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Original Article

The factors affecting morbidity, mortality and survival in patients who underwent intrapericardial resections due to non-small cell lung cancer

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ABSTRACT

Background: Complete surgical resection has been the gold standard in the treatment of lung cancer. Intrapericardial approach may be required to resect the advanced stage tumors completely. This study aims to compare the morbidity and mortality rates of intrapericardial and standard pneumonectomies.

Materials and Methods: The records of patients operated on due to non-small cell cancer between the years 2001 and 2008 were evaluated retrospectively. The data including age, sex, respiratory function tests, tumor site, cell type, stage, resection type, complications, mortality and survival rates were recorded. The morbidity, mortality and survival rates of intrapericardial and standard pneumonectomies were compared.

Results: The study included 126 cases with pneumonectomy (90 standard, 36 intrapericardial) with mean age of 56.6 ± 8.42 years. Major morbidity rates of intrapericardial and standard groups were 30.6% and 21.1% respectively, and the difference was not significant ($p = 0.233$). Mortality rates of intrapericardial and standard groups were 8.3% and 8.9% respectively, and the difference was not significant ($p = 0.533$). The mean survival of all patients was 24.13 ± 3.13 months. The survival rate was significantly in the intrapericardial group compared to standard group (23 months vs 32 months, $p = 0.03$).

Conclusions: Intrapericardial approach is a safe method in the treatment of locally advanced lung cancer without increasing morbidity or mortality.

Keywords: pneumonectomy, lung cancer, mortality

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Introduction

Despite developing technology and struggle lung cancer has kept still its rank as one of the deadliest cancers [1]. The stage of the disease and the physical characteristics of the patient determine the strategy of the treatment. A complete surgical resection is superior to both chemotherapy and radiotherapy. Inoperability has decreased to acceptable rates by the improvements in staging and imaging modalities.

The surgical dissection especially is difficult in centrally located tumors, tumors invading pulmonary artery or veins, in the presence of lymph nodes attacking the hilar structures, hilar fibrosis or previous dissections. Opening the pericardium may usually be necessary in these situations to control the hilar vessels [2,3]. It also helps to access the proximal pulmonary artery and superior vena cava (SVC) when the centrally located tumor invade the pericardium.

The aim of the current study is to analyze the morbidity and mortality in patients who underwent pneumonectomy between 2001 and 2008 due to non-small cell lung cancer (NSCLC) by comparing the results of patients with standard pneumonectomy to pneumonectomy performed through the intrapericardial approach.

Material and Methods

The medical records of all patients with resections due to non-small cell lung cancer between 2001 and 2008 were evaluated retrospectively. The age, sex, pulmonary function tests (vital capacity and forced expiratory volume in the first second), location, histopathology and stage of the tumor, type of resection, morbidity, mortality, and survival of the cases were noted. Patients with incomplete resections, completion pneumonectomies, N2 disease detected by mediastinoscopy and cases with incomplete data were excluded from the study.

A thorough physical examination, routine biochemical tests, pulmonary function tests, arterial blood gas analysis, and fiberoptic bronchoscopic examination were performed in all cases. Computed thoracic tomography (CT) was performed in all cases to better localize the tumor and evaluate the mediastinal lymph nodes. The histopathological diagnosis was reached by either transbronchial or trans-thoracic needle biopsy. A positron emission tomography (PET/CT) was performed to exclude a distant metastasis and detect mediastinal lymph node invasion since 2003. In centrally located

tumors and patients with tumors over 3 cm a cranial magnetic resonance imaging (MRI) was performed.

Before surgery, all patients underwent pulmonary function tests to calculate the FEV1 and a perfusion scintigraphy was performed in patients with FEV1 less than 800 mL. A pO₂ over 60 mmHg and pCO₂ less than 45 mmHg were the limits of arterial blood gas analysis for performing the surgical resection. Patients with a history of heart disease, active chest pain, dysrhythmia, or age over 70 were referred to a cardiologist assess the cardiac risk. The cardiac risk was assessed by the consultant cardiologists according to the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. To detect the situation of the mediastinal lymph node standard or extended mediastinoscopy was performed in all cases. Patients with N2 disease were referred to oncology for neoadjuvant therapy, and with N3 disease for definitive chemotherapy. The pathology reports were examined, and patients were re-staged according to 8th TNM staging system reported by the international association of the study of lung cancer (IASLC) [4].

Standard posterolateral thoracotomy was performed in all cases after rigid bronchoscopy and double lumen endotracheal intubation under general anesthesia. Pulmonary vessels were stapled in the standard group while they were sutured with non-absorbable sutures in the intrapericardial group. Bronchi were closed with stapler in all cases. A prolene mesh was used when necessary to restore the pericardial defects. The opening of the pericardium was not routine. However, in cases where either pulmonary veins or artery was invaded intrapericardially, or presence of invasion of the superior vena cava or atrium then the pericardium was opened. Furthermore, when the hilar dissection was not possible due to fibrotic lymph nodes or dense adhesion the pericardium was opened. Chest wall resection was added to the planned procedure in cases with tumors invading the chest wall.

After the operation, all cases were monitored in the intensive care unit for at least 24 hours and patient-controlled analgesia was provided. Patients were seen at the outpatient unit after discharge every 3 months for the first 2 years and every 6 months then on to detect any possible recurrences. All minor and major complications were noted. Arrhythmias of any kind that deteriorated the general condition of the patient and required medical treatment were accepted as major complication.

Exitus in the first 30 days and 90 days was accepted early and late mortality rates, respectively. Survival data were provided from either outpatient records or phone calls to the patients or their relatives. The study was approved by the institutional review board (No: 2020-31) and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Categorical variables were depicted as percentages and frequencies while continuous variables as means and standard deviation. Chi square test was used to compare the categorical data and Student's t-test was for comparing the means of the groups. To calculate the survival Kaplan-Meier survival analysis and for comparing the groups log-rank test were performed. Because the statistical calculations were based on the data of all cases included in the study period, the power analysis was not performed. IBM SPSS (version 15.0, SPSS Inc. Chicago, Illinois, United States) was used to perform all calcu-

lations and $p < 0.05$ was accepted as statistical analysis.

Results

During the study period a total of 393 patients underwent pulmonary resection, and 126 out of these were pneumonectomy. The remaining cases were lobectomy (201), segmentectomy (18), completion pneumonectomy (6), incomplete resection (12), N2 or N3 patients (57), and lost follow-up (23) and not included in the statistical analyses. Out of 126 pneumonectomy cases 36 were performed through the intrapericardial approach. This group was compared to remaining 90 cases with standard pneumonectomy with respect to morbidity, mortality, and survival.

Forty-two of the cases were male and the mean age of all cases was 56.6 ± 8.42 (Table 1). The rate of patients with neoadjuvant therapy was higher in the intrapericardial group but the difference did not reach statistical significance. Moreover, the tumor stage was more advanced in the intrapericardial group than the standard group.

Table 1. Clinical characteristics of the patients.

	Standard pneumonectomy (n=90)	Intrapericardial pneumonectomy (n=36)	P
Years	56.7±8.71 (39-76)	56.5±8.37 (35-72)	0.860
Sex (Male, Female)	M: 81 (90%) F: 9 (10%)	M: 32 (%88) F: 4 (%12)	0.540
Tumor Location (Right-Left)	R: 33 (36%) L: 57 (64%)	R: 23 (63%) L: 13 (37%)	0.009
FEV1 (L)	1.97±0.75	1.89±0.53	0.530
Co-morbidity	56 (62%)	24 (66%)	0.680
Neoadjuvant Therapy	5 (5.5%)	6 (16%)	0.070
Histopathology (Adenocarcinoma-SCC)	Adenocarcinoma: 39 (43%) SCC: 51 (57%)	Adenocarcinoma: 14 (39%) SCC: 22 (61%)	0.690
TNM Stage	Stage II: 34 (38%) Stage IIIa: 50 (57%) Stage IIIb: 6 (5%)	Stage II: 4 (12%) Stage IIIa: 30 (82%) Stage IIIb: 2 (6%)	0.020
Indications for intrapericardial pneumonectomy		SPV invasion: 15 (42%) IPV invasion: 5 (14%) Atrium invasion: 6 (16%) PA invasion: 3 (8%) SVC invasion: 3 (8%) Difficult hilar dissection: 2 (6%) Anatomic variation: 2 (6%)	

Abbrev.: SPV; superior pulmonary vein, IPV; inferior pulmonary vein, PA; pulmonary artery, SVC; superior vena cava, SCC; Squamous Cell Carcinoma

Table 2. The distribution of the complications.

	Standard pneumonectomy n=19 (21.1%)	Intrapericardial pneumonectomy n=11 (30.6%)	P
Arrythmia	23 (26%)	11 (31%)	0.650
Bronchopleural fistula	11 (12%)	6 (16%)	0.520
Hemorrhage	5 (6%)	2 (5%)	0.640
Pneumonia	6 (7%)	3 (8%)	0.710
Hoarseness	2 (2%)	1 (3%)	0.630
Empyema	4 (4%)	1 (3%)	0.550
Pulmonary emboli	1 (1%)	1 (3%)	0.490
Vena cava superior thrombus	-	1 (3%)	-
Cerebral emboli	-	1 (3%)	-
Myocardial infarction	2 (2%)	-	-

Arrhythmias were the most frequent symptom in both groups whereas bronchopleural fistula was the most mortal complication (Table 2). Major morbidity rate was calculated in the intrapericardial group and the standard group 30.6% (11 cases) and 21.1% (19 cases), respectively, but the difference did not reach statistical significance ($p = 0.263$). The treatment of arrhythmias was provided by the consultant cardiologist of the hospital. A total of seven cases developed postoperative hemorrhage and all required thoracotomy to control the source of bleeding. The most demanding complication was bronchopleural fistula experienced in 17 cases. The initial intervention was tube thoracostomy and appropriate antibiotics in all cases. The fistula was minor and responded to the treatment in seven cases. Two out of 10 remaining cases underwent omentoplasty in the early postoperative period. Thoracostoma was performed in the remaining eight cases. After serial debridement of the cavity omentoplasty was added in the cases. Two cases were not eligible for omentoplasty and followed at outpatient debridement and wound dressing. In cases with pneumonia appropriate antibiotics were given and pulmonary physiotherapy was also added. Mechanical ventilation was added to the treatment when the patient developed respiratory failure.

Three cases (8.3%) in the intrapericardial group died during the first month of operation. One of the two cases who had right pneumonectomy and partial vena cava superior resection died from thrombus development in the SVC, and the other died from cerebral emboli. The last patient with left pneumonectomy in this group died from pulmonary embolism. In the standard group the rate mortality in the first 30 days was 8.9% (8 cases).

Six cases died from pneumonia and respiratory failure because of bronchopleural fistula development and the remaining 2 died from myocardial infarction. The difference between the mortality rates of the groups was not statistically significant ($p = 0.533$). Univariate analysis showed that right pneumonectomy affected both morbidity and mortality when compared to left pneumonectomy ($p = 0.002$).

The mean survival of all cases was 24.13 ± 3.13 months (Figure 1). Intrapericardial and standard groups had 23 ± 6.37 months and 32 ± 5.53 months of mean survival times, respectively, and the difference was found statistically significant ($p = 0.030$). In survival analysis age (over 60, 21 months vs younger 60, 37 months) and advanced tumor stage (stage 3, 22 months vs stage 2, 39 months) were found to significantly affect the survival adversely ($p = 0.001$).

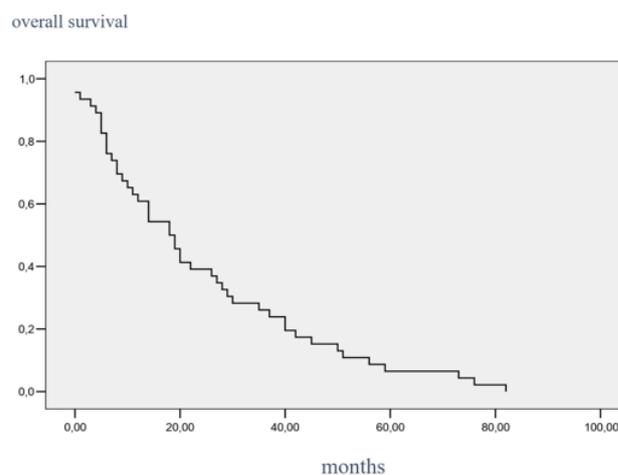


Figure 1. Overall survival of all patients

Discussion

Complete resection is sine qua non in the treatment of lung cancer surgery. To reach this goal extended resections are required when necessary [5,6]. These extended resections carry more morbidity and mortality when compared to standard procedures [7,8]. Hilar dissection is especially difficult in the presence of centrally located tumors invading pulmonary artery or veins, attacked and fixed lymph nodes preventing the vascular dissection, and previous hilar dissection. These situations require intrapericardial approach to control the vascular structures to make complete resection possible [9]. Allison reported that intrapericardial approach was especially safer and faster in the treatment of tumors invading the pericardium in 1946 [10]. Later, in 1948 Brock reported intrapericardial approach (Block dissection pneumonectomy) as more curative operation [11].

In this series the most frequent indication for opening the pericardium was the invasion of the pulmonary veins like many series in the literature [9,12,13]. In contrast, Dartavelle et al. reported on 30 cases of T4 tumors invading the superior vena cava [14]. In the recent decades some advanced staging techniques, transesophageal echocardiography (TEE), and videopericardioscopy (VPC), have been used to better delineate the intrapericardial invasion and to prevent futile thoracotomies and incomplete resections [15-17]. During the study period TEE was unavailable and videopericardioscopy was rarely performed. The superior vena cava invasion ranked the 5th place and a graft was used to restore the continuity.

The morbidity and mortality rates of pneumonectomies performed due to lung cancer has been reported as low as 24% to 59% and from 3% to 12% respectively [7,18,19]. Although right pneumonectomies have higher morbidity and mortality rates it was rarely reported that intrapericardial pneumonectomies carried higher rates compared to standard approach. Intrapericardial pneumonectomies had acceptable morbidity and mortality rates despite of higher supraventricular arrhythmia rates. Krowka et al reported that the reason for post-operative arrhythmias were pericardial irritation, intrapericardial ligation of the pulmonary vessels, extended resections, longer operation time, and atrial injury [20]. In a large series with 259 cases Foroulis et al reported that right pneumonectomy over left and intraparin this serieericardial pneumonectomy over standard pneumonectomy had higher arrhythmia risk [21]. The overall

morbidity rate in this series was around 24% and was at the lower edge of the literature. The possible reason could be the definition and classification of the complications were not uniform. Whereas the overall mortality of the study was 8.7% and was close to the upper limit of the study. The advanced tumor stage and high rate of right pneumonectomy could explain the relatively high rate of mortality.

The most challenging complication after pneumonectomy is the development of bronchopleural fistula. The risk of BPF has been reported between 2.1% and 8%, and intrapericardial ligation of the vessels did not increase the risk [22]. In this study the rate of BPF was higher than the literature, and, the risk was found higher in the intrapericardial group besides. Existence of more advanced tumor stage and higher number of right pneumonectomy in this group might explain this discrepancy. Furthermore the study was performed in a teaching hospital. The operations were performed by various surgeons and fellows with different experiences.

Pricopi et al reported on that the right side, advanced age, and advanced tumor stage increased the mortality whereas the extent of the resection did not change it in a series with 2064 cases [19]. Similarly, Park et al pointed out that pneumonectomy had higher mortality rates when compared to lesser resections, but he also reported that intrapericardial approach did not affect the mortality rate significantly [23].

The five-year survival of non-small cell lung cancer was reported between 21% and 31% in the literature [24,25]. In a series consisting of 55 pneumonectomies with stage IIIA overall survival was found 29%, and interestingly 42% of the group had 20% five-year survival rate despite of N2 metastases [26]. Riquet et al reported on 32% five-year survival rate in a large series consisting of 1466 patients of whom 342 had extended pneumonectomy [27]. In that study advanced age, advanced tumor stage, extended pneumonectomy, and adenocarcinoma adversely affected the survival, but right pneumonectomy did not affect the survival when compared to left side. In the current study the five-year survival rate was found 21%. The possible reason for this relatively low survival rate could be higher number stage III cases than stage II. Similarly, advanced age and advanced tumor stage adversely affected the survival. The reason for lower survival rate in the intrapericardial group could be higher tumor stage in the group.

Limitations of the study

The retrospective nature of the study, limited number of patients, insufficient number of cases representing the subgroups, and inhomogeneity of the groups with respect to tumor stage were the limitations of the current study. Moreover, the study comprises limited number of variables affecting the morbidity, mortality, and the survival. Other limitations of the study might be missing clinical characteristics of the cases like TNM subsets and insufficiencies in the follow up such as local and systemic recurrences.

As a conclusion, intrapericardial dissection could be necessary in the treatment of locally advanced non-small cell lung cancer to reach a complete resection with all negative tumor margins. Invasion of proximal pulmonary vessels, pericardium or left atrium may adversely affect the prognosis, but they do not affect the operability. Though intrapericardial approach increase the supraventricular arrhythmia rates it can be performed with acceptable morbidity and mortality rates.

Declaration of conflicting interests

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Ethics approval

The study was approved by the Ethics Committee of Health Sciences University (No: 2020-31).

Authors' contributions

AP; Conceived and designed the analysis, collected the data, contributed data/analysis tools, performed the analysis, co-wrote the paper, MN; contributed data/analysis tools, co-wrote the paper MM; co-wrote the paper.

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