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Completion pneumonectomy: Indications and outcomes in non-small cell lung cancer

Tamamlayıcı pnömonektomi: Küçük hücreli dışı akciğer kanserinde endikasyon ve sonuçlar

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ABSTRACT

Background: This retrospective single-center study aims to review the indications and outcomes of completion pneumonectomy after primary resection due to non-small cell lung cancer.

Methods: Of a total of 452 patients who underwent pneumonectomy between January 2004 and August 2017 for non-small cell lung cancer, 29 (24 males, 5 females; mean age 59.9±7.1 years; range, 45 to 72 years) were performed completion pneumonectomy. Patients' indications, factors affecting early and late-term outcomes, operative mortality and survival rates were analyzed.

Results: Operative mortality rate was 24.1%, including two intraoperative and five postoperative deaths. Complication rate was 44.8% and the most frequent complication was bronchopleural fistula with 24.1%. Study population was divided into two groups. While elective completion pneumonectomy group (n=19) consisted of recurrent malignant tumor patients, rescue completion pneumonectomy group (n=10) consisted of patients performed urgent pneumonectomy due to a bronchopulmonary complication developing after an anatomic lung resection. The morbidity and mortality rates for elective completion pneumonectomy and rescue completion pneumonectomy were 26.3% and 21.1%; and 70% and 30%, respectively. The morbidity for rescue completion pneumonectomy was significantly higher than elective completion pneumonectomy (p=0.016). Advanced age and presence of any preoperative risk (comorbidity and neoadjuvant treatment) were related to higher operative mortality (p=0.019 and p=0.049, respectively). The median survival after completion pneumonectomy was 19.5 months (95% confidence interval 17.2 to 21.9 months).

Conclusion: The morbidity and mortality rates of completion pneumonectomy are higher than standard pneumonectomy. Rescue completion pneumonectomy is related to higher postoperative risk, but has better survival. The most significant complication after completion pneumonectomy is bronchopleural fistula. Advanced age and presence of any preoperative risk are related to statistically significantly higher mortality in completion pneumonectomy. Nevertheless, completion pneumonectomy is still a significant treatment option in selected patients.

Keywords: Completion pneumonectomy; early mortality; indication; non-small cell lung cancer; survival rate.

ÖZ

Amaç: Bu retrospektif, tek merkezli çalışmada, küçük hücreli dışı akciğer kanseri için primer rezeksiyondan sonra yapılan tamamlayıcı pnömonektominin endikasyonları ve sonuçları incelendi.

Çalışma planı: Küçük hücreli dışı akciğer kanseri nedeniyle Ocak 2004-Ağustos 2017 tarihleri arasında pnömonektomi geçiren toplam 452 hastanın 29'una (24 erkek, 5 kadın; ort. yaş 59.9±7.1 yıl; dağılım, 45-72 yıl) tamamlayıcı pnömonektomi uygulandı. Hastaların endikasyonları, erken ve geç dönem sonuçlarını etkileyen faktörler, ameliyat mortalitesi ve sağkalım oranları analiz edildi.

Bulgular: Ameliyat mortalitesi oranı %24.1 idi ve bu oran iki ameliyat sırası ve beş ameliyat sonrası ölümü içeriyor idi. Komplikasyon oranı %44.8 idi ve en sık komplikasyon %24.1 ile bronkoplevral fistül idi. Çalışma popülasyonu iki gruba ayrıldı. Elektif tamamlayıcı pnömonektomi grubu (n=19) rekürren malign tümör hastalarından oluşur iken kurtarma tamamlayıcı pnömonektomi (n=10) grubu anatomik bir akciğer rezeksiyonundan sonra gelişen bronkopulmoner bir komplikasyon nedeni ile acil pnömonektomi uygulanan hastalardan oluştu. Elektif tamamlayıcı pnömonektomi ve kurtarma tamamlayıcı pnömonektomi için morbidite ve mortalite oranları sırasıyla %26.3 ve %21.1; %70 ve %30 idi. Kurtarma tamamlayıcı pnömonektomi için morbidite elektif tamamlayıcı pnömonektomiden anlamlı biçimde daha yüksek idi (p=0.016). İleri yaş ve ameliyat öncesi risk bulunması (komorbidite ve neoadjuvan tedavi) daha yüksek ameliyat mortalitesi ile ilişkili idi (sırasıyla, p=0.019 ve p=0.049). Tamamlayıcı pnömonektomiden sonra ortalama sağkalım 19.5 ay idi (%95 güven aralığı 17.2-21.9 ay).

Sonuç: Tamamlayıcı pnömonektominin morbidite ve mortalite oranları standart pnömonektomiden daha yüksektir. Kurtarma tamamlayıcı pnömonektomi daha yüksek ameliyat sonrası risk ile ilişkilidir fakat daha iyi sağkalıma sahiptir. Tamamlayıcı pnömonektomiden sonra en önemli komplikasyon bronkoplevral fistüldür. Tamamlayıcı pnömonektomide ileri yaş ve ameliyat öncesi risk varlığı, istatistiksel olarak anlamlı şekilde daha yüksek mortalite ile ilişkilidir. Bununla birlikte, tamamlayıcı pnömonektomi seçilmiş hastalarda hala önemli bir tedavi seçeneğidir.

Anahtar sözcükler: Tamamlayıcı pnömonektomi; erken mortalite; endikasyon; küçük hücreli dışı akciğer kanseri; sağkalım oranı.

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Completion pneumonectomy (CP) is defined as the complete removal of remaining lung after an ipsilateral partial pulmonary resection.[1] It has higher morbidity and mortality than standard pneumonectomy.[2] Completion pneumonectomy for non-small cell lung cancer (NSCLC) can be performed due to malignant or non-malignant causes. It is performed for malignant disease because of local recurrence or a second primary cancer. On the other hand, it is also performed for non-malignant causes such as early bronchopleural fistula (BPF), lobar torsion or anastomotic dehiscence after sleeve lobectomy.

Nowadays, the number of CPs is increasing with the increase in the number of bronchoplasty techniques and limited lung resections in the treatment of lung cancer. The ratio of CP in all pneumonectomies ranges from 5 to 16.4% at recent studies[2-9] and it is often preferred in malignant etiologies.[2-4] In this retrospective single-center study, we aimed to review the indications and outcomes of CP after primary resection due to NSCLC.

PATIENTS AND METHODS

A total of 1965 anatomical pulmonary resections were performed due to NSCLC between January 2004 and August 2017 including 452 pneumonectomies at University of Health Sciences Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital. Among these, CP was performed on 29 patients (24 males, 5 females; mean age 59.9±7.1 years; range, 45 to 72 years). These patients represented 6.4% of all pneumonectomies performed during the same period. The results were analyzed for two main indications for CP: Elective CP (ECP) was performed for local recurrence of a malignant tumor or second primary lung cancer, and rescue CP (RCP) was performed for major bronchopulmonary complications after initial lung resection for cancer. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The records of these patients were analyzed retrospectively with regard to demographic characteristics, preoperative risk factors (comorbidity and neoadjuvant treatment), pulmonary functions, indication for operation, operating time for both surgeries, duration of hospital stay, operative complications, operative findings, histology, lymph node metastasis, tumor size, stages of lung cancer, adjuvant therapy, the state of complete (R_0) and incomplete (R_1) resection at the surgical margin, extent of operation, operative mortality, postoperative major cardiopulmonary morbidity and survival.

All data were obtained from hospital records, operation reports, patient charts, and national survival database. All patients were analyzed in terms of operative mortality and survival. The survival was calculated as the duration between the days of CP and death. The factors affecting survival and mortality were assessed statistically. Cardiac disease, hypertension, diabetes mellitus, history of tuberculosis and chronic obstructive pulmonary disease (COPD) were recorded as comorbidities. Neoadjuvant treatment was defined as a preoperative risk factor in addition to comorbidities. When preoperative assessment for patients with pulmonary function tests was considered insufficient, quantitative perfusion scintigraphy, maximal oxygen consumption and stair climbing tests were performed.

All patients were staged according to the eighth edition of the Tumor, Node, Metastasis classification system for lung cancer described by International Association for the Study of Lung Cancer.[10]

The distinctive criteria proposed by Martini and Melamed[11] were used to distinguish between a local recurrence or metastasis and a second primary lung cancer.

Two main procedures were performed for bronchial closure depending on surgeon's preference. Mechanical closure was performed using automatic bronchial stapler (TA™ 30-4.8, Autosuture, US Surgical, Norwalk, Connecticut, USA) or 2/0 or 3/0 monofilament polypropylene non-absorbable suture (Prolene®, Ethicon, Inc., Somerville, NJ, USA) was used for the patients who underwent manual closure. In patients with potential risk for BPF (right pneumonectomy, neoadjuvant therapy, tuberculosis history, diabetes mellitus, etc.), the bronchial stump was supported by tissue flaps like parietal pleura, mediastinal adipose tissue, omentum or autologous fibrin sealant (Vivostat®, Vivostat A/S, Alleroed, Denmark). To achieve a complete resection, additional procedures were performed such as intrapericardial procedures, chest wall resection and carinal sleeve resection. ECP was performed by extrapleural dissection in 20 patients and systematic mediastinal lymphadenectomy was performed in all. One patient underwent myoplasty and omentoplasty. The discharged patients were followed in the outpatient setting. All complications and mortalities were recorded. Retrograde approach (dissection of the vascular structures after dividing the bronchus first) was preferred when there were dense adhesions and fibrosis around the hilum.

Operative mortality included all intra- and postoperative deaths during hospitalization or within

Table 1. Demographics and main characteristics of study population

Characteristics	n	%	Mean±SD	Min-Max
Demographic criteria				
Total	29			
Gender				
Female	5	17.2		
Male	24	82.8		
Mean age (year)			59.9±7.1	
Smoking history				
Nonsmoker				
Current smoker				
Primary surgery characteristics				
Median operation time (hours)			5.3±1.3	
Median hospital length of stay (days)			8.4	1-20
Mean FEV_1 (%)			79.9±15.6	
Operation type				
Lobectomy	25	86.2		
Bilobectomy	3	10.3		
Lobectomy and segmentectomy	1	3.4		
Histology type				
Adenocarcinoma	10	34.5		
Squamous cell carcinoma	18	62.1		
Large cell carcinoma	1	3.4		
Completion pneumonectomy characteristics				
Median operation time (hours)			4.8±1.1	
Median length of hospital stay (days)			9.4	0-38
Mean FEV_1 (%)			62.8±19.3	
Mean duration between primary surgery and completion pneumonectomy (month)			31.2±53.8	0.03-288
Type of the completion pneumonectomy				
Elective completion pneumonectomy	19	65.5		
Rescue completion pneumonectomy	10	34.5		
Location of the completion pneumonectomy				
Right	16	55.2		
Left	13	44.8		
Upper lobe	12	41.4		
Lower lobe	17	58.6		
Number of comorbidities and risk factors	18	62.1		
Type of comorbidity and risk factors				
Neoadjuvant therapy	6	20.7		
Diabetes mellitus	4	13.8		
Chronic obstructive pulmonary disease	3	10.3		
Coronary artery disease	3	10.3		
Hypertension	1	3.4		
History of tuberculosis	1	3.4		

SD: Standard deviation; Min: Minimum; Max: Maximum; FEV_1: Forced expired volume in 1 second.

30 days after the CP, as well as the patients who were discharged earlier. Morbidity in this study was defined as cardiopulmonary complications that occurred during the hospitalization period after CP and included BPF, empyema, pneumonia, atelectasis, arrhythmia, myocardial infarction, respiratory failure necessitating mechanical ventilation for more than 48 hours and pulmonary embolism.

Statistical analysis

Statistical analyses were performed with Statistical Package for the Social Sciences version 20.0 software program (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean, standard deviations and percentages for qualitative variables. The Fisher's exact-two tailed test, Pearson's χ^2 test or binary logistic regression test was used to determine factors affecting mortality and survival. Survival was estimated using the Kaplan-Meier method. The comparison of survival between subgroups was calculated using the log-rank test. A *p* value of 0.05 or less was considered statistically significant.

RESULTS

During the study period, there were 29 patients who had CP due to primary NSCLC surgery and its urgent complications in our department. The demographics and the main characteristics of patients are given in Table 1. There were 16 patients (55.2%) aged 60 years and below where 13 patients (44.8%) aged above 60 years. Mean interval between the first operation and CP was 33 months (range, 10 to 74 months) for local recurrences and 174 months (range, 55 to 292 months) for second primary lung cancer.

In addition, 12 patients (41.4%) had comorbidities. In total, six patients (20.7%) underwent CP following neoadjuvant chemotherapy. These two patient groups were considered together as a preoperative risk group (62.1%). In addition, 11 patients (37.9%) received adjuvant chemotherapy.

Primary operation

The primary operation was performed in another center in two patients (6.9%). Indications included NSCLC in all patients. Patients' mean forced expired volume in 1 second (FEV_1) was 79.9±15.6%. Primary operation was on the right side in 16 patients (4 sleeve upper lobectomies, 2 sleeve inferior bilobectomies, 3 upper lobectomies, 5 lower lobectomies, 2 bilobectomies) and on the left side in 13 patients (1 sleeve upper lobectomy, 8 upper lobectomies, 3 lower lobectomies, 1 lower lobectomy plus lingulectomy). R_0 resection was achieved in 28 patients (96.5%). Median operation time was 5.1±1.3 hours.

The histological types are as follows: squamous cell carcinoma (n=18), adenocarcinoma (n=10), and large cell carcinoma (n=1). In terms of tumor and node status, 17 patients (58.6%) were T_1 and 20 patients (69%) were N_0. The mean tumor size was 3.2 cm (range, 0.5 to 7.5 cm). A total of 23 patients were stage I and II, while six patients were stage IIIA.

Completion pneumonectomy

There were 19 ECPs and 10 RCPs. The median interval between the primary operation and CP was 31.2 months (range, 0.03 to 288 months). Mean FEV_1 of the patients was 62.8±19.3%. Right CP was performed on 16 patients (55.2%) and left CP on 13 patients (44.8%). Intrapericardial dissection was required in 23 patients (79%). An extended resection included resection of the chest wall in two patients (6.9%), carinal sleeve in two patients (6.9%) and extrapleural dissection in 20 patients (69%). No patients had preoperative mediastinal lymph node metastasis, and mediastinoscopy was not performed in any patient. Mediastinal lymphadenectomy was completed in all ECP patients. All operations were performed through a posterolateral thoracotomy, using the previous skin incision. R_0 resection was achieved in 17 patients (89.5%) with ECP. Median operation time was 4.8±1.1 hours.

Indications for ECP included lung cancer in 19 patients (65.5%). Of these patients, 17 had recurrent lung cancer (89.5%), and two patients had second primary lung cancer (10.5%). In this group of patients, there were 11 squamous cell carcinomas and six adenocarcinomas. second primary lung cancer was defined as a second malignancy with a different cell type and other occurrence after more than two years from the primary resection. The cell type of the tumor at ECP changed from squamous cell carcinoma to adenocarcinoma in one patient at the second operation. Of the 19 patients who underwent CP due to NSCLC, 15 were stage I and II, while four were stage III. Sixteen patients were N_0, one patient was N_1 and two patients were N_2. The mean tumor size was 2.4 cm (range, 1 to 4.5 cm).

For RCP, five cases underwent the operation because of BPF, three cases because of bronchial anastomotic dehiscence of sleeve resection, one case because of lobar torsion and one case because of pulmonary destruction.

Morbidity

The overall morbidity after CP was 44.8% (Table 2). Seven patients had a BPF, one patient had an empyema,

Table 2. Main characteristics of postoperative mortality and morbidity for completion pneumonectomy

		Postoperative mortality			Postoperative morbidity		
	n	n	%	*p*	n	%	*p*
Total	29	7	24.1		13	44.8	
Gender				0.65			0.5
Female	5	1	20		2	40	
Male	24	6	25		7	29.2	
Age				**0.026**			0.35
≤60	16	1	6.2		4	25	
>60	13	6	46.2		5	38.5	
FEV_1 in %				0.63			0.57
≥60	12	3	25		4	33.3	
<60	17	4	23.5		5	29.4	
Type of the CP				0.46			**0.016**
ECP	19	4	21.1		5	26.3	
RCP	10	3	30		7	70	
Preoperative risk factors				**0.049**			0.7
Yes	18	6	33.3		9		
No	11	0	0		4		
Neoadjuvant therapy							0.62
Yes	6	1	16.7		2	33.3	
No	23	6	26.1		7	30.4	
Stage				0.47			**0.022**
I-II	15	4	26.7		4	26.7	
III	4	0	0		1	1.25	
RCP	10	3	30		8	80	
Histology type				0.55			0.47
Adenocarcinoma	11	3	27.3	0.63	4	36.4	0.35
Non-adenocarcinoma	18	4	22.2		5	27.8	
Right	16	4	25		4	25	
Left	13	3	23.1		5	38.5	
Location of the CP				0.63			0.59
Upper lobe	12	3	25		4	33.3	
Lower lobe	17	4	23.5		5	29.4	
Duration between primary surgery and CP				0.66			**0.016**
≤90 days	10	3	30		8	80	
>90 days	19	4	21.1		5	26.3	

FEV_1: Forced expired volume in 1 second; CP: Completion pneumonectomy; ECP: Elective completion pneumonectomy; RCP: Rescue completion pneumonectomy; Bold values: P<0.05.

three patients had prolonged mechanical ventilation (more than 48 hours), one patient had an arrhythmia, and one patient had pulmonary embolism. While the morbidity rate was 26.3% in ECP cases, it was 70% in RCP cases (p=0.016). When CP patients with lower lobectomy were compared to the other patients, postoperative morbidity was 29.4% and 33.3%, respectively (p=0.59). There was no significant effect of age, preoperative FEV1, comorbidity, adjuvant and neoadjuvant treatment, pneumonectomy side or histological type on morbidity.

Mortality

Intraoperative mortality was seen in two (6.9%) patients and they were both ECP patients. One patient died following bleeding and coronary artery ischemia,

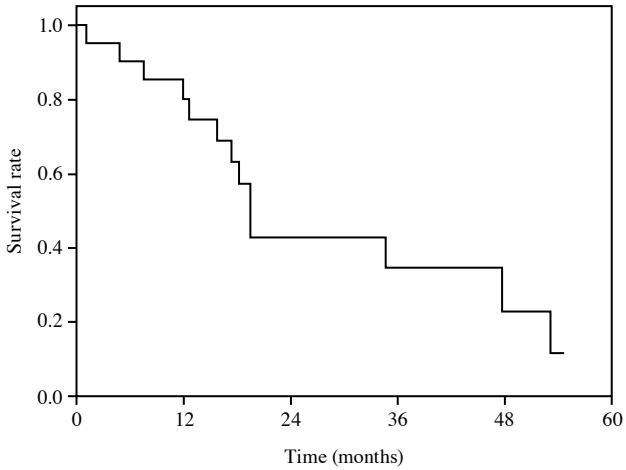

Figure 1. Overall survival of patients after completion pneumonectomy.

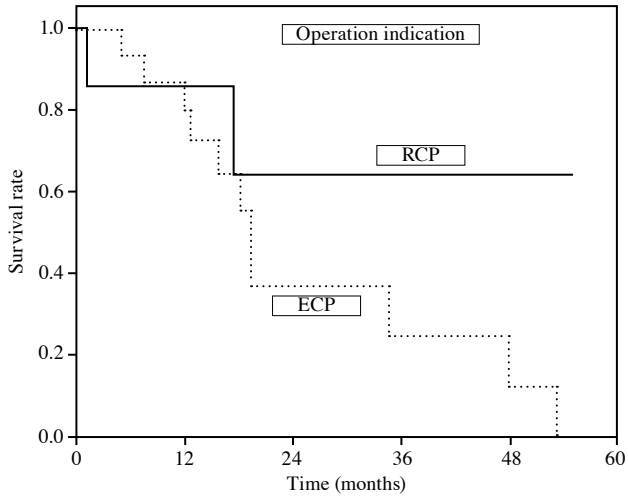

Figure 2. Actuarial survival curve for ECP and RCP patients (Log-rank test, P=0.24).

ECP: Elective completion pneumonectomy; RCP: Rescue completion pneumonectomy.

and the other died because of myocardial infarction. The overall operative mortality rate was 24.1% (n=7) (Table 2). Four patients were in the ECP group and three patients were in the RCP group. In the ECP group, other two patients died because of respiratory failure and myocardial infarction. In the RCP group, two patients died because of respiratory failure and empyema after BPF and other patient died because of myocardial infarction. The operative mortality of CP was 25% for the right side and 23% for the left side (p=0.63). Advanced age and presence of a preoperative risk factor had a significantly negative effect on postoperative mortality. While postoperative mortality rate was 6.2% in the patients aged 60 and

Table 3. Mortality and morbidity rates of completion pneumonectomy in different series

			Intraoperative mortality	Overall operative mortality	Morbidity
	Year	n	%	%	%
Current study	2017	29	6.9	24.1	44.8
Pan et al.[14]	2014	56	0	8.9	44.6
Puri et al.[33]	2013	35	NA	11	61
Tabutin et al.[18]	2012	46	NA	15	56
Cardillo et al.[3]	2012	165	0.6	10.5	54.5
Akın et al.[34]	2011	54	0	14.8	42.5
Sherwood et al.[13]	2005	26	0	23	46
Jungraithmayr et al.[4]	2004	86	0	20.2	37.2
Guggino et al.[20]	2004	55	0	16.4	58.5
Miller et al.[2]	2002	115	0.9	21	62.6
Verhagen et al.[6]	1996	37	0	16.2	29
Al-Kattan et al.[5]	1995	38	0	2.6	18
Massard et al.[24]	1995	37	5.4	10.8	24
Faber[17]	1993	27	4.3	4.3	0
McGovern et al.[29]	1988	113	5.3	12.4	38.1

NA: Not available.

below, this rate was 46.2% in the patients over the age of 60 (p=0.026). Although postoperative mortality was 33.3% in the presence of preoperative risk factor, there was no postoperative mortality in the remaining patients (p=0.049).

Follow-up

Follow-up was completed in all patients. Mean follow-up was 47 months (range, 0.7 to 335.8 months) after primary surgery and 15.7 months (range, 0 to 54.7 months) since CP. Including all 29 patients, median survival was 19.5 months, three- and four-year actuarial survival was 22.9% (Figure 1). For ECP patients, four-year actuarial survival was 12.3% and it was 64.3% for RCP patients (p=0.23) (Figure 2). The four-year survival was lower among patients receiving neoadjuvant therapy compared to those who did not (0% vs. 31.8%, p=0.003). The survival rates were lower in female patients (p=0.54), advanced age (p=0.15), left CP patients (p=0.42), CPs after lower lobectomy (p=0.42), R_1 resections (p=0.56) and N_2 diseases (p=0.7); however, it did not show any statistical significance. A review of the national database revealed that 20 patients (69%) died. During follow-up, disease progression occurred in nine patients (31%); four of them were local recurrence and five were distant metastasis. Seven of the patients with recurrent malignancy were in the group of ECP, and two in the group of RCP. Six patients (20.7%) were alive and disease-free at the end of follow-up.

DISCUSSION

Completion pneumonectomy is defined as the removal of the lung or what is left of it from a previous ipsilateral lung resection. It is one of the most difficult procedures and associated with high morbidity and mortality. Despite high postoperative risk, in NSCLC patients with local recurrence, survival is significantly higher compared to chemoradiotherapy.[12] Kasprzyk et al.[12] reported median survival time in patients with local recurrence treated with chemotherapy, chemoradiotherapy, and CP as 11.1 months, 14.4 months, and 27.1 months, respectively.

Completion pneumonectomy rate among standard pneumonectomies ranges from 5% to 16.4% in the different series (2.4-9). In our study, this rate was 6.4% similar to the results of recent studies. We found out that the patients who underwent ECP were more frequent particularly in the last 10 years. This can be associated with the use of more sensitive monitoring techniques and the increase in diagnosis of local recurrence or second primary lung cancer.

In our series, postoperative mortality rate (24.1%) was slightly higher than other published CP series (Table 3). The rate is reported between 2.6% and 23% in the literature.[5,13] It can be said that the difference between postoperative mortality rates depends on the selection of the patients. In fact, in our study, most of the patients were in advanced age group. Moreover, 62.1% of the patients were risky patients who either had comorbidity or received neoadjuvant therapy. In our patients, postoperative mortality was mostly caused by cardiopulmonary problems. The cause of mortality was myocardial infarction in three patients, BPF in two patients, and respiratory failure in other two patients. Another important issue that increased postoperative mortality was performing CP due to major pulmonary complication of the first operation. The morbidity and mortality rates are much higher in RCP patients than in ECP patients. Although this difference was not statistically significant in our study, it was approximately one and a half times more for RCP (30% vs. 21.1%). Pan et al.[14] found postoperative mortality of 27.3% and morbidity of 90.9% in RCP patients. This is parallel to our RCP patients with a postoperative mortality rate of 30% and morbidity of 70%. Likewise, Muysoms et al.[15] reported postoperative mortality as 37.5% in the patients who underwent RCP due to an early complication of primary operation. Terzi et al.[16] found an operative mortality of 57% if CP was performed for an early complication of sleeve resections.

Complication rates after CP are quite high. In our study, postoperative major cardiopulmonary complication rate was 44.8%. In different studies, this rate is reported in a wide range from 0 to 62.6% (Table 3).[2,17] The high mortality and morbidity rates in our series correlate with the outcomes of CP cases in the studies of Miller et al.[2] and Sherwood et al.[13] In these studies, mortality rates are 23% and 21%, and morbidity rates are 46% and 62.6%, respectively.

The most common complication after CP was BPF (7 of 29, 24.1%) in our study. Four of them were RCP patients (4/10, 40%) and three of them were ECP patients (3/19, 15.8%). Completion pneumonectomy was performed on two of four patients in RCP group due to BPF, and on the other two patients due to anastomotic dehiscence after sleeve resection. However, BPF developed in these patients also after pneumonectomy. Similar to our findings, in another study, BPF rate in RCP patients was 36.4%.[14] Bronchopleural fistula rate in CP patients is higher than standard pneumonectomy. In our institution, the rate of BPF after standard pneumonectomy for NSCLC

has been 11.3% for the past 17 years (53 of 467). When we reviewed predisposing factors in seven BPF patients from CP group, it was found that two patients received neoadjuvant therapy and one patient had previous tuberculosis history. Postoperative mortality was detected in three of the CP patients with BPF (3 of 7, 42.9%). The development of BPF is defined as a risk factor for postoperative mortality in our study. Similar results were reported for both CP and standard pneumonectomy in the literature.[18] In our series, BPF was seen mostly on the right side, same as in the literature (6 of 7 patients).[2,19,20] The cause of BPF after CP is mainly peripheral incision of the main bronchus compared to standard pneumonectomies as a result of hilar adhesions.[21] Supporting the bronchial stump with tissue flaps is a useful surgical technique to prevent fistula particularly in right pneumonectomies, in patients receiving neoadjuvant therapy, and in patients with diabetes. In our current practice, we mostly use parietal pleura and mediastinal adipose tissue to strengthen the bronchial stump in these patients.

Watanabe et al.[22] used and supported median sternotomy as a standard way for CP to control the pulmonary vessels better. However, resection using this method will be difficult in case of intensive hilar adhesion or chest wall resection. Zhang et al.[23] preferred the standard posterolateral approach, removing the fifth rib, without considering the primary incision. When dissection of pulmonary vessels gets difficult, intrapericardial manipulation should be preferred as a safer and more effective surgical technique.[15] It is seen that this method is used in 59.5% of the patients in one of the studies, and in 89% of the patients in another.[20,24] Although there was difference between two studies with regard to disease etiology and number, injury rate of main vessels was 16.2% in the group on whom intrapericardial dissection was performed with a percentage of 59%, and the incidence of vascular injury decreased to 10.9% in the method with intrapericardial ligation of 89%. Likewise, intrapericardial dissection was preferred in a great majority of the patients in our series due to hilar adhesion (79.3%). In this method, only one patient had severe hemorrhage, and afterwards mortality was observed as a result of intraoperative coronary artery ischemia (4.3%). In a study analyzing 60 CP patients and providing the intraoperative difficulty level, seven main vessel injuries, one esophageal injury, one diaphragm laceration, six pleural space contaminations, and four incomplete cancer resections were seen as a result of technical challenges.[25] In our study, there was no significant difference between the duration of primary surgical operation and CP operation (p=0.19). Similarly, duration of hospital stay was also close to each other, and there was no significant difference detected (p=0.7).

Higher operative mortality and morbidity was reported for right standard pneumonectomy.[26,27] Similarly, Jungraithmayr et al.[4] and Chataigner et al.[19] found that mortality rate was significantly higher on the right CP than on the left side. However, as in our study, some previous studies could not show a significant effect of right and left CP on postoperative mortality and morbidity.[2,3,14,23,28] Similar to the study of Miller et al.,[2] there was no significant difference in cardiopulmonary complications between right CP (56.2%) and left CP (30.8%) in our study (p=0.26). In addition, similar to this study, six of the seven BPF cases developed after the right CP operation. Tabutin et al.[18] found that operative mortality was significantly higher in CP patients with lower lobectomy. However, in our study, the rates were close to each other and there was no significant difference (23.5% vs. 25%, p=0.63). The factors that have a significantly negative effect on postoperative mortality were advanced age and presence of preoperative risk factor (p=0.026 and p=0.049, respectively). In particular, the negative effect of advanced age was emphasized in other reports as well.[2,14,18,19] Similar to our study, in addition to the negative effect of advanced age on mortality, Chataigner et al.[19] have also revealed the negative effects of additional risk factors, particularly the coronary artery disease. In our study, all three patients with preoperative coronary artery disease resulted in operative mortality.

Completion pneumonectomy might cause technical challenges and hemorrhage during operation, due to intensive hilar and intrapericardial adhesions as a result of previous operation or neoadjuvant therapy.[15,21,24,25,29] Also, intraoperative mortality risk is higher than standard pneumonectomy.[30] Massard et al.[24] and McGovern et al.[29] reported that the intraoperative mortality rate was 5%. We observed intraoperative mortality in two patients (6.9%), and both of them were ECP patients.

Postoperative mortality and morbidity in CP are higher than in standard pneumonectomy.[2,19,31] In our department, postoperative mortality rate of the patients who underwent standard pneumonectomy is 6.4%. Considering the postoperative mortality rate of 24.1% in CP patients, it can be suggested that careful selection of CP patients, good planning of operations, good evaluation of risks and benefits, detailed cardiopulmonary examinations in ECP, and consideration of possible other therapeutic options are

essential. Stereotactic body radiotherapy for medically inoperable or elderly patients has recently emerged as a safe and non-invasive alternative to CP.[32]

In our series, median survival for CP was 19.5 months, and both three- and four-year overall survival was 22.9%. While four-year survival for ECP was 12.3%, four-year survival was 64.3% (p=0.23) for the patients who underwent CP due to early complication of primary operation (RCP group). Median survival was significantly better in CP patients who had not received neoadjuvant therapy (34.6 months vs. 11.9 months, p=0.003). Puri et al.[33] reported this as 24 months for benign CP and 36 months for malignant CP. Parallel to our study, Tabutin et al.[18] stated that survival was significantly better particularly in young patients. Of the patients who underwent CP due to NSCLC, local or distant tumor recurrence was detected in seven patients (7/15, 46.7%), which was considered to be an important reason for the low survival rate.

Our study has some limitations. First, it was a retrospective and single-centered study. Second, there were several different surgical teams performing the surgeries.

In conclusion, based on the findings from our single-center study, we suggest that rescue completion pneumonectomy has a higher risk of mortality and morbidity than elective completion pneumonectomy. Although postoperative risk is higher in rescue completion pneumonectomy, survival rate is better than elective completion pneumonectomy. The most frightening complication after completion pneumonectomy is bronchopleural fistula. It is important to show utmost care during surgery and to take precautions to avoid fistula formation particularly in right completion pneumonectomy operations. Advanced age and presence of preoperative risk factors in completion pneumonectomy affect postoperative mortality negatively. However, in terms of long-term outcomes, elective completion pneumonectomy has relatively better results than chemoradiotherapy in the treatment of non-small cell lung cancer. Completion pneumonectomy patients should be carefully selected with a thorough preoperative evaluation. In completion pneumonectomy patients, preference of intrapericardial dissection may facilitate surgery, and pulmonary artery should be approached retrogradely in difficult dissections.

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