). The most important side effect is a temporary drop in the white blood cell number due to the effect of chemotherapy on the bone marrow. This typically occurs seven to 14 days after chemotherapy is given. The low blood cell count creates a risk of developing a life threatening or fatal infection. Other possible side effects include hair loss, numbness in fingers and toes (called neuropathy), hearing loss, diarrhoea, skin rash, and loss of renal function (Lilenbaum, 2008). Since side effects increase with every cycle of chemotherapy, not more than three or four cycles of chemotherapy are recommended (National Comprehensive Cancer Network, 2007).

5. Clinical Relevance of Physiotherapy in the Treatment of Lung Cancer

Chemotherapy in lung cancer patients stage IIIB/IV may improve survival and palliates symptoms (Socinski et al. 2003). This is achieved by improved protocols concerning chemotherapy and targeted therapies based on a better knowledge of the genetic mechanisms of the disease. Nevertheless two problems, which are directly related to the disease itself and side effects of chemotherapy are not yet faced within most treatment approaches: the patient’s activity level is tremendously limited while receiving chemotherapy. Thus quality of life is reduced due to the fact that symptoms have not only an effect on the patient’s physical capacity, but also on the patient’s social status and psychological state (Kosmidis, 1996). As already mentioned in chapter 3 in quality of life studies of lung cancer patients it was emphasized that initial quality of life was considered to be the strongest prognostic factor for survival (Montazeri et al. 1998). According to Kvale et al. in patients with lower quality of life scores, pain and anxiety are often high and also the incidence of dyspnoea is higher (2007).

Since the reduced functioning of daily activities leads to a diminished quality of life, both problems can be addressed within one treatment approach. Activities of daily living, such as walking stairs or walking short distances often lead to severe breathlessness and exhaustion in advanced lung cancer patients. The physical activity level is tremendously reduced which makes the patient very dependent on others.
A standardized questionnaire such as the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer) covers several dimensions, such as the functional or performance status, disease- and treatment-related symptoms, anxiety, depression, and subjective well-being, as well as social role functioning, family and social support (Manegold & Schwarz, 1996). This questionnaire gives patients the opportunity to be actively involved in their treatment and provides a detailed impression about the patient’s QOL.

Formerly lung cancer patients were advised to take physical rest, in order to reduce symptoms such as dyspnoea and exhaustion. Thus negative consequences are often not taken into consideration: A lack of exercise leads to a fast progressing muscular dystrophy. Activities of daily life are harder or even impossible to perform. Therefore exhaustion causes a reduced performance status. A vicious circle is created which might be used to explain the connection of physical inactivity and the worsening of symptoms and side effects.

By developing a strength and endurance training for advanced lung cancer patients, we hope to maintain their physical capacity or even achieve small improvements. This might already have a huge effect on the patient’s quality of life.

Several studies showed that endurance training will have a positive effect on symptoms of COPD patients. Mador et al. (2004) stated that the six-minute walk distance, endurance exercise time, and quality of life (as measured by the Chronic Respiratory Questionnaire) significantly increased in COPD patients after rehabilitation which includes endurance training. Bekkering et al. (KNGF guidelines for physical therapy in patients with chronic obstructive pulmonary disease, 2003) states that patients with COPD may tend to avoid exercise and this causes their general physiological condition to deteriorate further. The COPD guidelines recommend a combination of strength and endurance training in order to maintain the patient’s activity level and to ease symptoms. Since severe COPD patients and lung cancer patients show many of the same symptoms, such as dyspnoea and cough, a similar treatment approach should be considered. Currently there is no evidence, which proofs that exercise might have a positive impact on the quality of life in lung cancer patients. Therefore we designed a research protocol in order to measure and scientifically detect the effects of a strength and endurance training on the quality of life in advanced lung cancer patients.

We hope that this protocol will have a positive influence on integrating the clinical aspect of physiotherapy into the treatment of cancer patients.
5.1. Review about Physical Activity in NSCLC Patients

Relevant articles, that are dealing with the same question, whether or not muscle strength and endurance training will have a positive impact on the quality of life in NSCLC patients stage IIIB/IV, receiving chemotherapy, are rather difficult to find. Previous studies vary greatly concerning their conclusion and are often low in evidence. Generally it has to be mentioned that only within the last ten years the interest in the relationship between physical activity and cancer increased considerably. Only within this time new studies have been conducted dealing with the effects of physical activity on the progression of cancer (Dimeo, 2001).

In articles dealing with related topics, following questions were meant to be answered:

- Is there a relationship between physical activity and the risk of developing cancer?
- Does physical therapy have a positive impact during or after receiving cancer treatment?
- Does a multidisciplinary rehabilitation program including endurance training have a positive effect on pulmonary function and exercise capacity of lung cancer patients?

Most studies concerning exercise for cancer patients have demonstrated physiological and psychological benefits. Unfortunately most of this research is limited because it did not involve randomized controlled trials and often used small sample sizes (Mc Ardle et al. 2007). For instance Temel et al. conducted a pilot study of an exercise program for patients with advanced NSCLC in 2008. The study’s aim was to examine the feasibility of an exercise program for patients with advanced NSCLC patients. The results showed that just under half of the participants were able to complete the intervention. However those who completed the program experienced an improvement in symptoms related to lung cancer.

5.2. Physical Training in the Rehabilitation of Tumour Patients

According to previous research the following statement can be made:

After the completion of a cancer therapy, 70% of oncological patients suffer from limitations concerning their physical capacity and increased fatigue (Smets et al. 1993). These results can be attributed to the disease itself as well as to therapy. Cancer and its therapy have often as result an organic and functional change, which causes a restriction in oxygen supply of the muscle cells. This means that patients have to excessively exert themselves after therapy while performing activities of daily life.
Several studies have shown that a specific training program after cancer therapy can reduce these symptoms. By means of that, physical capacity can be increased considerably and the level of fatigue simultaneously decreased (Dimeo et al. 1998).

According to Dimeo (2001) it is currently not known that such training programs show harmful effects to the immune system.

5.3. Exercise and the Risk of Developing Cancer
The question whether or not exercise can reduce the risk of developing cancer, can not be clearly answered with the help of previous scientific research studies. According to Dimeo (2001) some studies state that exercise may reduce the risk of developing cancer, but their significance is greatly reduced due to methodological limitations.

By any means it can be emphasized that intensive physical activity will never cause a pathological activation of the immune system and its related cancer progression. This means that exercise does not increase the risk of developing cancer.

5.4. Exercise as an Accompanying Procedure during Cancer Therapy
Based on previous studies that mainly used animals, the question whether or not physical activity leads to a decrease in tumour growth can not be clearly answered. The studies show by all means controversial results. Due to the previous state of knowledge it can not be concluded that physical activity should play a role in the therapy of cancer patients.

Some studies however show that a training program after or during cancer therapy, decreases the intensity and frequency of side effects, especially the fatigue syndrome and the psychological stress (Mock et al. 1997).

According to Mc Ardle et al. (2007) exercise studies in clinically depressed populations support the positive effects of regular physical activity on depressive symptoms. However it is not described how exercise alleviates depression.

This leads us to the conclusion that physical activity as an accompanying therapy may have a positive effect on the side effects of cancer.

Dimeo (2001) states on the other hand, that a general conclusion about the harmlessness of a trainings program can be made too soon. This conclusion can not be admitted by means of the actual data records. Further research is needed here.
5.5. Conclusion

Very few data is available about the effects of a strength and endurance training carried out during the time patients receive chemotherapy. There is need for clarification whether a physical training program conducted during the time patients receive cancer therapy would have a positive effect.

How should such a training program be designed, so that positive results can be seen?

This is the starting point of our study. Is it possible to counteract the muscle atrophy with a specifically designed training program and therefore keep or even increase the patient’s physical capacity? However a positive influence on the patient’s physical activities should not only be focused on the increased muscular and cardiovascular functions.

This study also focuses amongst others on the patient’s quality of life and their ability to be independent in activities of their daily life. For that reason a randomized, stratified and controlled study including a controlled strength and endurance training is planned to be conducted.

The controlled conduction will be secured by regular approval of measurements such as the MBS and the 6-minute walk test.

6. Physiotherapeutical Strength and Endurance Training

Since ADL functioning is typically strongly affected by symptoms caused by the disease itself and side effects related to chemotherapy (Stafford et al.), the designed training program aims at keeping and improving the patient’s quality of life. Continuous strength and endurance training are considered as effective training methods to counteract many negative signs and symptoms (Mc Ardle et al. 2007).

The aim of a combination of strength and endurance training is to keep the original strength capacity by preventing any further muscle atrophy and to build up affected muscle groups.

The main problem in oncological patients is a general decrease in muscle tissue due to an increase in immobilisation during each stationary stay at the hospital (Mc Ardle et al. 2007). Exercise can produce an increase in the size of muscle fibres as well as changes in their capacity for ATP production, the energy source of each muscle cell (Widmaier et al. 2006).

Progressing atrophy of all types of muscle fibres is often the consequence of the immobilisation and disuse of any muscle. The regularity, with which a muscle is used, as well as the duration and intensity of its activity, affect the properties of the muscle.
Exercise with a relatively low intensity but long duration, produces increases in the number of mitochondria in the fibres that are recruited in this specific type of activity. In addition the number of capillaries also increases, which improves blood supply during activity. These changes lead to an increase in the capacity for endurance activity with a minimum of fatigue.

Additionally endurance training produces positive changes not only in the skeletal muscles but also in the respiratory and circulatory systems. Such changes improve the delivery of oxygen and fuel molecules to the muscle.

In contrast, short-duration, high intensity exercise, affects primarily the fast-glycolytic fibres, which are recruited during strong contractions. Due to the increased synthesis of actin and myosin filaments, these fibres undergo an increase in fibres diameter.

Glycolytic activity is also increased by increasing the synthesis of glycolytic enzymes. As a result of such high-intensity exercise muscle strength increases and atrophy is prevented.

Because different types of exercise produce quite different changes in the strength and endurance capacity of a muscle, an individual must choose a type of exercise compatible with the type of activity he or she would like to perform (Widmaier et al. 2006).

### 6.1. Endurance Training

Endurance is the capacity to perform a certain activity as long as possible and to overcome fatigue (Robergs & Roberts, 2000). Endurance capacity is limited by different factors:

- Stroke volume
- Local metabolic changes
- Changes in control of muscle activity
- Psychosomatic processes

Depending on the patient’s precondition, the training aims at optimizing each patient’s endurance capacity. This requires, that physical activity needs to be measured objectively, in order to individualize each training plan according to data measured before the first training started.

The type of endurance training depends on the treatment goal. Endurance training can be further specified by the amount of muscles used, the type of energy supply (aerobic, anaerobic), as well as the choice of exercise.

Patients with NSCLC have reduced exercise tolerance and associated dyspnoea, which are primarily due to airway obstruction (Polain et al. 2003).
In this study, it is important to measure endurance capacity, therefore the six minute walk test will be used.

The six minute walk test (6MWT) serves as a good modality for objective evaluation of functional exercise capacity (ATS Statement: Guidelines for the Six-Minute Walk Test, 2002). Since walking is an activity performed daily by all but the most severely impaired patients, this trial measures any effect concerning endurance training, by making use of the 6MWT. It evaluates the global and integrated responses of all the systems involved during exercise (ATS Statement: Guidelines for the Six-Minute Walk Test, 2002). Because most activities of daily living are performed at submaximal levels of exertion, the 6MWT reflects the functional exercise level for daily physical activities.

Additionally the patient will be instructed to make use of the Modified Borg Scale (MBS) to grade the intensity of dyspnoea.

### 6.2. Individualized Training Intensity

In this study individualized endurance training requires following factors:

- Determination of the actual functional capacity prior to the beginning of the intervention
- Determination of the intensity level according to the individual endurance capacity
- Constant control of the intensity level during training episodes

The 6MWT will be done before and after the intervention. The 6MWT is a practical, simple test that requires a 100-ft hallway (30 metres), but no exercise equipment, besides a heart rate monitor and a stop watch. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of six minutes. The self-paced test assesses the submaximal level of functional capacity, since most patients do not achieve maximal exercise capacity. As preparation for the test a 30 metres distance will be marked on the floor of the hallway. Every three metres a tape will be fixed to the floor. Additionally two more striking tapes will mark the floor at the start and the end of the distance to show the patient the point of turning. In case of severe breathlessness (MBS 5 or higher) the patient may stop and rest during the test.

To enable the patient to rest, a chair will always be available in the hallway. Furthermore sturdy shoes have to be worn and the patient may use any walking aid that may contribute to his/her walking. Because most activities of daily living are performed at submaximal levels of exertion, the 6MWT may better reflect the functional exercise level for daily physical activities (ATS Statement: Guidelines for the Six-Minute Walk Test, 2002).
Although the distance measured is the primary outcome measure, improvements during repeated evaluations may be also recognized by reduced symptoms with the same distance walked.

The Modified Borg Scale (MBS) has the potential to provide quick and easy information and is used to determine the patient’s subjective state of dyspnoea. Shortness of breath is one of the most common and significant complaints of patients with lung cancer and therefore often one of the most limiting factors concerning endurance training (Virtual Medical Centre, 2008).

The magnitude of the training response measured using the above mentioned tests, depends on the patient’s initial fitness level. Patients who rate low at the start of the intervention have considerable room for improvements (McArdle et al. 2007). Training-induced physiologic adaptations depend primarily on the intensity of overload and the specificity of the training program.

Thus two important factors formulate an aerobic exercise program (McArdle et al 2007):

1. Cardiovascular overload must be sufficiently intense to increase stroke volume and cardiac output
2. Cardiovascular overload must occur from activation of sport-specific muscle groups or muscles which are used in activities of daily life to enhance local circulation and the muscle’s “metabolic machinery”

6.2.1. Endurance Training within Study
In order to train as specifically as possible, patients will walk in the hallway every day after starting the intervention. To train at a moderate intensity, we have to determine the patient’s maximum heart rate (HRmax) before calculating the right intensity.

A formula for estimating HRmax that has high accuracy for non-fit males and females is as follows (McArdle et al. 2007):

\[ \text{HR max} = 208 - 0.7 \times \text{age (y)} \]
The Karvonen method is used to establish the training threshold:

\[ \text{HR threshold} = \text{HR rest} + 0.50 \times (\text{HR max} - \text{HR rest}) \]

*depending on the patients training intensity 0.50, 0.55, or 0.60

Mc Ardle et al. state that the aerobic capacity improves if exercise regularly maintains heart rate between 55 and 70% of heart rate reserve (HRR) (2007).

We conducted a pilot study on six lung cancer patients stage IIIB/IV at the Vivantes Hospital in Neukoelln in November 2008 to test if the designed protocol will be realistic and easily conductible. When performing the Six Minute Walk Test, we observed that two out of six subjects struggled the most with dyspnoea and were not able to walk as fast as 55%-60% of their HRR. In this case the heart rate was not the predicted value, but the dyspnoea the patients suffered from. Due to that fact we decided that the patients will be allowed to walk on their own speed if they experience severe dyspnoea while performing the test. We will set the training intensity depending on the patient’s score on the MBS. The MBS will be used as device to measure and evaluate the patient’s dyspnoea prior, during and after the training session. The heart rate will be measured with a heart rate monitor, which will be put around the patient’s chest prior to the training. The patient will wear the watch, which is used to monitor heart rate on his/her left wrist.

The training principle of overload claims that regular application of a specific exercise overload enhances physiologic function to induce a training response (Mc Ardle et al. 2007). Thus exercising at intensities greater than normal stimulates highly specific adaptations so the body functions more efficiently.

The training principle of specificity refers to adaptations in metabolic and physiologic functions that depend upon the type and mode of overload imposed. This means that specific exercise elicits specific adaptations to create specific training effects (Mc Ardle et al. 2007).
According to these principles we designed our training program:

- MBS (Modified Borg Scale) is used to determine training intensity and firstly measured prior to intervention

  → Patients grading the MBS with 0, 0.5, or 1 will train at an intensity of 60% of HRR
  → Patients grading the MBS with 2 or 3 will train at an intensity of 55% of their HRR
  → Patients grading the MBS with 4 will train at an intensity of 50% of HRR
  → Patients grading the MBS with 5 or higher will train at their own intensity or might decide to end their training session
  → MBS will be repeated after three minutes and if the patient scores different then prior to the training the intensity will be adjusted

Table 1: Modified Borg Scale

<table>
<thead>
<tr>
<th>SCALE</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Breathlessness At All</td>
</tr>
<tr>
<td>0.5</td>
<td>Very Very Slight (Just Noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very Slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight Breathlessness</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Some What Severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe Breathlessness</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very Severe Breathlessness</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very Very Severe (Almost Maximum)</td>
</tr>
<tr>
<td>10</td>
<td>Maximum</td>
</tr>
</tbody>
</table>

(Burdon et al. 1982)
• Grading will take place regardless of any oxygen substitution
• The training program is scheduled for a period of nine weeks (three cycles of chemotherapy)
• Training will take place every day of the week (including the weekend)
• Patients will train in the hallway for six minutes without stopping completely (only in case of severe breathlessness, MBS 5 or higher)
• Patients will be encouraged by the physiotherapists and informed about any necessary adjustments in their walking velocity
• MBS will be measured again after the training session in order to compare any change in the shortness of breath

Additionally to walking six minutes in the hallway, stair walking is added to the training, which is meant to improve both the patient’s strength and endurance.

Stair walking:
• The patient will walk stairs for two minutes and the amount of stairs he/she is able to walk within this time will be reported
• If the patient will reach the tenth stair during the two minutes, he/she will turn and walk down
• Sturdy shoes have to be worn
• If the patient does not feel comfortable walking to the nearest staircase, the patient may safe his/her energy and may be brought to the staircase in a wheelchair
• The patient is allowed to take rest any time and as long as he/she needs to
• The patient is allowed to use the handrail as support
• Any walking aid (crutches or stick) is allowed to be used
• The exercise is performed every other day
• Dyspnoea will be measured with the MBS prior, after one minute, and after training and the results will be compared after nine weeks of intervention
• The amount of stairs the patient walks will be documented in the patients documentation file (see 7.10.) after each training session and results will be compared after nine weeks of intervention
6.3. Strength Training
In this treatment program we combine four different strength exercises training trunk stability, leg, arm, and abdominal musculature.
In order to make the training as functional as possible, we rather put emphasis on many repetitions instead of an increased weight load. These exercises are called endurance-building exercises, concentrating on musculature endurance, not muscular strength and power (McArdle et al. 2007). We will include concentric, eccentric and as well isometric exercises in our training program to imitate activities of daily life as close as possible.
Patients will repeat a certain exercise as many times as possible in order to find out the maximal amount of repetitions possible for that specific patient. The greatest amount of repetitions will be equalized with 100% of training intensity. For example if a patient is able to perform a specific strengthening exercise 20 times, this will be regarded as 100%.

The main goal of these exercises is to maintain the patient’s actual muscle strength or even achieve improvements concerning muscle power.

6.3.1. Strength Training within Study
Our training program is designed as the following:
• Prior to the intervention, each patient has to perform each exercise with as many repetitions as possible
• According to the patient’s individual results, the amount of repetitions will be determined (maximal amount of repetitions possible = 100%)
• Patients will perform three sets at 50% of their maximal capacity (20 repetitions maximum= ten repetitions training)
• In case a patient can only perform two sets at 50% of his or her maximal capacity, the patient might skip the third set
• After each set a break of one minute will be held
• The exercises are performed every other day
• After two cycles of chemotherapy the maximal amount of repetitions possible is tested again in order to have a better control of the individual training intensity
• In case of any change in the maximal amount of repetitions possible, the training intensity will be adjusted while receiving the third and last cycle of chemotherapy
The strength exercises mainly focus on strengthening the upper limb and the pelvic girdle, due to the fact that the Barthel Index covers many activities that have to be performed with the arms. The strength of the arms is needed for activities such as feeding, washing face, combing hair, shaving, cleaning teeth and dressing. Activities such as getting on and off the toilet and transfers from bed to chair will be improved by strengthening the pelvic girdle and therefore the stability of the trunk.

Exercises:
- Bridging
- Theraband exercise biceps
- Theraband exercise triceps
- Isometric sit up exercise

The four exercises have to be performed as follows:

Bridging:
- The patient lies supine in bed with the hands aside
- The knees will be positioned in a 110° flexed angle with the feet on the mattress
- The knees have to be put shoulder width apart
- The pelvis is lifted up from the bed until the pelvis, knees and shoulders form a diagonal line
- The patient is not allowed to use the strength of the arms to push the pelvis up
- The mentioned position has to be hold for two seconds before slowly dropping the pelvis back
- To prevent that the patient's feet slip over the surface of the bed, a cushion or a blanket is put in front of the feet
- The exercise is performed at 50% of the patient's maximum intensity (→ maximum intensity = amount of repetitions the patient is able to perform without any compensation, eight repetitions = four repetitions as training intensity)
While conducting our pilot study we experienced that some patients are not able to fully lie on their back due to severe breathlessness. In this case, these patients are allowed to have the head board of their bed raised up to a position in which the patient feels comfortable to perform the exercise.

Furthermore the pilot study showed that not every patient is able to keep his/her legs shoulder width apart due to a loss of strength in his/her adductors. In this case the physiotherapist may help the patient to keep his/her legs together.

Figure 1: Bridging

Figure 2: Theraband Biceps

Theraband Biceps:

- The exercise is performed with a green Theraband
- The patient stands with the feet shoulder width apart
- The Theraband is fixed under the feet
- The patient grasps the Theraband with both hands
- The Theraband has to be wrapped around the patient’s fingers until it is tightened
- The elbows have to be kept close to the body and are not allowed to move away from the body during the exercise
- The palms of the hands face upwards
- The patient pulls the Theraband into direction of the shoulders by flexing the elbow until the end range of motion (until tissue approximation)
- The shoulders are not allowed to be lifted up during the exercise
- The exercise is performed at 50% of the patient’s maximum intensity (maximum intensity = amount of repetitions the patient is able to perform without any compensation, 20 repetitions maximum = Ten repetitions training intensity)
Theraband Triceps:

- The exercise is performed with a green Theraband
- The Theraband is wrapped around a sturdy object (e.g. end of bed) at level of the patient’s belly button
- The patient grasps the Theraband with both hands
- The patient stands shoulder width apart
- The Theraband is wrapped around the patient’s fingers until it is tightened
- The elbows have to be kept close to the body and are not allowed to move away from the body during the exercise
- The palms of the hand are facing towards the floor
- The elbows have to be kept straight during the exercise
- The patient pulls the Theraband straight along the side until the arms reach ~ 20° extension
- The exercise is performed at 50% of the patient’s maximum intensity (maximum intensity = amount of repetitions the patient is able to perform without any compensation, 20 repetitions maximum = Ten repetitions training intensity)

Regarding these two exercises the pilot study showed, that some patients did not have the strength in their fingers to hold the Theraband tight during the exercises. In this case the patient will repeat the exercise as long as he/she is able to hold the Theraband tight. Another situation showed that one out of six patients was not capable of doing the exercises bilateral. The patient had metastases around the shoulder area and therefore a paralyzed arm. In this case the patient will perform the exercise only with the unaffected arm.

Figure 3: Theraband Triceps
Isometric sit ups:

- The patient lies supine in bed with the arms crossed over the chest
- The knees are positioned in a 110° flexed angle with the feet on the mattress
- To assure that the patient’s feet will not slip over the surface of the bed, a cushion or a blanket is put in front of the patient’s feet
- The patient lifts the trunk slightly from the bed
- Shoulder blades have to be lifted up from the surface of the bed
- The patient holds the position for two seconds until the trunk is again brought back to the mattress
- The exercise will be performed at 50% of the patient’s maximum intensity (maximum intensity = amount of repetitions the patient is able to perform without any compensation, ten repetitions maximum = five repetitions training intensity)

6.4. Breathing Techniques
The physiotherapeutical intervention also includes a breathing technique treatment that will take place every day while receiving three cycles of chemotherapy.

The breathing techniques include the active cycle of breathing (ACBT), which is designed to reduce airway obstruction and improve the clearance of secretions from the lung (Watson & Poland, 2001). It is a relatively new method, which presents many advantages such as independent application, control of treatment by the patient himself and encouragement of physical activities (Papadopoulou & Tsanakas, 2007). It may be performed in either side lying, supine or sitting position, depending on the patients will. The cycle is made of the breathing control, the deep breathing exercise and the forced expiration technique/ huff. The physiotherapist will give the patient the following instructions:
Breathing control:

- The patient will rest one hand on the abdomen and will keep the shoulders and chest relaxed
- The patient will breathe normally and will let the hand rise while breathing in
- The patient will sigh out gently
- The patient will gradually increase the depth of breathing over a few seconds
- The patient will ensure that the shoulders remain relaxed

Deep breathing exercise:

- The patient will take three to four deep breaths in, allowing the lower chest to expand
- The patient tries to ensure that neck and shoulders are relaxed
- The patient will hold the air in for three seconds after breathing in
- The patient will let the air out gently

Forced expiration technique/huff:

- The patient will take a half breath in and will steadily blow the air out through an open mouth
- This will be followed by a breathing control technique
- The patient will repeat the huff
- The patient will breath in much deeper and will steadily blow the air out through an open mouth
- Breathing control will be repeated

The number of cycles/breaths that will be performed depends on the patient’s level of breathlessness. The cycle will be repeated until the patient feels exhausted. The techniques are carried out once a day under supervision of the physiotherapist.

7. Study Design

7.1. Planning of Study

The clinical trial is a prospective randomized controlled trial and is set up for two years starting in July 2009. The recruitment of patients will take place in the Vivantes Hospital Neukoelln in Berlin.
The study serves to measure and scientifically detect the effectiveness of a physiotherapeutical strength and endurance training (as described in chapter 6) conducted while the patients receive three cycles of chemotherapy. Within the study at least 60 patients are recruited over a period of two years. The starting date of the study is the 01.03.2009.

### 7.2. Inclusion Criteria

- WHO 0, 1, 2, 3 or a Karnofsky score of 40-100
- Patients with newly diagnosed advanced stage IIIB and IV NSCLC
- $\geq 18$ years
- willing to participate in study
- stable clinical condition
- receive an in-patient chemotherapy treatment at the oncological department of the Vivantes Krankenhaus in Neuköln/Berlin
- Signed consent form (see 7. 12)

Table 2: WHO (Zubrod) scale, Karnofsky scale

<table>
<thead>
<tr>
<th>WHO (Zubrod) scale</th>
<th>Karnofsky scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Asymptomatic</td>
<td>100 Asymptomatic</td>
</tr>
<tr>
<td>1 Symptomatic, but</td>
<td>90 Normal activity, minor symptoms</td>
</tr>
<tr>
<td>ambulatory (able to carry</td>
<td>80 Normal activity, some symptoms</td>
</tr>
<tr>
<td>out light work)</td>
<td>70 Unable to work, cares for self</td>
</tr>
<tr>
<td>2 In bed &lt; 50% of day</td>
<td>60 Occasional assistance with needs</td>
</tr>
<tr>
<td>(unable to work but able</td>
<td>50 Considerable assistance</td>
</tr>
<tr>
<td>to live at home with some</td>
<td>40 Disabled, full assistance needed</td>
</tr>
<tr>
<td>assistance)</td>
<td>30 Needs some active supportive care</td>
</tr>
<tr>
<td>3 In bed &gt; 50% of day</td>
<td>20 Very sick, hospitalisation needed</td>
</tr>
<tr>
<td>(unable to care for self)</td>
<td>10 Moribund</td>
</tr>
<tr>
<td>4 Bedridden</td>
<td>0 Dead</td>
</tr>
</tbody>
</table>

(NICE guideline, 2005)
7.3. Exclusion Criteria

- participation in similar clinical studies
- epilepsy
- symptomatic cardiovascular disease
- rheumatic disorders whose symptoms could worsen by the use of an exercise therapy
- patients who are bedfast

7.4. Break Criteria

- Fever
- Infects
- Hb < 8
- Psychological instability
- Clinical complications

7.5. Randomization

Prior to the study’s conduction, all participants will be randomly divided into two groups. In order to guarantee a perfect randomization at baseline a computerized randomisation program will be used. An equally sized intervention and control group will result exclusive of any influence.

7.5. Outcome Measures

The aim of the study is to investigate if a combination of strength and endurance training has a positive impact on the patient’s quality of life and their functioning of daily activity if the training program will be conducted during the time the patients receive chemotherapy. The main variables of interests of this study are the EORTC-QL-C30 and the Barthel Index. The EORTC-QLQ-C30 questionnaire defines the treatment side effects and includes the functional or performance status, disease- and treatment-related symptoms, anxiety, depression, and subjective well-being, as well as social role functioning, family and social support. The Barthel Index is used to determine the patients functioning of daily life while receiving chemotherapy. These two outcome measures will be measured prior to and after the intervention. Accordingly both questionnaires will be filled in prior and after three cycles of chemotherapy (in total nine weeks of training). Additional endpoints are the Six Minute Walk Test, to assess functional capacity before and after completion of the exercise program, and the MBS to grade intensity of dyspnoea.
Regarding this analysis following questions will be considered:

- Is physiotherapeutical strength and endurance training a possible and well tolerated intervention in patients receiving intensive chemotherapy treatment?
- Is it possible to maintain or even improve the patient’s quality of life by carrying out an additional strength and endurance training?
- To what extend is it possible to improve the patient’s independence concerning his or her ADL functioning?
- Is it realistic to reduce any feeling of dyspnoea while completing activities of daily life?
- Does the training have a positive effect on the patient’s quality of life?

7.7. Methods

For the conduction of our designed research study, we included the following methods:

Patients with stage IIIB or VI NSCLC and a good performance status (WHO 0, 1, 2, 3 or a Karnofsky score of 40-100) are admitted to this trial. Every participant should be at least 18 years old and receive an in-patient chemotherapy treatment at the oncological department of the Vivantes Krankenhaus in Neukoelln/Berlin.

The patients receive chemotherapy to improve survival, regain disease control and improve quality of life. Chemotherapy is a combination of a single-third generation drug and a platinum drug (NICE guideline, 2005).

Regardless of any conventional physiotherapeutical treatment, patients receive muscle strength and endurance training to ease symptoms and negative side effects.

All participants are randomly divided into two groups:

Group A: physiotherapeutical strength and endurance training under the supervision of a licensed physiotherapist while receiving chemotherapy. The exercises given mainly aim at improving each patient’s functionality. Usual care is also provided as instructed by responsible physicians. The training will be given while the patients receive chemotherapy. The chemotherapy consists of three cycles whereof each cycle lasts three weeks.

Group B: no physiotherapeutical strength and endurance training while receiving chemotherapy. Usual care is provided as instructed by responsible physicians.
7.7.1. Usual Care
Usual care comprises all different aspects of therapy normally provided by the hospital. The intervention does not replace the usual care, but is defined as an addition to it.

7.7.2. Conventional Physiotherapy
- If needed patients from the control group are allowed to receive conventional physiotherapy treatment such as breathing techniques
- In case of a fracture, patients of both groups may receive mobilization techniques that enhance the patient’s range of motion (ROM)

7.8. Measurements
7.8.1. EORTC QLQ C-30 Questionnaire
The EORTC QLQ-C30 (see Appendix 12.4.) is a 30-item self-reporting questionnaire developed to assess the quality of life of cancer patients. It is grouped into five functional areas (role, physical, cognitive, emotional and social functioning). Additionally there are three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual questions concerning common symptoms in cancer patients, and two questions assessing overall QOL (European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire, 2007). Since 1993 this questionnaire is mainly used in clinical studies (Aaronson, 1988). The EORTC QLQ-C30 questionnaire will be administered prior to the study’s physiotherapeutical intervention. Results will be compared to outcomes taken at the end of nine weeks of intervention. Montazeri et al. (1998) stated in their review that the EORTC QLQ C3-30 questionnaire together with the EORTC QLQ-LC13 was found to be the best developed instrument to measure quality of life in lung cancer patients.

7.8.2. The Barthel Index:
Is a rating score that is used to assess the patient’s level of independence in activities of daily life. It includes activities such as feeding, transfers, personal toilet, walking, descend and ascend stairs, dressing and controlling bowel and bladder function. Each activity is scored with either 0,5,10 or 15 points whereby 0 defines the complete dependence and is given when the patient cannot meet the given criterion. 15 points are given when the patient can carry out
the task completely independent. Overall scores range from 0-100. The scores are intended to reflect the amount of time and assistance a patient requires. The Barthel index is used as one of the outcomes of the study and will be applied before the start of the training program and after completion of the training program and the results will be compared. The patient has to fill in the scores him/herself, but the physiotherapist will be present to answer any questions concerning the rating of the activities (Mahoney & Barthel, 1965).

7.8.3. Six Minute Walk Test
The most important indication to perform the Six Minute Walk Test is to measure outcomes before and after treatment in people with moderate to severe heart and lung disease. Since the Six Minute Walk Test can also be used to measure functional status (Enright, 2003), this test was picked to evaluate any training effects.
See 6.1. Endurance Training, 6.2. Individualized Training Intensity, and Appendix I

7.8.4. Modified Borg Scale
See 6.2. Individualized Training Intensity and 6.2.1. Endurance Training within Study
### 7.9. Time Schedule of Measurements and Training

Table 3

<table>
<thead>
<tr>
<th>Measurements and Training</th>
<th>Prior to training</th>
<th>Weekly</th>
<th>After training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checking of the Inclusion-/Exclusion criteria</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Consent</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemoglobin Laboratory Test</td>
<td></td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Blood Pressure, Pulse, Temperature</td>
<td></td>
<td>every day</td>
<td></td>
</tr>
<tr>
<td>EORTC-QLQ-C30</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Six Minute Walk Test</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Six Minute Walk Test as Training</td>
<td>-</td>
<td>every day</td>
<td>-</td>
</tr>
<tr>
<td>Stair Walking</td>
<td>-</td>
<td>every other day</td>
<td>-</td>
</tr>
<tr>
<td>Strength Exercises Maximum Repetitions Measurement</td>
<td>X</td>
<td>after two cycles of chemotherapy</td>
<td>-</td>
</tr>
<tr>
<td>Strength Exercises as Training</td>
<td>-</td>
<td>every other day</td>
<td>-</td>
</tr>
<tr>
<td>Modified Borg Scale</td>
<td>X</td>
<td>every day</td>
<td>X</td>
</tr>
<tr>
<td>Conventional Physiotherapy</td>
<td></td>
<td>if prescribed</td>
<td></td>
</tr>
<tr>
<td>Breathing Techniques</td>
<td>-</td>
<td>every day</td>
<td>-</td>
</tr>
</tbody>
</table>
7.10. Documentation

A documentation file will be established for each participant and all needed results will be documented in the file after each training session. Additionally to the results of the training, all unexpected occasions will be reported. If the patient is not able to receive any physiotherapeutical treatment due to fever, infects, a low haemoglobin count, psychological instability or clinical complications, this will also be carefully documented. To ensure confidentiality, all written participant information and data will be secured in a locked filing-cabinet. Data will be transferred onto an electronic database with password protection. Participants will be assigned identity numbers to be used on written information to conceal their identity, and ensure anonymity and confidentiality of information. An example of a documentation sheet can be found on the next page.
Documentation Training Results

Date: ____________

Patient: ____________

Age: ____________

Barthel Index Score (prior to intervention): ____________

EORTC-QLQ-C30 Score (prior to intervention): ____________

Resting heart rate (prior to each training session): ____________

Endurance Training:

Karvonen Method: HR threshold = HR rest + 0.50/ 0.55/ 0.60 (HR max – HR rest)

MBS before training: _____ HR: _____ → HR training: _____

MBS after 3 minutes: _____ HR: _____ → HR training: _____

MBS after training: _____ HR: _____ → HR training: _____

Stair walking:

MBS before training: ____________

MBS after ten stairs: ____________ Total time needed: ____________

MBS after training: ____________

Strength Training:

Bridging: 100% Repetitions: ____________ → 50% repetitions training: _____

Theraband biceps: 100% Repetitions: _____ → 50% repetitions training: _____

Theraband triceps: 100% Repetitions: _____ → 50% repetitions training: _____

Isometric sit ups: 100% Repetitions: _____ → 50% repetitions training: _____
### 7.10.1 Suggested Data Collection in Excel Tables

Table 4: Measurements taken prior to and after intervention

<table>
<thead>
<tr>
<th>Patient</th>
<th>6MWT prior to intervention</th>
<th>6MWT after intervention</th>
<th>EORTC prior to intervention</th>
<th>EORTC after intervention</th>
<th>Barthel prior to intervention</th>
<th>Barthel after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2</td>
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</tbody>
</table>
7.11. Proposed Data Analysis

The outcome measures used within this research study will be recorded prior to and after the intervention. The obtained data will be statistically analyzed.

Descriptive Statistics:
The mean strength values and distance will be calculated to summarise data from participants of both groups. The standard deviation will also be calculated to describe the results dispersion.

Interferential Statistics:
Collected data will be statistically analyzed in attempt to support our hypothesis, and enable inferences to be made to the population of interest.
To find out whether our intervention has an effect, an repeated measures ANOVA should be conducted with a significance value $p = <0.05$. The repeated measures ANOVA will be used since results within groups and between groups will be statistically analyzed. Since we make use of four different outcome measures, each questionnaire and test has to be analyzed separately.
Barthel Index:
Since the Barthel Index is used as one of our outcome measures, results of this test can be considered as dependent variable. We would like to analyze the effects of a strength and endurance training on the patient’s level of independence in activities of daily life. Due to the fact that the Barthel Index is considered as a ratio scale, a mixed design ANOVA should be used.

EORTC QLQ C-30:
Additionally the EORTC QLQ C-30 questionnaire will be used to assess the patient’s quality of life. Since this questionnaire consists of six different dimensions (See 7.11.1 Figure 7), each aspect determining the patient’s quality of life has to be analyzed individually.
The questionnaire consists of three different answer categories. Within the first five questions the patient can choose between answer “yes and no”. Since this represents a nominal scale a Chi square test has to be performed. Question six to 28 can be considered as an ordinal scale and therefore analyzed by making use of a Mann-Whitney U-test. The same test will be used for question 29 and 30.

Six Minute Walk Test:
The effects of a strength and endurance training on the distance walked within six minutes should be analyzed. Therefore results received from the Six Minute Walk Test can be considered as dependent variable. Since distance is measured in metres, this outcome can be considered as a ratio scale. Accordingly a mixed design ANOVA should be chosen.

Modified Borg Scale:
The Modified Borg Scale is used to determine the patient’s subjective state of dyspnoea. This scale is an example of an ordinal scale. Consequently a Mann-Whitney U-test has to be performed.

A post hoc test will be used to find specific differences.
7.11.1 Data Presentation:

Data will be tabulated and presented graphically to enable visual interpretation and make comparison of results clearer.

Figure 5: Example of table presenting results of both groups after performing the Six Minute Walk Test after the intervention

Figure 6: Example of table presenting average distance walked after six minutes (prior and after the intervention)
7.12. Ethical and Judicial Requirements

The investigator is in charge of the patients consent to the study. He or she has to inform the patient about the study and has to collect a written consent from every patient. The aims, methods, advantages and possible risks of the study have to be made clear to the patient in advance.

The consent has to be signed before any action concerning the study will be taken.

It has to be made clear to every patient that the participation in the study can be withdrawn at any times for any reason. The decision of a patient to drop out from the study will not have any disadvantages for him/her and the doctor will continue the treatment in any case.

The patient consent questionnaires have to be kept in the patient’s dossier and have to be recorded in the document file.

On the next page an example of a patient consent form can be found.
I, ............................................., herewith confirm, that I will participate in the study and that I am aware of the design, methods, advantages and possible risks of this study.

- The physician,....................., has orally informed me about every detail of the study.

- My data will be processed intimately and the results of the study will be published anonymous.

- I have the right to drop out of the study at any times for any reason and am aware of the fact that this will not have any consequences for myself.

- During the participation of the study I will follow the instructions of the investigator at any times and will make my best effort to add as good as possible to the results of the study.

Patient:  
Investigator:

Place and Date:  
Place and Date:

Signature:  
Signature:
8. Discussion
Since Montazeri et al. (1998) state that at baseline quality of life was the best predictor of both response to the treatment and survival, it would be of our interest to start with a well designed physiotherapy treatment before baseline. In order to improve the patient’s functional capacity and motivation, patients will start to train a couple of weeks before receiving three cycles of chemotherapy. Depending on the outcomes of this study, it will be easier to recruit patients for such a more time-consuming program. As we might already proof that the patient’s quality of life will benefit from a temporary physiotherapy treatment, it might also be possible to proof that the patient’s condition prior to treatment, has influence on the patient’s progression throughout the entire chemotherapy treatment.

In working together with advanced lung cancer patients, it is ethically not justifiable to deprive patients of any kind of physiotherapeutical intervention. Therefore we decided that patients from both groups are allowed to receive conventional physiotherapy treatment such as breathing techniques and mobilization techniques. The intervention group is therefore consciously not compared to a group which receives no physiotherapeutical treatment. Any changes within the outcome measures therefore result out of the training effect created by additional exercises.

Since a statistically significant mean increase in the six minute walk distance (6MWD) in a group of participants is often much less than a clinically significant increase in an individual patient, we believe that the 6MWD in advanced lung cancer patients cannot be predicted using reference equations derived from a healthy population.

9. Personal Statement
Based on the conduction of the pilot study at the Vivantes Hospital in Neukoelln, we can confidently state that a physiotherapeutical strength and endurance training for lung cancer patients stage IIIB/IV will be realistic to accomplish.
We personally experienced the low level of physical activity in these patients and the accompanied lack of quality of life. We find it of high relevance to integrate the clinical aspect of physiotherapy much more into the treatment of lung cancer patients. Despite the fact that lung cancer patients in this stage of their disease will only have a few more weeks/months to live, we find it of high importance that additionally to the already given palliative treatment, a training program will be part of the cancer therapy and will be
given tailor made to each individual. We are positive that an increased level of strength and endurance will help these patients to perform their activities of daily life with fewer symptoms and will therefore classify their quality of daily life on a higher basis.

The design of this study was a great challenge for us. In order to come up with a realistic and conductible study, it was necessary to acquire as much knowledge about lung cancer and its clinical picture. We expect that this project will have a positive influence on the development of integrating the clinical aspect of physiotherapy into the treatment of cancer patients and hope that further research in this topic will by degrees lead to more positive findings and therefore to a better insight in the relevance of physical training in cancer patients.

10. Summary

Palliative chemotherapy offers an improvement in survival in NSCLC patients. In patients with a good performance status, first-line platinum-based chemotherapy regimes are recommended.

Although side effects are reduced compared to former therapies, patients still experience severe side effects and unpleasant symptoms. Since all symptoms have not only an effect on the physical activity level, but also have a psychological impact and influence the patient’s social status, quality of life (QOL) is often tremendously reduced. In performing activities of daily living patients often depend on other people and therefore are not able to keep their activity level up.

It is a considerable challenge in the field of physiotherapy to maintain the patient’s strength and mobility. Maintenance of the patient’s physical fitness might also improve the patient’s tolerance level concerning chemotherapy, since symptoms and side effects might be reduced. As a result physiotherapy might not only have a positive impact on the patient’s activity level and independence, but also affect the patient’s psychosocial status, which again influences the patient’s quality of life. Therefore we set up a research study in order to detect the effects of physiotherapy on the quality of life in advanced lung cancer patients.

For the conduction of this randomized controlled trial, which will start in July 2009, we include patients with stage IIIB/IV NSCLC and a good performance status (WHO 0, 1, 2, 3 or a Karnofsky score of 40-100). Every participant should be at least 18 years old and receive an in-patient chemotherapy treatment at the oncological department of the Vivantes Krankenhaus.
in Neukoelln/Berlin. All participants will be randomly divided into two groups. The intervention group will receive a specially designed combination of strength and endurance training, whereas the control group will not receive this additional training. The patient will receive this additional physiotherapeutical training while receiving three cycles of chemotherapy.

Blood pressure, heart rate, temperature and haemoglobin will be regularly checked and documented to test the patient’s condition. In both groups participants will fill out the Barthel index and the EORTC QLQ C-30 questionnaire prior to and after the intervention in order to report the patient’s activity level and quality of life.

The obtained data will be statistically analyzed and interpreted in the end of the designed intervention. Additionally the Six Minute Walk Test will be used to test the patient’s endurance capacity and level of dyspnoea while making also use of the Modified Borg Scale. Any effects in the patient’s strength will be reported and analysed by the amount of repetitions a patient can perform in one specific exercise.

The aim of our study is to test the impact of physiotherapy with a combination of strength and endurance training on quality of life in NSCLC patients stage IIIB/IV, receiving chemotherapy as palliative treatment.
11. References


Maghfoor, I. & Perry, M. (2005), Lung Cancer Non Small Cell, *Emedicine*


12. Appendix

In this chapter flowcharts can be found, which aim at facilitating the conduction of the study’s different interventions. Each flowchart should serve as a guide through the study’s procedure and contributes to a standardized conduction
12.1. Flowchart Conduction of Study

Recruitment of at least 60 patients in
Vivantes Hospital Neukoelln/ Berlin
Starting date: 01.03.2009

**Inclusion criteria:**
- WHO 0, 1, 2, 3/ Karnofsky score 40-100
- Newly diagnosed advanced IIIB/ IV NSCLC
- > 18 years
- Willing to participate
- Stable clinical condition
- Patient receives inpatient chemotherapy treatment at the oncological department (Vivantes Krankenhaus)
- Signed consent form

**Exclusion criteria:**
- participation in similar clinical studies
- epilepsy
- symptomatic cardion vascular disease
- rheumatic disorders
- patients who are bedfast

**Randomization:**
- A computerized randomization program is used to divide participants into two equally sized groups

**Measurements taken prior to intervention:**
- EORTC QLQ C-30 questionnaire & Barthel Index is filled out by patients
- Six Minute Walk Test performed

**Strength Training:**
- performed every other day

**Endurance Training:**
- performed every day (including stair walking)
- Received data reported documentation file/ Excel tables

**Data analysis:**
- Data is statistically analyzed
- Results are tabulated and presented graphically
12.2. Flowchart Endurance Training

**Vivantes**

Flowchart Endurance Training (6MWT)

- Patient is informed about procedure
- Ask patient to wear comfortable footwear
- Patient is asked to score on MBS prior to test
- Calculate target heart rate during training
  \[ \text{HR max} = 208 - 0.7 \times \text{age (y)} \]
  \[ \text{HR threshold} = \text{HR rest} + 0.50 \times (\text{HR max} - \text{HR rest}) \]
  *depending on the patient's training intensity 0.50, 0.55, or 0.60

<table>
<thead>
<tr>
<th>MBS</th>
<th>State of Dyspnoea</th>
<th>Target training intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No breathlessness at all</td>
<td>60% HRR</td>
</tr>
<tr>
<td>0.5</td>
<td>Very very slight</td>
<td>60% HRR</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
<td>60% HRR</td>
</tr>
<tr>
<td>2</td>
<td>Slight Breathlessness</td>
<td>55% HRR</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>55% HRR</td>
</tr>
<tr>
<td>4</td>
<td>Some what severe</td>
<td>50% HRR</td>
</tr>
<tr>
<td>5+6</td>
<td>Severe breathlessness</td>
<td>Own intensity</td>
</tr>
<tr>
<td>7+8</td>
<td>Very severe breathlessness</td>
<td>Own intensity</td>
</tr>
<tr>
<td>9</td>
<td>Very very severe</td>
<td>Own intensity</td>
</tr>
<tr>
<td>10</td>
<td>Maximum</td>
<td>Own intensity</td>
</tr>
</tbody>
</table>

- Any walking aid is allowed to be used/oxygen substitution
- Heart rate monitor is put around patient’s chest
- Patient stands in front of “START” line
- Tape is used to mark every three meters on floor/“START“ and “END” is marked
- Heart rate monitor and stop watch need to be organized

- Patient starts walking/PT controls heart rate by making use of pulse watch
- Patient turns every time as “30 metre mark” is reached
- MBS: after 3 minutes Adjusting training intensity if necessary
- MBS: after 6 minutes
- Distance is measured after 6 minutes and data reported in documentation file

- PT informs patient about any needed adjustments concerning the intensity (pace)
- MBS: after 3 minutes Adjusting training intensity if necessary
- MBS: after 6 minutes
- Distance is measured after 6 minutes and data reported in documentation file
12.3. Flowchart Strength Training

Patient is informed about procedure

Ask patient to wear comfortable clothes
Green Theraband needs to be organized
Maximum amount of repetitions possible needs to be tested prior to training

Maximum amount of repetitions= 100%
Training intensity= 50%

After two cycles of chemotherapy the maximum amount of repetitions is tested

Data is reported in documentation file
**Exercises**

### Bridging
- Patient lies supine in bed/ hands aside
- Knees positioned in a 110° flexed angle/ feet on mattress
- Knees put shoulder width apart
- Pelvis is lifted up from bed until pelvis, knees and shoulders form a diagonal line
- Patient is not allowed to use strength of arms to push pelvis up
- Keep position for two seconds before slowly dropping pelvis back
- To prevent that the patient’s feet slip over the surface of the bed, a cushion or a blanket is put in front of the feet
- Head board is allowed to be lifted up
- Exercise is performed at 50% of the patient’s maximum intensity

### Isometric Sit Ups
- Patient lies supine in bed/ arms crossed over chest
- Knees are positioned in a 110° flexed angle with feet on mattress
- To assure that feet will not slip over surface of the bed, a cushion or a blanket is put in front of the patient’s feet
- Patient lifts trunk slightly from bed
- Shoulder blades lifted up from surface of bed
- Patient holds position for two seconds until trunk is again brought back to mattress
- The exercise will be performed at 50% of patients maximum intensity

### Theraband Biceps
- Exercise is performed with a green Theraband
- Patient stands with feet shoulder width apart
- Theraband is fixed under feet
- Patient grasps Theraband with both hands
- Theraband has to be wrapped around fingers until it is tightened
- Elbows have to be kept close to body and are not allowed to move away from body during the exercise
- Palms of the hands face upwards
- Patient pulls Theraband into direction of shoulders by flexing elbow until end range of motion
- Shoulders are not allowed to be lifted up during the exercise
- Exercise is performed at 50% of the patients maximum intensity

### Theraband Triceps
- Exercise is performed with a green Theraband
- Theraband is wrapped around a sturdy object (e.g. end of bed) at level of the patient’s belly button
- Patient grasps Theraband with both hands
- Patient stands shoulder width apart
- Theraband is wrapped around the patient’s fingers until it is tightened
- Elbows have to be kept close to body and are not allowed to move away from body during the exercise
- Palms of hand are facing towards floor
- Elbows have to be kept straight during the exercise
- Patient pulls Theraband straight along the side until the arms reach ~ 20° extension
- The exercise is performed at 50% of the patients maximum intensity
12.4. EORTC QLQ C-30 Questionnaire

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers.

The information that you provide will remain strictly confidential.

Please fill in your initials: __ __ __

Your birthdate (Day, Month, Year) __ __ __

Today's date (Day, Month, Year) __ __ __

**No/ Yes**

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?

2. Do you have any trouble taking a long walk?

3. Do you have any trouble taking a short walk outside of the house?

4. Do you have to stay in a bed or a chair for most of the day?

5. Do you need help with eating, dressing, washing yourself or using the toilet?
During the past week:

Not at all = 1
A little = 2
Quite a bit = 3
Very much = 4

6. Were you limited in doing either your work or other daily activities?
   1 2 3 4

7. Were you limited in pursuing your hobbies or other leisure time activities?
   1 2 3 4

8. Were you short of breath?
   1 2 3 4

9. Have you had pain?
   1 2 3 4

10. Did you need to rest?
    1 2 3 4

11. Have you had trouble sleeping?
    1 2 3 4

12. Have you felt weak?
    1 2 3 4

13. Have you lacked appetite?
    1 2 3 4
14. Have you felt nauseated?
   1 2 3 4

15. Have you vomited?
   1 2 3 4

During the past week:

Not at all = 1
A little = 2
Quite a bit = 3
Very much = 4

16. Have you been constipated?
   1 2 3 4

17. Have you had diarrhoea?
   1 2 3 4

18. Were you tired?
   1 2 3 4

19. Did pain interfere with your daily activities?
   1 2 3 4

20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
   1 2 3 4

21. Did you feel tense?
   1 2 3 4
22. Did you worry?
   1 2 3 4

23. Did you feel irritable?
   1 2 3 4

24. Did you feel depressed?
   1 2 3 4

25. Have you had difficulty remembering things?
   1 2 3 4

26. Has your physical condition or medical treatment interfered with your family life?
   1 2 3 4

27. Has your physical condition or medical treatment interfered with your social activities?
   1 2 3 4

28. Has your physical condition or medical treatment caused you financial difficulties?
   1 2 3 4
For the following questions please circle the number between 1 and 7 that best applies to you

1 = Very Poor
7 = Excellent

29. How would you rate your overall health during the past week?
   1 2 3 4 5 6 7

30. How would you rate your overall quality of life during the past week?
   1 2 3 4 5 6 7