

# Postoperative exercise-based rehabilitation in lung cancer – aspects of kinesiotherapy

## Pooperacyjna rehabilitacja chorych na raka płuca – aspekty kinezyterapii

**Małgorzata L. Bernacka**<sup>1 (A,B,D,E,F)</sup>, **Jarosław Kużdżał**<sup>1,2 (A,B,D,E)</sup>,  
**Małgorzata Pieniążek**<sup>2 (D,E,F)</sup>, **Marta Sarota**<sup>1,2 (E,F)</sup>

<sup>1</sup> The Department of Thoracic Surgery and Surgical Oncology with Pulmonary Rehabilitation Unit, Jagiellonian University Medical College, The John Paul II Hospital in Krakow, Poland

<sup>2</sup> Faculty of Health Sciences Jagiellonian University Medical College, Krakow, Poland

### Key words

lung resection, pulmonary rehabilitation, physiotherapy, aerobic training, resistance training

### Abstract

**Introduction:** Surgery is the main modality for treatment of patients with stage I, II and, partly, III Non-Small Cell Lung Cancer (NSCLC). However, lung parenchyma resection and possible postoperative complications may impair respiratory and motor functions. Postoperative rehabilitation of patients with lung cancer requires the consideration of benefit-risk assessment, specific limitations and all aspects of multidisciplinary treatment.

**Aim:** The main aim of this narrative review was to analyze practical aspects of the published studies, especially the type and efficiency of rehabilitation and prognostic value of the end-points used.

**Methods:** Online literature databases: Medline, PubMed, CINAHL, Embase, Scopus and ScienceDirect were searched up to June 2015. Included papers consider postoperative rehabilitation in NSCLC, focused on kinesiotherapy.

**Results:** Combination of moderate to high-intensity aerobic training with submaximal progressive resistance training is reportedly associated with a measurable increase in VO<sub>2</sub>peak and 6MWT in patients operated on for lung cancer. This mixed method of training may improve quality of life and lengthen life expectancy. FEV<sub>1</sub> seems to be an unreliable parameter in the assessment of rehabilitation efficiency of in lung cancer patients. Patients who underwent adjuvant chemotherapy have worse results of postoperative rehabilitation and may require special training program. Efficiency of supervised training is better.

**Conclusions:** The findings of this narrative review suggest that postoperative exercise-based rehabilitation in patients with NSCLC appears to be well tolerated, safe and effective. Although there is an urgent need to confirm the great importance of this field of rehabilitation in larger randomized controlled clinical trials.

### Słowa kluczowe

resekcja płuca, rehabilitacja pulmonologiczna, fizjoterapia, trening wytrzymałościowy, trening oporowy

### Streszczenie

**Wstęp:** Leczenie operacyjne jest podstawową metodą postępowania w przypadku niedrobnokomórkowego raka płuca (NSCLC) w I, II i częściowo w III stopniu zaawansowania. Niemniej resekcja miąższu płuca oraz możliwe powikłania pooperacyjne mogą pogorszyć wydolność układu oddechowego i powodować ograniczenia funkcjonalne w zakresie narządu ruchu. Pooperacyjna rehabilitacja chorych na raka płuca wymaga uwzględnienia skuteczności, bezpieczeństwa, ograniczeń i aspektów multidyscyplinarnego leczenia tej grupy pacjentów.

**Cel:** Nadrzędnym celem tego przeglądu narracyjnego była analiza praktycznego aspektu opublikowanych badań, a zwłaszcza rodzaju i skuteczności interwencji rehabilitacyjnej oraz rokowniczego znaczenia obranych punktów końcowych.

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**Metoda:** Przeszukano elektroniczne bazy danych Medline, PubMed, CINAHL, Embase, Scopus oraz ScienceDirect do czerwca 2015. Do przeglądu włączono artykuły opisujące efekty rehabilitacji pooperacyjnej w NSCLC, a zwłaszcza kinezyterapii.

**Wyniki:** Połączenie treningu wytrzymałościowego średniej i wysokiej intensywności z submaksymalnym treningiem ze wstrzaskanym oporem wykazało wymiarną skuteczność w zwiększeniu  $VO_{2peak}$  oraz 6MWT u operowanych z powodu raka płuca. Może się to wiązać z poprawą jakości i długości życia pacjentów.  $FEV_1$  nie wydaje się być wiarygodnym parametrem oceny skuteczności rehabilitacji pooperacyjnej w tej grupie chorych. W przypadku pacjentów poddawanych chemioterapii adjuwantowej wyniki rehabilitacji są gorsze. Ta grupa chorych może wymagać odrębnego programu ćwiczeń. Większą skuteczność rehabilitacji wykazują badania z zastosowaniem treningu nadzorowanego.

**Wnioski:** Wyniki tego przeglądu narracyjnego sugerują dobrą tolerancję, bezpieczeństwo i skuteczność kinezyterapii u chorych na NCLSC. Niemniej istnieje pilna potrzeba potwierdzenia znaczącej roli tej formy rehabilitacji w dużych randomizowanych, kontrolowanych badaniach klinicznych.

## INTRODUCTION

With regard to the rehabilitation of patients after surgical treatment of lung cancer, we still have no knowledge based on the results of high quality research. Numerous doubts about the programming of rehabilitation in this group of patients needs to take aspects of symptomatology as well as oncological, surgical and pulmonary therapy into account.

Symptoms associated with lung cancer (shortness of breath, weakness, cachexia, anemia), compounded by the toxic effects of chemotherapy and consequences of pulmonary resection, are not the only obstacle in treatment and rehabilitation of this group of patients. Old age, smoking, lack of pro-health behavior and the presence of comorbidities also result in additional reduction of cardio-respiratory system adaptability in the postoperative period. A sedentary lifestyle, decreased activity in terms of everyday activities and improper dietary habits contribute to a progressive decrease in muscle mass. Anxiety and depressive disorders as well as insomnia may increase fatigue associated with cancer. These aspects make the rehabilitation of patients with lung cancer particularly challenging.

## STUDY AIM

The aim of this article is to present selected studies on the highest methodological value, undertaking the aspect of programming postoperative physiotherapy in patients with lung cancer. Particular attention was paid to the assessment of the efficacy and individualization of various physio-

therapy forms and the identification of the substrate difficulties in their realization and documentation.

## MATERIAL AND METHODS

A review of electronic databases was conducted: MEDLINE, PubMed, CINAHL, EMBASE, Scopus and ScienceDirect up to June 2015 by conducting searches using the following keywords: lung cancer, non-small cell lung cancer (NSCLC), physiotherapy, rehabilitation, exercise, lung resection, thoracic surgical procedures. The criterion for inclusion into the study was the use of kinesiotherapeutic procedures in the research project in patients operated on because of non-small-cell lung cancer. Analysis of the publications was carried out with particular attention to the type, intensity, frequency, duration of exercise and the selection of research endpoint measurement methods. We considered both the studies comparing the effectiveness of various kinesiotherapy methods and the use of kinesiotherapy compared to no rehabilitative intervention. Due to the small number of studies for review, we included both trials with and without randomization. The excluded articles were reviews or those written in languages other than English.

## RESULTS

Heterogeneity regarding the endpoint of the studies, multitude of rehabilitation procedures and diverse methodological quality of the studies did not allow the use of meta-analysis and formed the premise for develop-

ment of a narrative review. From the results, we finally selected ten studies that met the adopted inclusion criteria. Four of them were randomized and contained the most appropriate data in light of the posed clinical questions (Table 1).

Jones et al. studied the effect of moderate and high intensity endurance training on cardio-respiratory efficiency and quality of life in patients after Non-Small Cell Lung Cancer surgery. The supervised continuous endurance training was conducted on an ergometer, with individually selected load, increasing from 60% to 70% of the maximal load. In the last 4 weeks of exercises, endurance interval training was added to the continuous exercise. The  $VO_{2peak}$  value in the whole group did not show a statistically significant increase (1.1 ml/kg/min;  $p = 0.11$ ), however, there was a significant increase in patients who did not receive adjuvant chemotherapy (1.7 ml/kg/min;  $p = 0.008$ ). The maximal load increased after training in the whole group by an average of 9W, and this difference was statistically significant. Patients receiving chemotherapy, compared with those only operated on, demonstrated in the study: a smaller increase in  $VO_{2peak}$  (0.3 vs. 1.7 ml/kg/min) and greater absence in rehabilitation sessions (28% vs. 7%). The authors believe the reason for the lack of significant increase in  $VO_{2peak}$  to be inclusion of patients undergoing adjuvant chemotherapy in the study group.<sup>1</sup>

Edvardsen et al.<sup>2</sup> noted a clinically meaningful and statistically significant increase in  $VO_{2peak}$  by  $4.5 \pm 3.4$  ml/kg/min in patients treated for lung cancer and who underwent post-operative rehabilitation. The difference

Table 1

Description of the appraised studies				
Author (year)/ Randomization	Studied population, diagnosis, stage of disease, treatment	Duration of intervention, frequency and time of performing exercise	Type, form, training intensity	Measurement tools
Salhi et al. <sup>10</sup> (2015) Study with ran- domization	70 patients, NS- CLC I-III st., SCLC and mesotheli- oma . Treatment with in- tention of radical- ism: surgery (50% lobectomy, 16% pneumonecto- my); surgery + CHTH or RTH; RTH, CRT).	3 x week, for 12 weeks (super- vised exercise). Two types of training-as in the adjacent case. Control group not subjected to exercise.	Resistance training with load 50% 1RM; 3 series, 8 repetitions + endurance 20 min (treadmill, cycloergome- ter) with load 70% of max. Static training on vibrating platform (WBVT) + endur- ance as above. Control group was not sub- jected to exercise. The study assessed phys- ical efficiency parameters in the 3 groups and com- pared the studied groups to each other.	<b>6-MWT</b> Statistically ( $p < 0.0001$ ) and clinical- ly significant increase in resistance train- ing group, statistically non-significant ( $p$ = 0.06) increase in WBVT group, no in- crease in non-exercising group.  <b>VO<sub>2peak</sub></b> No significant increase compared to any of the exercising with non-exercising groups.
Edvardsen et al. <sup>2</sup> (2015) Study with ran- domization	61 patients op- erated on due to NSCLC (54% in I st.) thoracotomy (84%) vs. VATS (16%). (pneumonecto- my 16%; lobecto- my 51%). Adjuvant CHTH 30%, RTH 11%.	Training started 4-6 weeks before surgery and con- tinued 3x week (60 min) for 20 weeks (super- vised exercise). Control group was not subject- ed to exercise.	Warm-up, interval endur- ance training on treadmill at 80-95% HRmax intensi- ty, training with increasing resistance (progressive re- sistance training - PRT) of upper and lower limbs and trunk, 3 series, 6-12 RM each, breathing exercises.	<b>VO<sub>2peak</sub></b> Increase by $4,5 \pm 3,4$ ml/kg/min of the val- ue after 20 weeks of rehabilitation relative to the value from 4-6 week after the sur- gery. In the control group there was a de- crease by $-0,6 \pm 2,7$ ml/kg/min. The differ- ence between the studied groups after 20 weeks was 5.0 ml/kg/min (30.3%) ( $p <$ 0.001).  <b>Endurance, strength (measured 1RM), and muscle mass, DLCO</b> There was a statistically significant differ- ence between the studied groups in favor of patients undergoing rehabilitation (rela- tive to baseline).  <b>FEV<sub>1</sub></b> No significant ( $p = 0.738$ ) differences between the studied groups (relative to baseline).
Stigt et al. <sup>3</sup> (2013) Study with ran- domization	49 patients, NS- CLC, surgical treatment with ad- juvant CHTH in 33%. Over half of the participants sub- jected to lobecto- my or bilobecto- my, 9% pneumo- nectomy.	Training started in the 4 <sup>th</sup> week after discharge from hospital, held 2 x week for 12 weeks (60 min) (supervised exercise). Con- trol group was not subjected to exercise.	Endurance training on cy- cloergometer with 60-80% load and resistance training.	<b>6-MWT</b> Statistically significant ( $p = 0.037$ ) in- crease in the average distance from 524 m before surgery to 567 m 3 months after discharge from the hospital in the group subjected to exercise. The non-statistical- ly significant ( $p = 0.079$ ) reduction in the average distance from 555 m before sur- gery to 491 m 3 months after discharge from hospital in the control group. After 3 months - statistically significant ( $p = 0.024$ ) difference of 94 m (in relation to the pre-surgery values) between the groups in favor of the group subjected to exercises.
Granger et al. <sup>8</sup> (2013) Pilot study with randomization	15 patients surgi- cally treated, 10 with diagnosed NCLSC I-IV st. In 5 cases, malign- ant tumors were not confirmed. 12 patients partici- pated in the study in home condi- tions.	Exercise super- vised in the hos- pital (until leaving hospital) approx. 4 days, 2 x day. Continuation 2 x week for 8 weeks (60 min in home conditions – with- out supervision). Control group was not subject- ed to exercise.	Endurance training on cy- cloergometer or treadmill with 70% max. load; resis- tance exercises of upper and lower limbs with 80% max. load; stretching exer- cises.	<b>6-MWT</b> Statistically significant ( $p = 0.024$ ) differ- ence between the groups in favor of the exercising group. 2 weeks after surgery both groups report- ed a reduction in 6-MWT distance. Af- ter 12 weeks after surgery both groups re- ported an increase in 6-MWT distance, compared to the pre-operative period, however, it was higher in the group sub- jected to exercise.

Peddle-McIntyre et al. <sup>9</sup> (2012) Prospective study without control group, without randomization	17 patients, NS-CLC I-IIIB st. (94%); SCLC, 82% surgically treated (lobectomy 71%, pneumonectomy 12%), 29% adjuvant CHTH.	10 weeks; 3 x week (supervised exercise). Study without control group.	Resistance exercises at intensity of 60-85% 1RM. Initially, more number of repetitions with smaller loads' later, greater loads with lesser number of repetitions, breathing and stretching exercises.	<b>6-MWT</b> Statistically significant ( $p < 0.001$ ) increase in the distance by an average of 94 m. <b>The strength of the arm and lower limb muscles (evaluated using 1RM, in kg)</b> - statistically significant ( $p < 0.001$ ) increase. <b>The endurance of the muscles of the arms and lower limbs (assessed by number of reps with load of 70% 1RM)</b> - statistically significant increase $p = 0.01$ .
Arbane et al. <sup>6</sup> (2011) Study with randomization	53 patients, NS-CLC I-IV st., all underwent surgery (thoracotomy, VATS).	5 days of rehabilitation in hospital conditions, continuation for 12 weeks in home conditions; 2x day for 5-10 min for each exercise. Control group was not subjected to exercise.	Endurance training on exercise bike. Resistance training of lower limbs. Home rehabilitation – walks and resistance exercises.	<b>6-MWT</b> On the 5 <sup>th</sup> day after the surgery both groups reported a reduction in 6-MWT distance in relation to the pre-operative values. 12 weeks after surgery, both groups reported an increase in 6-MWT distance. However, there were no statistically significant differences in distance between the two groups ( $p = 0.47$ ), or within groups comparing the distance before the surgery to the distance 12 weeks after surgery ( $p = 0.89$ ).  <b>Thigh quadriceps muscles strength</b> The difference between the two groups was statistically significant ( $p < 0.05$ ) when comparing pre-operative strength to strength 5 days after surgery. Analogous comparison of the pre-operative period and 12 weeks after surgery showed no statistical significance of the studied differences.
Riesenberg et al. <sup>5</sup> (2010) Study without randomization	45 patients, NSCLC I-IIIB st.; SCLC, 89% operated on (62% lobectomy, 20% pneumonectomy). More than 1/3 of the participants required RTH or CHTH.	Beginning up to 2 weeks after completion of oncological treatment. 28 days; everyday for 30 min (exercises supervised in hospital conditions). Study without control group.	Interval endurance training on cycloergometer with submaximal load.	A substantial increase in work performance and 6-minute walk test ( $p < 0.001$ ). Heart rate at rest was reduced ( $p < 0.05$ ) and heart rate variability (indicator of the efficacy of endurance training) was significantly increased ( $p < 0.001$ ). Moreover, there was also a significant improvement in quality of life ( $p < 0.001$ ) and fatigue ( $p < 0.001$ ).
Jones et al. <sup>1</sup> (2008) Prospective, pilot study, without control group, without randomization	20 patients NS-CLC I-IIIB st., 80% operated on (lobectomy 71%, pneumonectomy 6%).	Training started 4 weeks after surgery, held 3 x week for 14 weeks (extending duration 15-45 min), (supervised exercise). Study without control group.	Endurance training on cycloergometer: constant with 60-70% max. load and constant, as above, in combination with interval (30 sec of exercise with 100% load+60 sec interval; 10-15 intervals).	<b>VO<sub>2peak</sub></b> Increase in VO <sub>2peak</sub> after rehabilitation by 1.1 ml/kg/min – no statistical significance ( $p = 0.11$ ). Excluding patients undergoing adjuvant chemotherapy from analysis increased statistical significance of VO <sub>2peak</sub> changes ( $p = 0.008$ ).  <b>Peak training load</b> Statistically significant ( $p = 0.003$ ) increase after rehabilitation
Cesario et al. <sup>7</sup> (2007) Study without randomization	211 patients (25 in study group and 186 in control), NSCLC, surgical treatment.	4 weeks; 5 x week for 3 h (supervised exercise, in hospital conditions). Control group was not subjected to exercise.	Constant endurance training on cycloergometer (with 70-80% max load, for 30 min). Abdominal and upper and lower limb muscle exercises, breathing exercises	<b>6-MWT</b> In comparison to values before surgery: – statistically significant ( $p < 0.01$ ) increase in distance by an average of 95.6 m after 4 weeks in the exercising group, – in the control group, decrease in distance after 4 weeks.  <b>FEV<sub>1</sub></b> In comparison to values before surgery: – in exercising group after 4 weeks, statistically non-significant increase, – in the control group, statistically significant ( $p < 0.01$ ) decrease.

Sprit et al. <sup>4</sup> (2006) Pilot study, without randomization	10 patients, NSCLC I-IIIB st.; SCLC (1 patient), 90% surgical treatment (lobectomy + pneumonectomy)	Beginning of rehabilitation 3 months after the completion of treatment. Rehabilitation for 8 weeks; everyday for 70 min (supervised exercise in hospital conditions). Study without control group.	Endurance training on treadmill (20 min; 80% max walking speed calculated on the basis of 6-MWT), on cycloergometer (20 min; 60% of baseline peak load), resistance training of upper and lower limbs, 3 series, 15 repetitions each at intensity of 60% 1RM, general improvement exercises.	<p><b>6-MWT and peak training load on cycloergometer</b> Statistically significant increase after rehabilitation 6-MWT by an average of 145 m (<math>p = 0.0020</math>) and peak training load by 24 W (<math>p = 0.0078</math>).</p> <p><b>FEV<sub>1</sub>, DLCO and subjective assessment of dyspnea measured with the Borg Scale.</b> No statistically significant changes after rehabilitation FEV<sub>1</sub> (<math>p = 0.5469</math>).</p>
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Abbreviations: NSCLC – non-small-cell lung cancer, SCLC – small-cell lung cancer, st – stage, CHTH – chemotherapy, RTH – radiation therapy, CRT – chemoradiotherapy, PRT – progressive resistance training; 1RM one – repetition maximum – maximal force generated by the contraction of the muscle under maximum load; % 1RM – One way of determining the load in exercise resistance, 6MWT – 6-minute walk test, HRmax – maximal heart rate, DLCO – testing diffusing capacity of the lung for carbon monoxide, FEV<sub>1</sub> – forced expiratory volume in 1 second, FEV – forced expiratory volume, FVC – forced vital capacity.

between them and the non-rehabilitative control group, in which there was a decrease in  $VO_{2peak}$  during the postoperative period, was 5.0 ml/kg/min. The  $VO_{2peak}$  value of 12-15 ml/kg/min, allowing independence in activities of daily living, was exceeded by all patients in the treatment group, while the number of patients in the control group did not reach this value. The fact that patients with the lowest  $VO_{2peak}$  values achieved the greatest improvement in this parameter after exercising is of great significance. Moreover, the study showed a significant increase in the value of Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), an increase in strength of the quadriceps muscles, an increase in total muscle mass and improvement in the quality of life of patients undergoing rehabilitation. There were no statistically significant differences in Forced Expiratory Volume in 1 Second (FEV<sub>1</sub>) or balance. Resistance exercise and intensive interval training resulted in a slightly smaller increase in muscle strength of the lower limbs in patients undergoing chemotherapy. In the group not performing the exercise, the decrease in muscle strength of the lower limbs in patients treated with chemotherapy was significantly higher than in the group not subjected to such treatment. Furthermore, the study showed that in the event of poor exercise tolerance in patients treated for NSCLC, they can be successfully started after the completion of adjuvant chemotherapy treatment. The authors empha-

size the good tolerance of exercise with increasing resistance – Progressive Resistance Training (PRT) and high intensity endurance interval training (80-95% of maximal heart rate). What is more, sought in this combination of rehabilitation exercises, individualization of their intensity and long duration, are the causes of achieving a higher increase in  $VO_{2peak}$  values compared to the study by Jones et al.<sup>1, 2</sup>

Stight and al.<sup>3</sup> showed the impact of postoperative submaximal endurance training on improving exercise tolerance in patients surgically treated for NSCLC. Exercise resulted in a 35-meter increase of walking distance in the Six-minute Walk Test (6-MWT) as compared to pre-surgery values. Despite the optimization of analgesic treatment during the entire study, the rehabilitative group reported greater severity of pain at 3 and 6 months and greater limitations in performing daily activities at 3 months than in the control group.<sup>3</sup>

Spruit et al.<sup>4</sup> evaluated the effect of rehabilitation on exercise capacity and ventilation parameters in patients after the completion of lung cancer treatment procedures. Apart from one patient with advanced stage of the disease who was treated conservatively, the remaining patients underwent surgical treatment, some of them received adjuvant therapy. Endurance and resistance exercises, and 30-minute general rehabilitation exercises were included in rehabilitation. Individual threshold of training was based on information obtained

by the subjective feelings of patients, trying to maintain the intensity level at 4-6/10 on the dyspnea and Borg fatigue scales. Comparing the results of physical performance parameters before and after rehabilitation, the measured 6-MWT and the value of peak load on the ergometer, significant improvement was found in both cases (respectively 43.2% and 34.4% of baseline values). Subjective evaluation of dyspnea and fatigue (Borg Scale), as well as FEV<sub>1</sub> and DLCO did not change despite the conducted rehabilitation.<sup>4</sup>

Riesenberg et al.<sup>5</sup> studied the relationship between rehabilitation conducted in patients with lung cancer and parameters of exercise capacity and quality of life. Submaximal aerobic interval training on a cycloergometer was carried out in the study. Comparison of exercise tolerance parameters, assessed using the 6-MWT, and the value of the load on the ergometer before and after rehabilitation showed the statistically significant improvement. In addition, the amplitude variability of heart rate significantly increased and heart rate during resting decreased – the indicators of adaptation to the exercise and the effectiveness of endurance training.<sup>5</sup>

Arban and et al.<sup>6</sup> presented the results of their study questioning the effectiveness of rehabilitation in patients with NSCLC who have undergone a thoracotomy or Video Assisted Thoracoscopic Surgery (VATS). The study group were subjected to ergometer endurance training and re-

sistance training. The control group was not subjected to rehabilitation. There were no significant differences in the physical capacity between the two groups in the 4<sup>th</sup> week following surgery or comparing the physical activity from before the surgery with the activity in the 4<sup>th</sup> week following the operation. On the 5<sup>th</sup> day after surgery, there was reduction in the distance in the walking test (6-MWT) between the two groups in relation to the value before the surgery. However, 4 weeks after surgery, the results of the 6-MWT reached the values from before the surgery in both groups. In the tested group, there was no significant increase in quadriceps strength but there was a significant reduction in the control group on the 5<sup>th</sup> day after the surgery. After 4 weeks, there were no significant differences in muscle strength in both groups.<sup>6</sup>

Cesario et al.<sup>7</sup> conducted a study among patients with NSCLC treated surgically. 25 patients underwent endurance training (cycloergometer, treadmill), breathing exercises as well as exercises of the abdominal upper and lower extremities muscles. The remaining 186 people who refused to participate in rehabilitation comprised the control group. There were no significant differences in spirometric parameters after rehabilitation. The 6-MWT distance after rehabilitation was statistically significantly longer (297.8 before vs. 393.4 m. after rehabilitation). The results of this study suggest that undergoing rehabilitation at an early period may contribute to the improvement of exercise tolerance in patients operated on due to lung cancer.<sup>7</sup>

In the randomized study Granger et al.<sup>8</sup> evaluated the effectiveness of exercise in patients in which lung cancer was suspected or diagnosed. The kinesiotherapy program in the group treated with rehabilitation was based on endurance (treadmill, cycloergometer), resistance and stretching exercises. Postoperative verticalization, respiratory physiotherapy and stretching the chest and shoulder girdle was conducted in the control group. After 12 weeks of the study, there was a statistically significant

difference between the 6-MWT result of the two groups in favor of the rehabilitated group. In both groups, there was a better result in the walk test performed at 12 weeks, compared to the test performed 2 weeks after the surgery. No adverse events were noted. The credibility of this study was reduced by the 57% share of patients with benign lung diseases in the exercising group compared to the 12.5% share in the control group.<sup>8</sup>

In the study by Peddle-McIntyre et al.<sup>9</sup>, the patients treated for lung cancer underwent training that begun with a low intensity aerobic warm-up, but based on resistance exercises. Exercise intensity increased with time from 60% to 85% of 1RM (One-repetition Maximum – the maximal force generated by the contraction of the muscle with maximal load). This was supplemented by stretching and breathing exercises. The difference in 6-MWT after rehabilitation was 86 m,  $p < 0.01$  (538 m before vs. 452 m after 10 weeks of exercise). A statistically significant improvement was also achieved in muscle strength of the arms and lower limbs (as evaluated by 1RM) and endurance of arm and lower limb muscles (assessed by the number of repetitions with a load of 70% 1RM).<sup>9</sup>

Sahli et al.<sup>10</sup> conducted a study in patients radically treated for lung cancer and mesothelioma (various combinations of treatment: surgery, chemotherapy, radiotherapy). The authors compared the efficacy of resistance training with a static training on vibration platform. This type of training requires less effort and was considered as an alternative to resistance training in the context of improving neuromuscular control. Patients in both groups performed the 20-minute endurance training (treadmill, cycloergometer with load of 70% of the maximum tolerated by the patient). The third group included into randomization were patients not subjected to rehabilitation. Conventional resistance training resulted in a statistically significant increase in 6-MWT distance by 94 m ( $p < 0.0001$ ) compared to the post-surgery value. In the group training on

the vibrating platform, a clinically and statistically insignificant increase by 6-MWT 37 m ( $p = 0.06$ ) was observed, while the non-rehabilitated patients did not increase the distance (1 m;  $p = 0.95$ ). Despite the increase in  $VO_{2peak}$  in both exercising groups, there was no statistically significant increase in this parameter compared to the non-training group. Apart from that, the impact of radical treatment on selected cardio-respiratory parameters was tested. After radical treatment, and before the planned rehabilitation, there was a statistically significant reduction in average values of  $FEV_1$ , DLCO, 6-MWT (by 38 m) and  $VO_{2peak}$  with respect to the pre-treatment values.<sup>10</sup>

## DISCUSSION

The number of studies investigating the effect of exercise on the health of patients who have undergone surgery for lung cancer is small. The methodological quality of these studies is lessened by: small and sometimes heterogeneous group of participants, sporadic use of randomization, lack of control group, short duration of rehabilitation, inability to supervise exercises conducted outside the hospital<sup>6,8</sup>, rehabilitation of patients in whom diagnosis of lung cancer have not been confirmed<sup>8</sup>. The small number of cases may be due to post-operative complications, comorbidities constituting contraindication to intensive rehabilitation, difficulties in getting to rehabilitation sessions or diagnosis of the disease at an advanced stage. Not without significance is also lack of pro-health habits, lack of motivation to exercise and reluctance of patients to participate in postoperative rehabilitation. In the study by Jones et al.<sup>1</sup>, only half of the patients who met the inclusion criteria agreed to participation. In the study by Cesario et al.<sup>7</sup>, patients fulfilling the inclusion criteria but not expressing willingness to undergo rehabilitation qualified for the control group. In the study by Sahli et al.<sup>10</sup>, only 70 of the 121 patients included in the study underwent randomization.

The reliability of the research was decreased by the exclusion of patients due to inoperability or postoperative mortality and resignation of participants because of deteriorating health during adjuvant therapy. In the postoperative period, there was a decrease in physical capacity in part of the patients, preventing them from performing tests assessing endpoints (e.g. spirometric test, 6-MWT).

It is important to define the clinically significant, functional and prognostic endpoints of studies, evaluating the effectiveness of rehabilitation in patients operated on for lung cancer and the standardization of their measurements. The tests and studies such as  $VO_{2peak}$ , 6-MWT and DLCO are valuable tools in the qualification of patients for surgical treatment and may also be used to evaluate the effectiveness of perioperative rehabilitation in patients with lung cancer.

Improvement in  $VO_{2peak}$ , a key parameter of the spirometric test, has important clinical implications. It is an independent prognostic factor regarding the survival length of patients with NSCLC<sup>11</sup>. Research conducted on a population of patients with chronic but non-tumorous illness, have shown a relationship between cardiovascular and respiratory system capacity with reduced mortality. The improvement in  $VO_{2peak}$  by 3.5 ml/kg/min (1MET) increases the chances of survival in the population by 12-17%<sup>12,13</sup>. Not without significance is the impact of maintaining or achieving  $VO_{2peak}$  at a level of 12-15 ml/kg/min. This value corresponds to independence in daily functioning<sup>14</sup>. The greater improvement in  $VO_{2peak}$ , described by Edvardsen et al.<sup>2</sup>, occurring after rehabilitation of patients with the lowest baseline values of this parameter, correlates with observations of  $VO_{2peak}$  variability in exercise physiology. Persons with low active lifestyle gain greater improvements in  $VO_{2peak}$  after endurance exercise compared with trained persons. It is worth noting that the exercisers reach individual maximal threshold of oxygen consumption usually after 8-12 weeks of training. Increasing the intensity and frequency of training above this limit is not reflected in

the growth of  $VO_{2peak}$ , but improves endurance<sup>15</sup>. A limitation in the interpretation of  $VO_{2peak}$  is large individual (probably genetically determined) volatility of its growth, even with the implementation of identical endurance training.

There is also no clear position on when to start the rehabilitation of patients operated on for lung cancer. Stight et al.<sup>3</sup> suggested delaying the start of the rehabilitation up to 3-4 months after surgery in order to avoid increasing the severity of pain resulting from surgical treatment. There is no certainty as to whether such action postpones the undoubted benefits resulting from improved exercise tolerance. The patients after thoracotomy, despite some similarities to cardiosurgical patients (age, illness load), may require postponed implementation of intensive rehabilitation procedures. This is due to the specificity of surgical access. Thoracotomy, in comparison to sternotomy, may be the source of greater pain. In addition, resection of lung parenchyma permanently restricts gas exchange and requires longer adaptation of the patient to the new conditions of exercise tolerance.

The variation of  $VO_{2peak}$  associated with post-operative recovery is not known, which can affect the postponement of the beginning of studies in postoperative rehabilitation for fear of impeded result interpretation. They also did not examine what increase in the  $VO_{2peak}$  after rehabilitation can be considered as clinically significant in this group of patients. In the population of people with no cancer history a 15% increase in the value of  $VO_{2peak}$  (after aerobic training for 12-15 weeks, 3-5 times a week, at 50-75% of  $VO_{2peak}$  value level) was found to be clinically significant<sup>16,17</sup>. Other data suggest a 10% increase in the value of this parameter to be clinically significant in patients considerably debilitated in the course of POCHP<sup>18</sup>. For obvious reasons,  $VO_{2peak}$  predictive values for non-oncological patient populations cannot be translated to a population of patients with lung cancer.

Due to the nature of co-morbidities with lung cancer as well as chemo-

and radiation therapy used in its treatment, an important test to rank the effectiveness of rehabilitation can be DLCO. Edvardsen et al.<sup>2</sup> reported a statistically significant increase in the range of DLCO in patients after surgery for lung cancer rehabilitated with intensive resistance and endurance training. This is important especially for patients undergoing adjuvant treatment, given the proven effects of chemotherapy and radiotherapy on the processes of pulmonary fibrosis and reduced DLCO.

Failure to exercise during the postoperative period in patients with NSCLC can be one of the predisposing factors for disability and impaired functioning in daily life. This condition may persist for up to 2 years after surgical treatment.<sup>19</sup>

In the light of the research, the optimal rehabilitation program seems to be interval or combined training (continuous and interval) of moderate or high intensity combined with progressive resistance training<sup>1,2</sup>. The advantages of resistance training for oncological patients comprise less shortness of breath compared to the endurance training, improved muscle strength, an increase in their mass and reduced muscle fatigue. This translates into improved quality of life and functional efficiency<sup>20</sup>. Research suggests that interval training causes less shortness of breath compared to continuous training in patients with POCHP<sup>21</sup>, it takes less time and is more willingly taken up by exercising people.<sup>22</sup>

Adding resistance training to aerobic training not only results in the improvement of muscle strength and endurance, but also allows the intensification of aerobic training and can optimize the performance of  $VO_{2peak}$  and the 6-MWT<sup>2</sup>.

Seeking the causes of reduced  $VO_{2peak}$  after resection of lung parenchyma, the muscle weakness of the lower limbs and dyspnea reported by patients must also be taken into consideration. Not without significance is the decline in  $VO_{2peak}$  by even 25% reported in healthy patients, immobilized for 3 weeks<sup>23,24</sup>. The etiology of skeletal muscle weakness itself during lung diseases such as COPD is

not clearly understood. Similarly as in the case of lung cancer, it may be caused by muscles atrophy or myopathy<sup>1</sup>. What is interesting is the fact that the value of  $VO_{2max}$  can neither be limited to ventilation parameters nor diffusive capacity<sup>25,26</sup>.

Improved strength and endurance of the skeletal muscles, despite the lack of improvement in lung ventilation in spirometry, may explain the improvement of exercise tolerance for lung cancer patients with a history of rehabilitation (6-MWT,  $VO_{2max}$ ). Analogous observations have been earlier done with regard to POCHP patients<sup>27</sup>. The coexistence of lung cancer with COPD and coronary heart disease may lead to muscle dystrophy and their impaired function as a result of physical exercise intolerance secondary to ventilation and cardiovascular disorders<sup>28</sup>. The only possibility to interrupt pathological feedback between exercise tolerance and the decrease in capacity of the respiratory and circulatory systems seems to be the improvement in strength and endurance of the skeletal muscles confirmed in studies, aimed at these training objectives. In patients with lung cancer, additional factors hindering the increase in mass, muscle strength and endurance should be emphasized: increased catabolism of protein, loss of appetite due to illness and chemotherapy cancer related fatigue syndrome. Each of these aspects must be taken into account when conducting rehabilitation and adequate methods in order to marginalize their impact on the patient should be applied.

The lack of significant exercise influence in the course of post-operative treatment for lung cancer on the value of  $FEV_1$ <sup>2,4,7</sup> may be related to the frequent co-existence of COPD and bronchial hyper-reactivity. However, patients operated on for lung cancer, after lung parenchyma resection, and consequently thoracotomy, demonstrate the superiority of restrictive-type ventilation disorders.<sup>4</sup>

Important from the point of view of planning comprehensive perioperative rehabilitation is establishing an effective and safe frequency of con-

ducting training. Preoperative rehabilitation should be conducted in an intensified manner, daily, or even twice a day, with a submaximal strength and endurance load. It should take into account not only the effectiveness of conducted preoperative exercise, but the fact that surgery in this group of patients should be carried out shortly after the diagnosis of NSCLC. Jones et al.<sup>29</sup> conducted a study assessing the effect of preoperative rehabilitation on  $VO_{2peak}$  in patients with suspected NSCLC. Despite the shorter duration of preoperative training (compared with the study of these authors evaluating the efficacy of postoperative rehabilitation - Jones et al.<sup>1</sup>) a greater increase in  $VO_{2peak}$  was achieved. It is difficult to compare the efficacy and expect similar pre- and post-operative rehabilitation courses, given the limitations associated with the operating reduction of pulmonary parenchyma, a decrease in performance associated with limited perioperative activity, pain and the influence of adjuvant therapy.

However, post-operative rehabilitation should be maintained for a longer period of time, optimally daily, but can also be carried out effectively at a lower frequency, for example, three times a week. This frequency allows for improvement in exercise capacity in patients following lung cancer surgery<sup>2</sup> and is an opportunity to reduce the described risk<sup>3</sup> of postoperative pain severity. It may also reduce the share of patients who resign from participation in rehabilitation as well as facilitate a return to prior employment and social activity. The study on untrained but active people without a history of cancer showed the equivalence of intensive interval endurance training conducted 3 times a week with continuous training at an intensity of 65%  $VO_{2peak}$  performed 5 times a week.<sup>30</sup>

Pain limiting the shoulder girdle function on the operated side and the mobility of the trunk are also of significance.

In the randomized trial conducted by Reeve et al.<sup>31</sup> on a group of 76 patients who underwent thoracotomy due to lung cancer, the efficacy of

3-month postoperative rehabilitation was assessed. The rehabilitation program included supervised exercise increasing the mobility of the shoulder girdle on the operated side and chest mobility. There was no significant difference in the mobility of the shoulder joint or muscle strength of the shoulder girdle on the operated side compared with the un-exercising group. However, functional efficiency of the shoulder joint (operated side) significantly improved, and there was also a decrease in pain from the structures forming the shoulder girdle and chest.<sup>31</sup>

Many studies qualified patients not taking into account the homogeneity of medical procedures or diagnosis. Some studies have included individual patients treated conservatively due to lung cancer, sometimes trials included patients with a diagnosis other than NSCLC, for example, lung mesothelioma<sup>10</sup> or benign lung diseases<sup>8</sup>. It would be appropriate to standardize treatment groups regarding diagnosis, treatment method and prognosis.

Rehabilitation in thoracic surgery cannot be conducted in isolation from the constraints of the surgical approach and its consequences. It would be reasonable to isolate patients treated with access by thoracotomy from less invasive VATS access. The latter is associated with a smaller area of pulmonary resection, usually resulting in minor pain and enables improved functional abilities in the postoperative period. Stight and al.<sup>3</sup> prematurely completed the recruitment into their research program due to the introduction of the VATS procedure in the course of the study, which caused a reduction in the number of thoracotomy procedures.

The separation of pneumonectomy from less extensive lung parenchyma resection is also left for consideration. Excision of the entire lung is associated with a significantly higher risk of complications and results in more severe changes in the performance of the respiratory and circulatory systems.

In the research by Nugent et al.<sup>32</sup>, pneumonectomy was the source of a statistically significant reduction in  $VO_{2max}$  by 28% and Functional Vital



Capacity (FVC) by 35%. Lobectomy, despite significant, although smaller reductions in FVC by 14%, did not cause significant deterioration of  $VO_{2max}$ , barely 10%. Interestingly, despite undergoing pneumonectomy, patients did not subjectively (Borg Scale) feel the deterioration in exercise tolerance. In contrast to pneumonectomy, thoracotomy without resection of the pulmonary parenchyma or limited pulmonary resection does not seem to cause a significant reduction in the ability to perform physical exercise. Wedge resection was not associated with a significant decrease in or in relation to spirometry values or  $VO_{2max}$ . Thoracotomy without resection of the pulmonary parenchyma (inoperable patients) showed a decrease in FEV1 by 11%, without significant changes in FVC, Total Lung Capacity (TLC) or  $VO_{2max}$ . The authors perceive the causes of these disorders to be within cancer progression and severity of obstruction as well as complications due to the influence of radiotherapy on the respiratory system.<sup>32</sup>

Another study shows a significant but small decrease in  $VO_{2max}$  after lobectomy<sup>33</sup>.

Most of the referenced studies confirm the safety and lack of adverse events in the course of implementation of the rehabilitation program<sup>6-9</sup>. Edvardsen et al.<sup>2</sup> reported femoral neck fracture with balance exercises and the study by Peddle-McIntyre et al.<sup>9</sup> exacerbation of the shoulder and spinal pain. Sahli et al.<sup>10</sup> noted intensification of lumbar spine pain (probably unrelated to the training) and ankle joint injury – also without any connection to the conducted rehabilitation.

It seems justified to separate groups of patients in the light of the clinical presentation, prognosis, applied treatment and the proposed rehabilitation program. Patients with stage I-IIIa of the disease (distinguishing pre- and post-operative rehabilitation) and stage IIIB and IV (with limitations resulting from severity of the disease and chemotherapy) should be considered for separate research programs.

## CONCLUSIONS

The complex clinical picture and the course of treatment of patients with lung cancer makes it difficult to conduct research on the effectiveness of postoperative rehabilitation in a significant and multi-factor manner.

The studies published so far have many methodological and clinical limitations, and the data from literature only slightly bring us closer to developing guidelines based on the principles of Evidence Based Medicine (EBM). In the light of this study, the most effective and best-documented program of rehabilitation seems to be the combination of moderate and high intensity endurance training with submaximal training, with increasing resistance.

Optimal analgesia is an essential element during postoperative rehabilitation, as well as its relevance to the severity of the disease and the type of surgery. Spiroergometric examination and determining the result of maximal oxygen consumption ( $VO_{2max}$ ) on its basis is a valuable and reproducible method in assessing the ability of independence in activities of daily living. The evaluation of exercise capacity measured by the 6-MWT and DLCO measurement seem to be good endpoints of the study.

Given the greater availability and lower cost of implementing the 6-MWT, it would be justified to demonstrate the significant correlation between the results of  $VO_{2max}$  and the 6-MWT in assessing the effectiveness of perioperative rehabilitation for lung cancer in randomized trials. However, the purposefulness of determining spirometric parameters (e.g. FEV<sub>1</sub>) in order to assess the effectiveness of post-operative rehabilitation seems questionable due to the lack of significant variability of this parameter. Postoperative rehabilitation of patients with lung cancer is not associated with significant complications, but those undergoing adjuvant chemotherapy demonstrate its poorer tolerance. In the light of reliable scientific research, developing a consensus on the type, intensity, the time of beginning and the duration of

postoperative rehabilitation requires numerous studies of high methodological quality.

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**Address for correspondence**

Małgorzata Bernacka MD  
 Oddział Kliniczny Chirurgii Klatki Piersiowej  
 i Chirurgii Onkologicznej z Pododdziałem  
 Rehabilitacji Pulmonologicznej  
 Krakowski Szpital Specjalistyczny im. Jana  
 Pawła II  
 ul. Prądnicka 80, 31-202 Kraków, Poland  
 phone: +48 12 614 20 40; fax: +48 12 614 34-31  
 mobil: +48 535 455 911  
 e-mail: maledem@gmail.com