Turkish Journal of Thoracic and Cardiovascular Surgery 2019;27(2):212-218
http://dx.doi.org/doi: 10.5606/tgkdc.dergisi.2019.16474

Original Article / *Özgün Makale*

Can functional inoperability in lung cancer patients be changed by pulmonary rehabilitation?

Akciğer kanseri hastalarında fonksiyonel inoperabilite pulmoner rehabilitasyonla değiştirilebilir mi?

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ABSTRACT

Background: This study aims to investigate the effects of short-term intense pulmonary rehabilitation on respiratory function in patients with lung cancer who were defined as inoperable due to insufficient pulmonary reserve.

Methods: A total of 25 patients (24 males, 1 female; mean age 62 years; range, 50 to 72 years) who were histologically diagnosed as non-small cell lung carcinoma, considered functionally inoperable due to high risk of an estimated postoperative complication, and suitable for surgical resection according to tumor stage were included in the study. Patients received chest physiotherapy, self-walking and inspiratory muscle training for two weeks. The forced expiratory volume in one second, forced vital capacity, modified Medical Research Council dyspnea scale, six-minute walking distance, maximal inspiratory and expiratory pressures for respiratory muscle strength measurements, and predicted peak maximal oxygen consumption were examined.

Results: After pulmonary rehabilitation, there was statistically significant improvement in the six-minute walking distance (53 m, $p<0.001$), dyspnea perception ($p<0.001$), maximal inspiratory pressure (12 cm H_2O, $p<0.001$), forced vital capacity ($p<0.001$), predicted forced expiratory volume in one second (%) ($p=0.001$), forced expiratory volume in one second (Δ forced expiratory volume in one second= 150 mL, $p=0.001$; Δ maximum value of forced expiratory volume in one second: 650 mL), and predicted maximal oxygen consumption ($p<0.001$). At the end of the rehabilitation, 60% of the patients (n=15) reevaluated by the surgeons could be operated.

Conclusion: Short-term intensive pulmonary rehabilitation improves lung functions and exercise capacity while decreasing dyspnea perception. In our study, thanks to the gains derived from the exercise, approximately more than half of the patients could be operated. Therefore, it may be useful to refer patients to rehabilitation before establishing a decision of inoperability.

Keywords: Exercise, inoperable, lung cancer, lung function, pulmonary rehabilitation, walk test.

ÖZ

Amaç: Bu çalışmada yetersiz pulmoner rezerv nedeniyle inopere olarak tanımlanan akciğer kanserli hastalarda kısa süreli yoğun pulmoner rehabilitasyonun solunum fonksiyonu üzerindeki etkileri araştırıldı.

Çalışma planı: Histolojik olarak küçük hücre dışı akciğer kanseri tanısı almış, ameliyat sonrası öngörülen komplikasyon riskinin yüksek olması nedeniyle fonksiyonel olarak inopere olduğu düşünülen ve tümör evresine göre cerrahi rezeksiyon için uygun 25 hasta (24 erkek, 1 kadın; ort. yaş 62 yıl; dağılım, 50-72 yıl) çalışmaya dahil edildi. Hastalara iki hafta boyunca göğüs fizyoterapisi, serbest yürüyüş ve inspiratuar kas eğitimi verildi. Bir saniyedeki zorlu ekspiratuar hacim, zorlu vital kapasite, modifiye Medikal Araştırma Kurulu dispne skalası, altı-dakika yürüme mesafesi, solunum kas kuvveti ölçümleri için maksimal inspiratuar ve ekspiratuar basınçlar ve tahmini zirve maksimal oksijen tüketimi incelendi.

Bulgular: Pulmoner rehabilitasyon sonrasında; altı-dakika yürüme mesafesinde (53 m, $p<0.001$), dispne algısında ($p<0.001$), maksimal inspiratuar basınçta (12 cm H_2O, $p<0.001$), zorlu vital kapasitede ($p<0.001$), birinci saniyedeki zorlu ekspiratuar akımın beklenene göre yüzdesinde ($p=0.001$), bir saniyedeki zorlu ekspiratuar hacimde (Δ bir saniyedeki zorlu ekspiratuar hacim=150 mL, $p=0.001$; Δ bir saniyedeki zorlu ekspiratuar hacmin maksimum değerinde: 650 mL) ve tahmini maksimal oksijen tüketiminde ($p<0.001$) istatistiksel olarak anlamlı iyileşme vardı. Rehabilitasyonun sonunda, cerrahlar tarafından tekrar değerlendirilen hastaların %60'ı (n=15) ameliyat edilebildi.

Sonuç: Kısa süreli yoğun pulmoner rehabilitasyon akciğer fonksiyonlarını ve egzersiz kapasitesini iyileştirirken dispne algısını azaltır. Çalışmamızda, egzersizden elde edilen kazanımlar sayesinde hastaların yaklaşık yarısından fazlası ameliyat edilebildi. Buna göre, inoperabilite kararı almadan önce hastaları rehabilitasyona yönlendirmek yararlı olabilir.

Anahtar sözcükler: Egzersiz, inopere, akciğer kanseri, akciğer fonksiyonu, pulmoner rehabilitasyon, yürüme testi.

Received: May 16, 2018 *Accepted*: October 06, 2018 *Published online*: April 24, 2019

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Cite this article as:
Pehlivan E, Balcı A, Kılıç L. Can functional inoperability in lung cancer patients be changed by pulmonary rehabilitation? Turk Gogus Kalp Dama 2019;27(2):212-218

A majority of lung cancer patients have various degrees of chronic obstructive airway disease due to smoking for many years. Unfortunately, when this disease is diagnosed with lung cancer, respiratory function decreases independently of the lung cancer's stage.[1]

Borderline of inoperability in lung cancer surgery is not a concept drawn exactly. Patients with early-stage lung cancer may be potentially resectable. However, some patients cannot undergo surgery due to comorbidities and functional inoperability. According to guidelines, spirometry is recommended during the first stage of qualifying patients for lung cancer resection.[2] Previously published guidelines established independent boundary values for forced expiratory volume in one second (FEV_1) for planned lobectomy and pneumonectomy (1.5 L and 2 L, respectively).[3] Further guidelines added that FEV_1 should not be lower than 80% of the predicted value, both in the case of planned lobectomy and pneumonectomy.[4] Exercise testing is recommended if the FEV_1 is lower than 80%.[5] Maximal oxygen uptake (VO_2 max) obtained from exercise tests as well as signs of cardiac problems are important for the preoperative evaluation.[6] Maximal oxygen uptake >15 mL/kg/min is considered sufficient for performing lobectomy or segmentectomy.[7]

Pulmonary function and exercise tests are considered to predict the risk of postoperative complications and the decision of operation is established according to these parameters.[8] Patients predicted to be at high risk for postoperative complications are referred to chemotherapy or radiotherapy. These patients may lose their chance to undergo surgery even if they are operated after oncologic treatment, as it is known that these treatments cause various side effects.[9]

According to our literature research, many studies show that pulmonary rehabilitation is useful in lung cancer patients during the preoperative period.[10] However, to our knowledge, there is no research that investigated if functional or medical inoperability can be changed by pulmonary rehabilitation. Therefore, in this study, we aimed to investigate the effects of short-term intense pulmonary rehabilitation on respiratory function in patients with lung cancer who were defined as inoperable due to insufficient pulmonary reserve.

PATIENTS AND METHODS

Thirty-five functionally inoperable lung cancer patients histologically diagnosed as non-small cell lung carcinoma and referred to Pulmonary Rehabilitation Center were consecutively included in this prospective study. Inclusion criteria were patients who were only considered as inoperable because of their inadequate spirometric values for the planned surgery, without any additional disease to prevent exercise. Nine patients were considered drop outs due to problems related to the adaptation to the pulmonary rehabilitation program and follow-up. One patient was excluded due to pulmonary infection during the course of the exercise program. Thus 25 patients' (24 males, 1 female; mean age 62 years; range, 50 to 72 years) outcome measurements were examined. This study was a self-controlled non-randomized trial. The study protocol was approved by the Medipol University Non-Interventional Clinical Research Ethics Committee (Approval Number: 10840098-604.01.01-E.4623). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients received chest physiotherapy, free-walking and inspiratory muscle training, and underwent home-based pulmonary rehabilitation program for 15 days. They were asked to perform the exercise program and fill out the exercise follow-up form.

Chest physiotherapy consisted of diaphragmatic, pursed lip, and segmental breathing and coughing exercises. Patients were asked to walk daily in their homes, taking the distance calculated based on the walking distance obtained from the six-minute walk test (6MWT). The method of calculating the number of free walking laps based on the 6MWT was given below. Exercise intensity was predetermined to be 80% of the maximum heart rate. Exercise intensity was gradually increased taking the severity of dyspnea perception and fatigue ratio as the basis.

(Six-minute walking distance/6) × exercise time = distance to walk:

Distance to walk × 80%

If the distance to the corridor to be walked is known:

Distance to walk/corridor length= number of laps

Inspiratory muscle training was performed with an exercise tool (Powerbreathe®, International Ltd., England, UK) at a resistance range of 0-90. The training loads were adjusted to maintain 30% of the maximal inspiratory pressure (MIP) obtained as a result of the mouth pressure measurement. Patients were asked to perform inspiratory muscle training twice a day for 15 days.

Before and after the pulmonary rehabilitation, dyspnea perception during the activities of daily living was assessed with modified Medical Research Council dyspnea scale, while exercise capacity was assessed with 6MWT. Maximal inspiratory pressure and maximal expiratory pressure for the respiratory muscle strength measurement was performed with the MicroMicro-RPM® instrument of SensorMEDIC (MDSpiro; Maine, USA). Spirometry was conducted using the Sensor Medics model 2400 (Yorba Linda, CA, USA), in accordance with the European Respiratory Society/American Thoracic Society standards.[11] The peak VO_2 was determined based on the six-minute walking distance[12] according to the below formula:

"Predicted Mean Peak VO_2 (mL/kg/min) 4.948 +0.023*Mean 6MWD (meters)"

Statistical analysis

Statistical analyses were performed using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to analyze normally distributed variables. The sample size was calculated as 18 patients using the e-picos software (New York, USA). The Wilcoxon signed-rank test was used to compare the pre- and post-treatment data of the groups. Nonparametric variables were expressed as median (minimum-maximum), and descriptive variables as percent and median (minimum-maximum). The chi-square test was used for categorical variables. Significance level was accepted as $p<0.05$.

RESULTS

The demographic and clinical characteristics of the patients are summarized in Table 1. Before the exercise training session, all patients had limited respiratory reserves for the surgery (FEV_1 <80%). Patients had moderate or severe dyspnea perceptions and their walking distance was 83% of the expected value.

After the training session, there was statistically significant improvement in the FEV_1 ($p=0.001$), FEV_1 (%) predicted ($p=0.001$), six-minute walking

Table 1. Baseline characteristics of patients (n=25)

Variable	n	%	Median	Min-Max
Demographic characteristics				
Age (year)			62.00	50-72
Gender				
Male	24	96		
Female	1	4		
Smoking habit (pack × year)			62.00	30-160
Body mass index (kg/m^2)			24.33	17-40
Exercise capacity				
6MWD (m)			434.52	147-630
6MWD (%)			83.16	29-125
mMRC dyspnea scale (0-4)			2	1-4
Lung functions				
FVC (L)			2.13	1-3.04
FVC (%)			59.18	36-86
FEV_1 (L)			1.32	0.74-2.08
FEV_1 (%)			46.11	32-240
FEV_1/FVC			69.19	28.14-105.03
Respiratory muscle strength				
Maximal inspiratory pressure (cm/H_2O)			84.32	32-240
Maximal expiratory pressure (cm/H_2O)			129.08	70-193
PeakVO_2 (mL/kg/min)			14.94	8.33-19.44

Min: Minimum; Max: Maximum; 6MWD: Six-minute walking distance; mMRC: Modified Medical Research Council; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in one second; VO_2: Oxygen uptake.

Table 2. Effect of treatment on functional exercise capacity, dyspnea, respiratory functions, and respiratory muscle strength

	Before PR		After PR		Δ		
Variables	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
Exercise capacity							
6MWD (m)	434.52	147-630	488	168-730	53.48	0-150	<0.001
6MWD %	83.16	29-125	93.31	33-145	10.14	0-30	<0.001
mMRC dyspnea scale (0-4)	2	1-4	2	1-4	0	0-1	<0.001
Lung functions							
FVC (L)	2.13	1-3.04	2.25	1.36-3.28	0.11	-0.37-0.72	<0.001
FVC (%)	59.18	36-86	61.90	33-93	2.71	-12.10-19.80	0.11
FEV_1 (L)	1.32	0.74-2.08	1.48	0.88-2.26	0.150	-0.11-0.65	0.001
FEV_1 (%)	46.11	32-240	51,53	24-74	5.42	-4.59-20	0.001
FEV_1/FVC	69.19	28.14-105.03	72.93	27.39-104.10	3.74	-38.90-37.46	<0.001
Respiratory muscle strength							
MIP (cm/H_2O)	-84.32	-32- -240	-96.88	-51- -240	12.56	-4-54	<0.001
MEP (cm/H_2O)	129.08	70-193	134.6	75-213	1.84	-9-11	0.09
PeakVO_2 (mL/kg/min)	14.94	8.33-19.44	16.17	8.81-21.74	1.23	0-3.45	<0.001

Min: Minimum; Max: Maximum; PR: Pulmonary rehabilitation; 6MWD: Six-minute walking distance; mMRC: Modified Medical Research Council; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in one second; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; VO_2: Oxygen uptake. Significance level was set at $p<0.05$.

distance ($p<0.001$), modified Medical Research Council dyspnea scale ($p<0.001$), and MIP ($p<0.001$). We found an average 150 mL increase in the FEV_1. There were patients whose FEV_1 increased by 650 mL. Also, there was increased walking distance of approximately 53 m. There were patients with walking distance that increased by 150 m. An increase was also detected in peak VO_2 max, which was estimated from 6MWT ($p<0.001$). The differences in the respiratory functions, functional exercise capacity, dyspnea, and respiratory muscle strength are summarized in Table 2.

Sixty percent of the patients (n=15) who underwent preoperative pulmonary rehabilitation were operated. Forty percent of the patients (n=10) were still considered "inoperable" and referred to the oncology department.

DISCUSSION

Findings of our study showed that a 15-day intense pulmonary rehabilitation program improved lung functions, exercise capacity, respiratory muscle strength, dyspnea perception, and oxygen consumption in patients with lung cancer who were defined as inoperable due to insufficient pulmonary reserve. After the program, patients were referred to surgeons and reevaluated for operation. Sixty percent of the patients who underwent preoperative pulmonary rehabilitation were operated. According to the results, pulmonary rehabilitation can provide these patients with a second chance to have surgery. We should highlight that, to our knowledge, this is the first study that investigated the effects of pulmonary rehabilitation on functionally inoperable lung cancer patients.

Cardiopulmonary insufficiency, which causes functional limitation for resection, is the main reason for inoperability. Many patients with lung cancer are also diagnosed with chronic obstructive pulmonary disease, which increases the risk of postoperative complications. In a study,[13] 73% of males with lung cancer and 53% of females had clinically active chronic obstructive pulmonary disease. No medical treatment approach at this time could provide adequate or necessary lung function improvement and reduce postoperative complications.[14] In our study, there were no comorbidities except for respiratory problems and the patient population was considered to be inoperable because of the limitations of lung function test parameters only.

Pulmonary rehabilitation is a treatment approach that improves exercise capacity even in advanced chronic obstructive pulmonary disease patients.[15] Furthermore, there are studies that showed that pulmonary rehabilitation preoperatively decreases the risk of postoperative complications.[16] However, the number of randomized controlled trials performed in this area is small. Our literature search did not reveal any studies conducted with functionally inoperable patients. Moreover, we did not detect any studies in the literature that attempted to remove functional limitation in inoperable lung cancer patients. To our knowledge, our study is the first conducted in this area. Our findings showed that 60% of the patients who underwent preoperative pulmonary rehabilitation were operated. We think that we have investigated an important issue affecting the quality of life of in this patient population, which has not been investigated in the literature before.

The operation decision is a long process. There is an algorithm in preoperative risk assessment. Patients with preoperative FEV_1 and diffusing capacity of the lungs for carbon monoxide (DLco) >80% of predicted or predicted postoperative (ppo) FEV_1 and ppo DLco >60% of predicted are considered at low risk. If both ppo FEV_1 and ppo DLco are <60% of predicted, then it is necessary to evaluate patient's exercise capacity.[17] In this stage, field tests or cardiopulmonary exercise test may be performed. Maximal oxygen consumption obtained from exercise tests as well as signs of cardiac problems are important for the preoperative evaluation.[6] Maximal oxygen uptake >15 mL/kg/min is considered sufficient for performing lobectomy or segmentectomy.[7] An intermediate risk group consisted of patients with VO_2 max=10-15 mL/kg/min.[18,19] Our patients' FEV_1% were below 60% and VO_2 values estimated from 6MWT were in the intermediate risk group. Since such patients were included, surgeons consulted us regarding the possibility of patients' having a chance of surgery after pulmonary rehabilitation. In our study, there was a statistically significant difference in VO_2 max after pulmonary rehabilitation and VO_2 values exceeded 15 mL/kg/min.

Deficiency of FEV_1 is an important component of operability.[3] The number of patients who lose the chance for lung surgery due to limited lung functions and for receiving chemotherapy treatment is too great to be underestimated. Sekine et al.[20] reported that despite lower FEV_1, postoperative pulmonary complications and long hospital stay could be effectively prevented by rehabilitation. A prospective clinical trial[21] emphasized that pulmonary rehabilitation had positive effects before lung surgery by improving exercise capacity and pulmonary functions (FEV_1). In our study, significant improvement was found in the spirometric parameters after pulmonary rehabilitation. An average increase in FEV_1 of 150 mL was observed. In some patients, this increase was 650 mL. We think that pulmonary rehabilitation is an important treatment approach that should be practised particularly in patients with limited and borderline respiratory functions.

Exercise capacity is also another parameter considered during the inoperability decision. The consensus is that cardiopulmonary exercise testing should be performed if the preoperative risk assessment is lower than 80% in FEV_1 and DLCO.[22] Unfortunately, we were unable to perform the cardiopulmonary exercise test because our center lacks a cardiopulmonary exercise test laboratory. Six-minute walk test was used to determine the change in exercise capacity and predicted VO_2 max. There are many studies showing that pulmonary rehabilitation increases the exercise capacity in chronic obstructive pulmonary disease patients.[23] Similarly, functional exercise capacity increased in our study. There was an approximate increase of 53 m in patients' walking distance. This value was close to the minimum clinical significance of 54 m (six-minute walking distance). In addition, there were patients with walking distance that increased by 150 m. In these cases, the development of both pulmonary functions and exercise capacity are considered by the surgeons.

Dyspnea is common among lung cancer patients. Dyspnea symptom is present in the majority of cancer patients, particularly in those with chronic obstructive pulmonary disease.[8] A great number of studies consistently reported that exertional dyspnea was reduced after pulmonary rehabilitation.[24] Another study[25] indicated that preoperative pulmonary rehabilitation reduced dyspnea perception measured by Borg scale. Moreover, a study which enrolled chronic obstructive pulmonary disease plus lung cancer patients in a preoperative pulmonary rehabilitation program showed significantly decreased dyspnea.[21] In our study, dyspnea decreased in line with the literature.[21] We think that this improvement is secondary to increased lung function and respiratory muscle strength.

The use of inspiratory muscle training in the preoperative period is a new approach. In a randomized controlled trial in which inspiratory muscle training was used in preoperative cardiac patients, the study group's MIP values increased and hospitalization times were statistically significantly reduced.[26] In another study, researchers showed that a seven-day intensive pattern of preoperative pulmonary rehabilitation combined with inspiratory muscle training and aerobic endurance training may be a feasible rehabilitation strategy for elderly lung cancer patients.[27] In this study, inspiratory muscle strength increased with a 15-day inspiratory muscle training program. It may be assumed that this increase in inspiratory muscle strength is reflected in the pulmonary function test parameters. There is a need for comparisons between the different exercise modalities in this patient population.

In the literature, randomized studies reported variable durations for preoperative pulmonary rehabilitation, such as four weeks[28] or 10 sessions.[14] In our previous randomized controlled trial of patients who were planned to be treated due to previous lung cancer, we demonstrated that a one-week intensive physiotherapy program resulted in positive increase in oxygen saturation, decreased hospital stay, positive change in ventilation/perfusion ratio, and positive contribution to patient exercise capacities.[10] The present study also examined the efficacy of a short duration of 15 days and an intensive pulmonary rehabilitation in a different patient population. According to our results, a 15-day program is quite sufficient. On the other hand, clinicians may be concerned about being late to start chemotherapy. However, a retrospective analysis of data[29] reported that postponement of the treatment until 48 days after the diagnosis had no effect on survival.

Our study has some limitations. Firstly, we did not determine the clinical characteristics of patients who benefited more from pulmonary rehabilitation. Secondly, we did not include any control or placebo group without an exercise program. However, although this seems like a limitation, doing otherwise would not be ethically appropriate. There was only one female patient in our patient population. Moreover, cardiopulmonary exercise test was not performed since our center lacked a cardiopulmonary exercise test laboratory. Thus, studies with larger patient populations are needed to investigate the effects of pulmonary rehabilitation on respiratory function in patients with lung cancer.

In conclusion, our findings suggest that short-term intensive pulmonary rehabilitation has positive effects on lung functions, inspiratory muscle strength, exercise capacity, and dyspnea in patients with lung cancer defined as inoperable due to insufficient pulmonary reserve. After pulmonary rehabilitation, more than half of our patients could undergo surgery. Therefore, it may be useful to refer patients to pulmonary rehabilitation centers before establishing a decision of inoperability. Particularly patients with spirometric parameters at the borderline of functional limitation may thus be given a second chance for surgery.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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