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Original Article / Özgün Makale

Risk factors for malignancy-unrelated long-term respiratory events after pneumonectomy

Pnömonektomi sonrası maligniteden ilişkisiz uzun dönemde solunum olayları için risk faktörleri

Ümit Aydoğmuş,[1] Erhan Uğurlu,[2] Serkan Değirmencioğlu,[3] Figen Türk,[1] Gökhan Yuncu[4]

Institution where the research was done:
Medical Faculty of Pamukkale University, Denizli, Turkey

Author Affiliations:
Departments of [1]Thoracic Surgery, [2]Chest Diseases, [3]Medical Oncology, Medical Faculty of Pamukkale University, Denizli, Turkey
[4]Department of Thoracic Surgery, Liv Hospital, İstanbul, Turkey

ABSTRACT

Background: In this study, we aimed to evaluate late-onset, malignancy-unrelated respiratory events following pneumonectomy.

Methods: The medical data of 78 patients (73 males, 5 females; mean age 55.6±9.6 years; range, 32 to 79 years) who underwent pneumonectomy in our clinic between January 2009 and September 2014 were retrospectively analyzed. Preoperatively, data including smoking habits, comorbidities, the American Society of Anesthesiologists risk score, the EuroSCORE, neoadjuvant chemotherapy need, cancer cell type, and clinical stage were recorded. Postoperatively, data included complications and treatment modalities were recorded.

Results: The mean follow-up was 35.2±22.0 months (range 9 to 104 months). Malignancy-related respiratory events such as local relapse and a second primary lung tumor developed in 21 patients (35.0%). Non-malignancy-related respiratory events were seen in 18 patients (31.6%). Long-term, non-malignancy-related morbidity was more prevalent in the patients with high American Society of Anesthesiologists scores (p=0.01), preoperative forced expiratory volume in one second <60% (p=0.05), and a high EuroSCORE (p=0.04). In multivariate analysis, non-malignancy-related respiratory events were found to be statistically significantly more frequent in the patients with high American Society of Anesthesiologists scores (p=0.01) and preoperative forced expiratory volume in one second <60% (p=0.03).

Conclusion: Our study results suggest that patients undergoing pneumonectomy may develop both short-term and long-term respiratory morbidities, and patients with high preoperative American Society of Anesthesiologists scores and low forced expiratory volume in one second are at an increased risk for non-malignancy-related morbidity.

Keywords: Cancer; long-term care; lung; pneumonectomy.

ÖZ

Amaç: Bu çalışmada pnömonektomi sonrası geç başlangıçlı maligniteden bağımsız solunum olayları değerlendirildi.

Çalışma planı: Ocak 2009 - Eylül 2014 tarihleri arasında kliniğimizde pnömonektomi geçirmiş 78 hastanın (73 erkek, 5 kadın; ort. yaş 55.6±9.6 yıl; dağılım 32-79 yıl) tıbbi verileri retrospektif olarak incelendi. Ameliyat öncesinde sigara içme alışkanlıkları, eşlik eden hastalıklar, Amerikan Anesteziyoloji Derneği risk skoru, EuroSCORE, neoadjuvan kemoterapi ihtiyacı, kanser hücre tipi ve klinik evre kaydedildi. Ameliyat sonrasında komplikasyonlar ve uygulanan tedavi yöntemlerine ilişkin veriler kaydedildi.

Bulgular: Ortalama takip süresi 35.2±22.0 ay (dağılım 9-104 ay) idi. Hastaların 21'inde (%35.0) lokal nüks ve ikinci primer akciğer tümörü gibi malignite ile ilişkili solunum olayı gelişti. Malignite ile ilişkisiz solunum olayları 18 hastada (%31.6) görüldü. Amerikan Anesteziyoloji Derneği skoru yüksek olan (p=0.01), ameliyat öncesi birinci saniyedeki zorlu ekspiratuvar volüm <%60 olan (p=0.05) ve EuroSCORE'u yüksek olan (p=0.04) hastalarda uzun dönem, malignite ile ilişkisiz morbidite daha yaygın idi. Çok değişkenli analizde, Amerikan Anesteziyoloji Derneği skoru yüksek olan (p=0.01) ve ameliyat öncesi birinci saniyedeki zorlu ekspiratuvar volüm <%60 olan (p=0.03) hastalarda malignite ile ilişkisiz solunum olayları istatistiksel olarak anlamlı düzeyde daha sık idi.

Sonuç: Çalışma sonuçlarımız pnömonektomi yapılan hastalarda hem kısa dönem hem de uzun dönem solunum morbiditelerinin gelişebileceğini ve Amerikan Anesteziyoloji Derneği skoru yüksek olan ve ameliyat öncesi birinci saniyedeki zorlu ekspiratuvar volümü düşük olan hastalarda malignite ile ilişkisiz morbidite riskinin artmış olduğunu göstermektedir.

Anahtar sözcükler: Kanser; uzun dönem bakım; akciğer; pnömonektomi.

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Correspondence: Erhan Uğurlu, MD. Pamukkale Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, 20070 Kınıklı, Denizli, Turkey.
Tel: +90 258 - 296 57 55 e-mail: drerhanugurlu@gmail.com

Pneumonectomy is a surgical procedure of which complication rates are still high, and it has been recently performed mostly in the case of malignancy.[1] Furthermore, as it involves the loss of an organ, pneumonectomy is a debilitating surgery which often includes comorbidities that negatively affect the quality of life of patients.[1]

Some patients undergoing pneumonectomy may die due to morbidities related to circulatory and respiratory failure in the long-term.[2] Accordingly, some authors advocate the evaluation of data about mortality between 90 days and six months in patients undergoing pneumonectomy for the non-malignancy-related mortality risk.[3,4] Many studies have focused on short-term morbidity and mortality of pneumonectomy, and the complication rates are still high.[1,4,5] In addition, a number of studies have examined the factors related to long-term survival.[6-8] However, the incidence and the mechanism of circulatory and respiratory failure in the long-term is unclear.

In this study, we aimed to evaluate possible risk factors for the development of long-term non-malignancy-related respiratory events in patients undergoing pneumonectomy.

PATIENTS AND METHODS

An ethical approval was obtained from the institutional Ethics Board on Human Experiments of Medical Faculty of Pamukkale University, with the approval number 60116787-020/35871. The medical data of 83 patients who underwent pneumonectomy in our clinic between January 2006 and September 2014 were retrospectively analyzed. Two patients were excluded due to missing data, while three patients were excluded due to mortality within the first 90 days following the operation. As a result, 78 patients (73 males, 5 females; mean age 55.6±9.6 years; range 32 to 79 years) were included in the study.

Preoperative evaluation

All patients underwent thoracic computed tomography (CT), respiratory function test, electrocardiography, blood count analysis, and biochemistry tests preoperatively. Perfusion scintigraphy and cardiopulmonary stress tests were performed in patients in whom the highest forced expiratory volume in one second (FEV_1) was below 2,000 mL. Pneumonectomy was canceled in cases with an estimated FEV_1 capacity of the remaining lung lower than 800 mL or below 40%.

Data including smoking habits, comorbidities, American Society of Anesthesiologists (ASA) risk score, EuroSCORE, neoadjuvant chemotherapy need, cancer cell type, and clinical stage were recorded. Patients older than 65 years or who had related symptoms underwent an additional echocardiographic examination.

The patients were divided into three groups according to the EuroSCORE risk: class 1 (low risk): 0-2 points; class 2 (moderate risk): 3-5 points; class 3 (high risk): ≥6.

A total of 32 patients (41.0%) had comorbidities: diabetes mellitus in 12 patients (15.4%) and chronic obstructive pulmonary disease in nine patients (11.3%). Three patients have been taken bronchodilators.

The patients with lung cancer underwent positron emission tomography/CT (PET/CT) examination. The patients with lymphadenopathy, as assessed using PET/CT or CT underwent mediastinoscopy. Neoadjuvant treatment was given to the patients with Stage $T_{1\text{-}2\text{-}3}N_2$ and T_4N_0 at the discretion of the Thoracic Oncology Team.

Postoperative evaluation

All patients remained in the intensive care unit for at least one day following surgery. Routine monitoring of vital signs, daily blood counts, and biochemical tests were performed within the first three days. Daily posteroanterior lung X-rays were obtained within the first seven days. All complications, treatments applied, and management modalities related to the patients were recorded. Surgical mortality was defined as inhospital mortality or mortality within the first 90 days after surgery.

Long-term follow-up

Patients returned to the outpatient clinic for follow-up one week and one month after discharge from the hospital. All patients were scheduled for follow-up visits every three months for the first two years and every six months for subsequent years. Complaints and treatments received were recorded, and posteroanterior X-ray, blood count, erythrocyte sedimentation rate, and C-reactive protein tests were performed on a regular basis. In the long-term follow-up, medical records in our hospital, prescription records in the pharmacy, citizen registry records, and social security trust records were also evaluated.

Malignancy-related events were defined as respiratory problems in patients with locoregional relapse, pulmonary metastasis, malignant pleural effusion, or a secondary lung carcinoma. Non-malignancy-related long-term events were defined as in need of brochodilator, need for oxygen treatment,

Table 1. Distribution of non-malignancy-related long-term morbidity

Long-term morbidity	n	%
Requirement of continuous bronchodilator treatment	8	10.3
Oxygen dependency at home	1	1.3
Pleural effusion-thoracentesis	3	3.8
Pleural effusion-tube thoracostomy	1	1.3
Pneumothorax-tube thoracostomy	2	2.6
Re-admittance to the emergency department for respiratory distress	3	3.8
Pulmonary embolism	1	1.3
Tuberculosis	1	1.3
Pneumonia	2	2.6

emergency department admittance, pulmonary embolism, tuberculosis, recurrent pneumonia, pneumothorax, or pleural effusion developing following surgery.

Statistical analysis

For statistical analysis, PASW 17.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used to analyze outcomes. Descriptive data were expressed in mean and standard deviation. The chi-square and Fisher's exact tests were performed to analyze data. Only variables with a *p* value of 0.2 without a correlation were included in the multivariate analysis. A *p* value of <0.05 was considered statistically significant.

RESULTS

The mean follow-up was 35.2±22.0 (range, 9 to 104) months. Indications for pneumonectomy were a destroyed lung in five patients (6.4%) and non-small-cell lung cancer in 73 patients (93.6%).

A right pneumonectomy was performed in 35 patients (44.9%) and a left pneumonectomy was done in 43 patients (55.1%). The FEV_1 value was lower than 60% in seven patients (8.9%).

The mean duration of hospitalization was 11.7±9.8 (range, 5 to 66) days. A standard pneumonectomy was performed in 68 patients (78.2%); 18 patients (23.1%) received induction chemotherapy, and 12 patients (15.4%) received induction chemo-radiotherapy. A total of 46 patients (59.0%) received adjuvant chemotherapy, while 15 patients (19.2%) received adjuvant radiotherapy.

During follow-up, distant metastasis developed in 26 (33.3%), local-regional relapse in seven (9.7%), and secondary lung cancer in three patients (3.8%). In addition, 31 patients (39.7%) died during follow-up; causes of death were distant metastasis in 18 (23.1%), local relapse in six (7.7%), secondary lung cancer in one (1.3%), and non-malignancy-related causes in six patients (7.7%).

In addition, 11 patients required 14 invasive procedures during follow-up: five wedge resection of the lung, three tube thoracostomy, two rigid bronchoscopy, and four thoracentesis. The indication among the patients who received wedge resection was metastatic disease in three and a secondary lung carcinoma in two patients, and all of these patients survived at the time of the study completion.

During the study, morbidities which were reported are shown in Table 1. Four patients had more than one long-term respiratory incident. In three of the pleural effusion cases, collection was transudate, and in one patient, collection was regarded as having a parapneumonic effusion.

On the other hand, the probability of a long-term incident was not significantly different between the patients who had a right pulmonectomy (n=8, 22.9%) and those who had a left pneumonectomy (n=10, 23.3%) (p=0.99), between males (n=21, 28.8%) and females (n=1, 20%) (p=0.99), or between the patients who received standard resection (n=13, 28.8%) and extended resection (n=5, 29.4%) (p=0.52). Similarly, receiving induction therapy (p=0.75), pneumonectomy for non-small-cell lung cancer (p=0.33), smoking habits (p=0.76), having comorbidities (p=0.28), or receiving adjuvant chemotherapy (p=0.75) were not found to be risk factors (Table 2).

Long-term respiratory morbidity was higher in patients over 60 years of age (n=9, 34.6%) than in those below 60 years (n=9, 17.3%) (p=0.1) and, similarly, higher in patients with a higher EuroSCORE 66.7% in class 3 (n=2), 32.1% in class 2 (n=9), and 14.9% (n=7) in class 1 (n=7), (p=0.17). Only one of the patients who received adjuvant radiotherapy (6.7%) had long-term respiratory morbidity. Although long-term respiratory morbidity was not seen in the patients with an ASA

Table 2. Comparison of the non-malignancy related long-term morbidity with categorical variables

		Respiratory disorders		
	n	n	%	*p*
Age (year)				
≥60	26	9	34.6	0.1
<60	52	9	17.3	
Gender				
Male	73	21	28.8	0.99
Female	5	1	20.0	
Side				
Right pneumonectomy	35	8	22.9	0.99
Left pneumonectomy	43	10	23.3	
Resection				
Extended resection	17	5	29.4	0.52
Standard resection	61	13	21.3	
Malignancy				
Benign	5	2	40	0.33
Malign	73	16	21.9	
Stage 2	22	6	27.3	
Stage 3	21	4	19.0	0.88
Re-stage 1-2*	22	4	18.2	
Re-stage 3*	8	2	25.0	
Tumor diameter				
≤5 cm	46	8	17.4	0.25
>5 cm	27	8	29.6	
Induction therapy				
Chemotherapy	18	3	16.7	
Chemoradiotherapy	12	3	25.0	0.75
That is not	48	12	25.0	
ASA score				
1	20	0	0	
2	54	16	29.6	0.01
3	4	2	50.0	
FEV_1				
≥60%	71	14	19.4	0.05
<60%	7	4	57.1	
Cardiac risk score				
1	47	7	14.9	
2	28	9	32.1	0.04
3	3	2	66.7	
Smoking				
Non-smoker	12	2	16.7	
Less than 20 pack-year	40	10	325	0.76
More than 20 pack-year	26	6	23.1	
Comorbidity				
No comorbidity	32	5	15.6	0.28
Comorbidity	46	13	28.3	
Adjuvan				
No adjuvan chemotherapy	27	5	18.5	0.77
Chemotherapy	46	11	23.9	
No adjuvan radiotherapy	58	15	25.9	0.17
Radiotherapy	15	1	6.7	

* Pathological stage after neoadjuvant; ASA: American Society of Anesthesiologists; FEV_1: Forced expiratory volume in one second.

Table 3. Multivariate analysis of the non-malignancy related long-term morbidity

		Respiratory disorders		Multivariate analysis			
	n	n	%	*p*	Odds ratio	95%	CI
Age (year)							
≥60	26	9	34.6	0.2	1.3	-0.06	0.3
<60	52	9	17.3				
ASA score							
1	20	0	0				
2	54	16	29.6	0.005	2.93	0.08	0.43
3	4	2	50.0				
FEV_1							
≥60%	71	14	19.4	0.1	1.65	-0.07	0.7
<60%	7	4	57.1				
Cardiac risk score							
1	47	7	14.9				
2	28	9	32.1	0.08	1.78	-0.02	0.3
3	3	2	66.7				
Adjuvan radiotherapy	58	15	25.9	0.02	-2.38	-0.48	-0.04
No radiotherapy	15	1	6.7				

CI: Confidence interval; ASA: American Society of Anesthesiologists; FEV_1: Forced expiratory volume in one second.

score of 1, 16 patients with an ASA score of 2 (29.6%) and two patients with an ASA score of 3 (50%) had long-term morbidity (p=0.01). Similarly, long-term morbidity was found to be higher in patients with a preoperative FEV_1 lower than 60% (n=7, 57.1%) (p=0.05).

Multivariate analysis revealed that a higher ASA score was a significant risk factor for long-term post-pneumonectomy morbidity unrelated to malignancy (p=0.005) (odds ratio = 2.93) (95% confidence interval: 0.08-0.43). Meanwhile, non-malignancy-related long-term respiratory morbidity was significantly lower in patients who had adjuvant radiotherapy (p=0.02) (OR=2.38). Long-term, non-malignancy-related respiratory morbidity was higher in patients older than 60 years (p=0.2) with a preoperative FEV_1 lower than 60% (p=0.1) and with a higher cardiac risk score (p=0.08), although the difference was not significant (Table 3).

DISCUSSION

Higher ASA scores, older age, neoadjuvant treatments, comorbidities (particularly COPD), right pneumonectomy, and extended resection were found to be associated risk factors for post-pneumonectomy morbidity.[1,4,7,9] However, the long-term implications of these risk factors are not well-known. Long-term survival after pneumonectomy is primarily associated with the stage of lung cancer.[8] In addition, there are studies utilizing the Short-Form 36 Health Survey (SF-36), which contains subjective evaluations for quality of life of patients undergoing thoracic surgery.[10,11] Other problems in assessing the long-term quality of life of patients are non-compliant patients and life quality of patients which declines during adjuvant therapies.[11] Lung function of the patients who underwent pneumonectomy may deteriorate, if they receive adjuvant radiotherapy.[12] In this study, objectively recorded, non-malignancy-related long-term morbidity in patients who underwent pneumonectomy was evaluated.

Rodríguez et al.[4] found that right pneumonectomy was associated with a higher rate of cardio-respiratory complications and death within the first postoperative six months. Recently, there is growing evidence suggesting that neoadjuvant treatment is not related to higher morbidity and mortality.[8,9] Our results also showed that factors such as right pneumonectomy, neoadjuvant therapy, smoking, and extended resection, which were previously related to postoperative morbidity, were not found to significantly increase non-malignancy-related long-term respiratory morbidity.

Although some studies reported that a higher ASA score was a significant indicator of postoperative morbidity, others found it to be irrelevant.[4,5] In our study, preoperative ASA scores were found to be a significant indicator for long-term morbidity. Poor respiratory-function test results were also found to be a risk factor for poorer long-term quality of life for patients who underwent lung excision.[10]

Low preoperative respiratory functional capacity and higher cardiac risk scores were found to be related potential risk factors for long-term respiratory morbidity.

Toxicity of postoperative radiotherapy to the lungs is well-known, and accordingly, it is not recommended for patients with early stage non-small cell lung cancer (Stage I-II).[13] In contrast, our results showed lower long-term respiratory morbidity in patients who received adjuvant radiotherapy. This discrepancy can be explained in two ways: first, toxic effects of the radiotherapy were not seen, as there was no lung tissue at the target area of radiotherapy; second, patients with a poor general condition did not receive radiotherapy in our series to prevent possible side effects.

Non-malignancy-related, long-term, postoperative respiratory morbidity is mostly due to cardiopulmonary insufficiency.[12] Indeed, the most important threat for the patients with lung cancer undergoing pneumonectomy, particularly those in the early stages, is intervening disease for five-year survival.[12] This finding is in consistent with the findings indicating that preoperative low FEV_1 values were associated risk factors.

Furthermore, in patients undergoing cancer surgery, it is suggested to be used the ASA classification rather than Eastern Oncology Cooperative Group (ECOG).[14] In addition, the relationship among the ASA scoring, mortality and morbidity in early period in patients undergoing thoracic surgery is well-known.[15] In this study, high ASA scores were shown to be a strong risk factor for respiratory problems in late period. The EuroSCORE risk evaluation is a classification system for patients with cardiac surgery in the light of objective criteria.[16] For the Turkish society, this method was found with higher sensitivity and specificity according to other methods.[17] In our study, the patients with a high cardiac risk score had high respiratory problems in the late period. Thus, the EuroSCORE risk classification seems to be a good indicator of health problems in the late period. Cardiopulmonary system is affected in patients undergoing pneumonectomy and these patients who are at cardiac and pulmonary risks often experience impaired quality of life in the long-term.

The only problem of patients with pneumonectomy is not the failure of cardiopulmonary. Developing problems in the only remaining lung have almost always life-threatening aspect. These events which might threaten the life of a patient with a solitary lung were pneumonia (n=2), tuberculosis (n=1), and contralateral pneumothorax (n=2). Herniation of the remaining lung to the contralateral empty hemithorax and hyperinflation are also regarded as the underlying causative mechanisms for non-malignancy-related, contralateral pneumothorax.[18] Although pneumothorax is mild, it must be drained carefully, since the patient may not tolerate the changes secondary to pneumothorax and drainage. In our study, both patients were managed with no further events by tube thoracostomy and underwater sealed drainage.

Nonetheless, cross-sectional design and retrospective nature of this study is the major limitation. Although it is a single-center study with close monitoring of the patients, small sample size is another limitation. As most of the studies in the literature have addressed into survival following pneumonectomy, we believe that our contribution evaluating non-malignancy-related long-term morbidities is valuable.

In conclusion, our study results showed that higher American Society of Anesthesiologists scores and lower forced expiratory volume in one second were related risk factors for non-malignancy-related long-term respiratory morbidities. Although pneumonectomy is a procedure with low morbidity and mortality in experienced hands, long-term morbidity is remarkable due to locoregional or distant tumor relapse or non-malignancy-related cardiopulmonary morbidities. Therefore, patients undergoing pneumonectomy require close and long-term monitoring.

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