Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2021;46(4):1588-1595
DOI: 10.17826/cumj.980951

ARAŞTIRMA / RESEARCH

Effect of complications on survival after lung cancer surgery

Akciğer kanseri ameliyatı sonrası gelişen komplikasyonların sağkalıma etkisi

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Cukurova Medical Journal 2021;46(4):1588-1595

Abstract

Purpose: This study aims to investigate the effect of complications on survival after lung cancer surgery.
Materials and Methods: This is a retrospective study of 802 patients who underwent surgical operations for lung cancer at two centers between January 2002 and December 2019. All patients were retrospectively evaluated according to age, gender, cancer stage, surgical technique, biochemical tests, pulmonary function tests, pulmonary risk index, length of the hospital stay, and the existing number of complications.
Results: In total, 802 patients (%84 males, %16 females) with a mean age of 60 years (range 19-88 years) were included in the study. 5-year overall survival rate was 62.3%. 224 complications occurred in 180 patients (22.4%). The ten most common complications, respectively, were prolonged air leak (54), pneumonia (22), arrhythmia (19), respiratory failure (15), hemorrhage (17), atelectasis (10), pneumothorax-expansion defect (7), arrest (7) bronchopleural fistula (7), subileus-ileus (6). Cancer stage, the existing number of complications, advancing age, and tumor size are parameters that significantly affect survival. The occurs of one or more complications significantly adversely affects survival.
Conclusion: Although the morbidity and mortality of lung cancer surgery have decreased in recent years, it is still high. Advanced stage lung cancer, advancing age, enlargement of tumor size and occurs of complications that negatively affect survival. Careful preoperative preparation may play a role in increasing long-term survival, as well as preventing complications, and decreasing early mortality.
Keywords:. Lung cancer, postoperative, surgery, complications

Öz

Amaç: Bu çalışma ile akciğer kanseri ameliyatı sonrası komplikasyon gelişiminin sağ kalıma etkisini araştırmayı amaçladık.
Gereç ve Yöntem: Ocak 2002-Aralık 2019 tarihleri arasında iki merkezde operasyon uygulanan 802 akciğer kanserli olgular geriye dönük incelendi. Hastalarda, yaş, cinsiyet, kanser evresi, ameliyat tekniği, biyokimyasal değerleri, solunum fonksiyon testleri, pulmoner risk indeksi, postoperatif yatış süreleri ve gelişen komplikasyonlar analiz edildi.
Bulgular: 802 hastanın %84 ü erkek, %16 sı kadındı. Ortalama yaş 60 (19-88yaş) idi. Genel sağkalım 5 yıllık % 62,3 idi. 180 hastada (%22.4) 224 komplikasyon gelişti. En sık görülen on komplikasyon uzamış hava kaçağı (54), pnömoni (22), aritmi (19), solunum yetmezliği (15), hemoraji (17), atelektazi (10), pnömotoraks-expansiyon kusuru (7), arrest (7), bronkoplevral fistül(7), subileus-ileus(6) olarak sıralandı. Kanser evresi, komplikasyon gelişimi, ileri yaş ve tümör çapı anlamlı olarak sağ kalımı etkileyen parametrelerdir. Bir ve/veya birden fazla komplikasyon gelişmesi sağ kalımı önemli derecede kötü etkilemektedir.
Sonuç: Akciğer kanseri cerrahisinin morbidite ve mortalitesi son yıllarda azalmakla birlikte hala yüksektir. İleri akciğer kanseri evresi, yaşın ilerlemesi, tümör çapının büyümesi ve komplikasyon gelişmesi sağkalımı olumsuz etkilemektedir. Preoperatif dikkatli hazırlık, komplikasyon gelişmesini önlemek, erken dönem mortaliteyi azaltması yanında, uzun dönemde sağkalımı artırıcı rol oynayabilir.

Anahtar kelimeler: Akciğer kanseri, ameliyat sonrası, cerrahi, komplikasyonlar

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Geliş tarihi/Received: 10.08.2021 Kabul tarihi/Accepted: 22.10.2021 Çevrimiçi yayın/Published online: 19.11.2021

INTRODUCTION

Complications after lung cancer surgery increase morbidity and mortality. Complications occurred at a rate of approximately 30-40% in studies conducted on large patient series and databases[1, 2]. In our study, we aimed to reveal the variety, frequency, and affect of postoperative complications on survival in patients with lung cancer. A systematic complication classification that is accepted and frequently used in thoracic surgery has not yet in practical use. European Society of Thoracic Surgeons (ESTS) database was used for this purpose and this classification was named Thoracic Morbidity and Mortality (TM&M). Grade I-II includes minor complications, grade III-IV are major complications, and grade V evaluates as mortality[3]. Existent postoperative complications are the most important cause of early mortality.

Also, we planned this study to investigate its affect on late survival. The most common complication in thoracic surgery is pain. Due to the expected and subjective measurement of pain, we recorded the complications other than pain and examined its affect on survival with multivariate analysis. The stage of the disease is the most important factor in determining survival outcome in patients with lung cancer. By documenting the cancer stage, age, gender, FEV_1, FEV_1/FVC ratio, tumor size, pulmonary risk index, and existing number of complications, we aimed to reveal the effective ones.

MATERIALS AND METHODS

Primary lung cancer cases who underwent surgery and followed up in two university hospitals were retrospectively analyzed. Our study was approved by the ethics committee of bolu abant izzet baysal medical faculty with the date 02.02.2021 and the decision number 2021(30). Age, gender, cancer stage, surgical technique, biochemical test, pulmonary function tests, pulmonary risk index (PRI), length of postoperative hospital stay, and existing number of complications of 802 patients with lung cancer who underwent surgical operation between January 2002 and December 2019 were analyzed. The frequency of complications and their affect on survival were evaluated.

Preoperative evaluation

Preoperative radiological chest radiography and computed tomography imaging were performed in all patients. PET-CT has been routinely performed in recent years. Whole blood analysis, biochemical tests, and respiratory function tests were performed. If deemed necessary, advanced respiratory and cardiac assessment was performed. To determine the mediastinal staging of patients was performed by mediastinoscopy, except for patients whose peripheral diameters of 3 cm or less and without mediastinal lymph node involvement on PET-CT. Patients with N2 stage in the preoperative period were referred to the oncology clinic for neoadjuvant and/or oncological treatment. Surgery was undergone in eligible patients after neoadjuvant therapy.

Postoperative follow up

The patients were seen in the outpatient clinic every 3 months. Chest radiography and biochemical tests were performed at each control. After surgery, tomography scans were conducted every 6 months for the first 2 years and then once a year. Treatment responses of patients who received adjuvant oncological treatment were assessed at the appropriate time by PET-CT. All the patients who were operated on were referred to the oncology outpatient clinic.

Chemotherapy and/or radiotherapy treatment was given for patients with N1, N2 stage diseases and those with a tumor diameter greater than 4 cm and other appropriate indications. There were many different types of treatments initiated in different oncology clinics, so oncological treatment effect and disease-free survival times were not included in this study. During these follow-ups, obtained medical data of the patients were recorded.

Statistical analysis

Descriptive analyses are presented as counts with percentages. We carried out Kaplan-Meier survival analyses of our lung cancer patients for 5 years period. P value under 0.05 was considered as signs. After general survival analyses, we assessed grade, tumor widening, pulmonary risk index, age, gender affect on patients survival. We also assessed correlations between survival status and age, gender, complications (zero, one, or more) tumor grade, tumor wide, FEV_1, FEV_1/FVC, and pulmonary risk index. Linear regression analyses were conducted for survival predictors.

RESULTS

In total, 802 patients (%84 males, %16 females) with a median age of 60 years (range 19-88 years) were included in the study. Out of total 802 patients, 606 (%76) underwent thoracotomy, 160 (%19.5) VATS approach (video-assisted thoracoscopic surgery), and 36 (%4.5) hybrid technique. While the tumor diameter is on average 2.94 cm, its range varies between 0-20 cm. The mean FEV_1 level was measured as %80.82 (Table 1). The 5-year survival rate was %62.3. As a result of our study, we found overall survival was 127.00±35.66 months, with a 95% confidence interval: 57.037-196.96. Median survival was 127.00 months (confidence interval 57-196 months) (Figure 1). In our study, we observed that while gender did not significantly affect survival, more complications developed in the male gender (Figure 2). Survival was significantly lower in patients with complications ($p<0.0001$), especially in patients suffering more than one complication, the median survival was 31 months (CI 5.15-56.84) (Figure 3).

Table 1. Patient characteristics

Variable		**(mean±sd, n, %)**
Gender		
	Male	674, %84
	Female	128, %16
Surgical technique		
	Thoracotomy	606, %76
	VATS	160, %19.5
	Hybrid	36, %4,5
Age (year)		60 (19-88)
Diameter of tumor (cm)		2.94 (0-20)
FEV_1		%80,82
Length of hospital stay (day)		7,56±6,15
Stage		
	I	335, %42
	II	295, %37
	III	148, %18.5
	IV	20, %2.5

Table 2. Lineer regression analysis on survive (R^2 13,9).

	Beta	**t**	**p**
Complication	-1.42	-2.59	,010*
Age	-1.79	-3,79	,000*
Tumor widening	-1,06	-2.104	,036*
Stage	-1.52	-3.021	,03*

*p<0.05

Table 3. Distribution of surgery types.

Surgery types	N	%
RUL	197	24.5
LUL	144	18.0
LLL	99	12.3
LP	82	10.2
RLL	77	9.6
RP	56	7.0
SL	50	6.2
RLBL	47	.6.0
RML	28	3.5
RUBL	22	2.7
Total	802	100

RUL: Right upper lobectomy, LUL: Left upper lobectomy, LLL:Left lower lobectomy, LP:Left pneumonectomy, RLL:Right lower lobectomy, RP:Right pneumonectomy, SL:Sublobar resection (wedge and segmentectomy), RLBL:Right lower bilobectomy, RML:Right middle lobectomy, RUBL:Right upper bilobectomy.

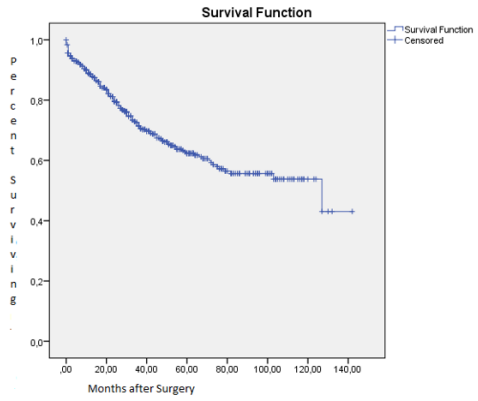

Figure 1. Overall survival chart.

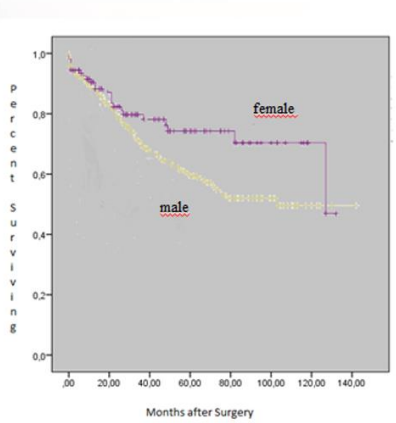

Figure 2. Survival chart by gender.

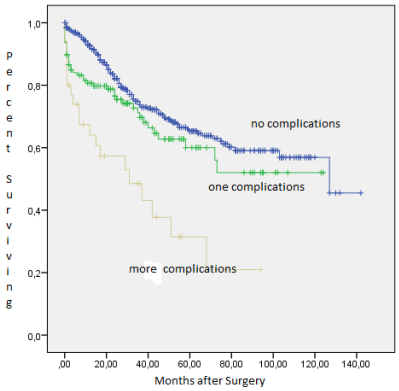

Figure 3. Complications (one or more) impact on survival.

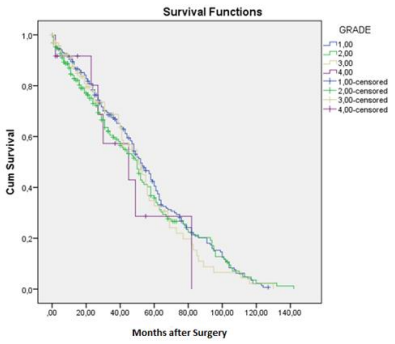

Figure 4. Survival chart by grade.

Table 4. Frequencies of complications

Complications	N	%
Prolonged Air Leakage	54	24.1
Pneumonia	22	9.8
Arrhythmia	19	8.5
Haemorrhage	17	7.6
Respiratory Failure	15	6.7
Atelectasis	10	4.5
Pneumothorax / Exp Defect	7	3.1
Arrest	7	3.1
Bronchopleural Fistula	7	3.1
Subileus-Ileus	6	2.7
Other	60	26.8
Total	224	100

Regression analysis showed that the cancer stage, the existence of complications, advancing age, and diameter of the tumor significantly affected survival (Table 2) (Figure 4). While PRI was important in overall survival analysis, it did not appear to be a predictor in linear regression analysis. While the FEV_1/FVC ratio does not significantly affect survival as a percentage, the higher FEV_1 level significantly increases survival. The most common surgery was right upper lobectomy (197, %24.5), the least was right upper bilobectomy (22, %2.7) (Table 3) Among all patients, 224 complications occurred in 180 (22.4%) patients. The ten most common complications, respectively, were prolonged air leak (54), pneumonia (22), arrhythmia (19), respiratory failure (15), hemorrhage (17), atelectasis (10), pneumothorax-expansion defect (7), arrest (7) bronchopleural fistula (7), subileus-ileus (6) (Table 4).

DISCUSSION

The optimal treatment of primary non-small cell lung cancer is surgical treatment. Although the morbidity and mortality of lung cancer surgery have decreased in recent years, it is still high. Morbidity and mortality continue to decrease with the development of minimally invasive surgical techniques and improvement in perioperative patient care. The frequency of complications varies in the range of approximately 30-40% in large series[2]. The morbidity rate of lobectomy surgery performed for lung cancer varies between 10-50%.[4] This large proportion of the morbidity could be due to the complications in the series were not regulated according to a standard. In our study, 224 complications occurred in 180 of 802 patients. Of the patients included in the study, 600 (%75) underwent thoracotomy, 160 (%20) with VATS, and 36 (%5) with hybrid technique.

In a study in which 4171 elderly patients (66-80 years) were included, 38.3% pulmonary, 24.5% cardiac, and 16.1% noncardiopulmonary complications were observed in patients who underwent lobectomy for stage I non-small-cell lung cancer. Factors associated with the development of complications were determined as being over the age of 75, have a male gender, the existence of a comorbid index, tumor size, and patients being treated outside of a training hospital. The 30-day hospital mortality rate has been reported as 4.2%[5]. In our study, we did not examine the elderly population separately. However, we reached the data that complications increase and survival decreases with advancing patient age.

Pain is a common complication after thoracotomy. It was reported at rates varying between 5% and 80%, depending on its definition and grade. On average, one out of every two patients develops significant pain. Some common causes of pain are intercostal nerve damage, bone injuries, ligament, and rib joint strains. Besides, skin, soft tissue, muscle, and intrapleural incisions increase pain in severity and extend beyond the original borders of the wound. Therefore, muscle-sparing incisions can reduce this pain. For these reasons, there is less pain in the VATS approach that limits rib retraction[6, 7]. In this study, the pain was not evaluated in the complication classification because it developed to different degrees in almost all patients.

There are different opinions in the main sources and literature regarding the frequency and classification of complications that develop after lung cancer surgery. In the study of Thorpe et al[8]. ARDS, anastomotic stenosis, pneumonia, bronchial stenosis, atelectasis, oesophagopleural fistula, persistent air leak, disease recurrence, anastomotic dehiscence, bronchopleural fistula, bronchial stenosis, empyema, haemothorax, pleuro-cutaneous fistula, lung torsion, and diaphragmatic hernia were listed as common complications. The ten most common complications in our study were listed as prolonged air leak, pneumonia, arrhythmia, respiratory failure, hemorrhage, atelectasis, pneumothorax-expansion defect, arrest, bronchopleural fistula, subileus-ileus. In our previous review article which was included in the Textbook, it was reported that the most common complication was prolonged air leak, consistent with our current study[7]. In another study, it was reported that prolonged air leak is the second most common postoperative complication after arrhythmia and it is the second most common reason for the delay in a discharge after postoperative pain[9].

Prolonged air leak after lung resections is one of the important causes of morbidity. Prolonged air leak over 5 days is the cause of 5.9% of the morbidity after segmentectomy, 9.6% of the morbidity after lobectomy, and 0.4% of the morbidity after pneumonectomy[10,22]. Varela et al.[11]. In their study, it was found that air leak over 5 days was associated with important pulmonary complications such as atelectasis, pneumonia, and empyema. In our data, we found prolonged air leak as the most common complication with 54 patients. Since our data includes a large 17-year period, the prolonged air leak has

considered 7 days in the first years and 5 days in the last years.

Postoperative hemorrhage is an important cause of morbidity-mortality in thoracic surgery patients. The need for at least 4 units of blood transfusion after lung resection is 2.9% in lobectomy and 3% in pneumonectomy. In most cases, the bleeding focus may not be found. Sirbu et al.[12]. In their study in which they examined the 1960 patients who underwent thoracotomy operation, found that the most common reason for rethoracotomy (52%) was bleeding. In the same study, it was observed that the source of bleeding was mediastinal and bronchial vessels (23%), intercostal vessels (17%), or pulmonary vessels (17%), but no bleeding focus was detected in the majority of cases (41%)[12].

Although arrhythmias are the most common complications after thoracic surgery operations, important cardiovascular complications such as myocardial infarction, heart failure, right-to-left shunt, thromboembolism, and heart herniation may develop[13]. Despite supraventricular arrhythmias are most common, ventricular arrhythmias may also develop at a lower rate (mean: 6%). Although varying in different series, atrial arrhythmias are observed between 8% and 37% of patients who underwent thoracotomy. Atrial fibrillation is the most common arrhythmia. Atrial arrhythmia develops with an average rate of 9.3% after simple exploration and biopsy, 11.6% after lobectomy, 18% after pneumonectomy, and 17.6% after esophageal surgery[14]. Arrhythmias that occur after thoracic surgery typically have the highest incidence on the second day, but they also occur in the first three days postoperatively. Arrhythmias revets to sinus rhythm within a week in 90% of patients.

The most common postoperative infection is postoperative pneumonia (POP). The incidence of POP development has been reported between 2.1-40% and the mortality rate between 19-67%[15,16,23]. Its pathophysiology and causative pathogens are not well studied. [15,16] Airway colonization is considered to be a potential risk factor[16]. Studies have been shown that airway bacterial colonization is approximately 40% in patients with lung cancer[15,16,17]. It was thought that pathogenic bacteria (Haemophilus influenza, Staphylococcus aureus, Streptococcus pneumonia, Moraxella catarrhalis, Pseudomonas aeruginosa, Klebsiella pneumonia, etc.) colonizing the airways spread during the operation and cause infection[16,17,18]. Bernard et al.[17]. reported that 50% of all POP were caused by streptococcal species and h. influenza, while Sok et al.[18]. showed that gram-negative pathogens are responsible for 71% of POP, while streptococcus species cause only 10% of the infection. Risk factors in the development of POP; smoking, COPD, Malignancy, comorbid disease, advanced age, etc.) POP generally develops within the first week after the operation[16].

Thorpe et al.[8] emphasized in their review of postoperative complications that thoracic surgery is experiencing a revival today. They attributed this to the increased number of surgical resections due to the diagnosis of lung cancer and the widespread use and development of VATS[8]. As a result, postoperative complications are common and have become very important.

Perioperative complications adversely affect survival in lung cancer[19,20,24]. Fernandez et al.[20] guided complications in the study of 29,899 patients registered in their database. Lobectomy was performed most frequently with 69%. The most common complications were reported as arrhythmia (14%), pneumonia (4.3%), reintubation (3.8%), delirium (2%), and acute kidney injury (1.4%). By dividing the development of complications into 3 periods, they identified the complications that worsen survival in each period. While 12 complications occurred in the first 90 days, four complications, delirium, blood transfusion, reintubation, and pneumonia have occurred between 3-18 months. After 18 months, sepsis and blood transfusion were found to be associated with a worse prognosis. As a consequence, the development of complications adversely affects survival. This affect depends on what the complication is and when the complication occurs[20]. In this study, the multivariate analysis of complications significantly worsened survival with tumor stage. Median survival drops to 31 months, especially when multiple complications occurred. In a study examining patients who underwent bilobectomy, it was reported that the development rate of complications was between lobectomy and pneumonectomy. It was emphasized that bilobectomy should be preferred over pneumonectomy. It was concluded that precautions should be taken against the complications of the pleural space and the development of bronchopleural fistula[21]. In our clinic, we prefer bilobectomy rather than pneumonectomy.

In conclusion, despite the morbidity and mortality rates of lung cancer surgery have decreased in recent

years, they are still high. Advanced lung cancer stage, advancing age, increase of the diameter of the tumor and occur of complications negatively affect on survival. This situation requires more attention to prevent complications. Careful preparation in the preoperative period and preventing complications can play a role in decreasing early mortality and increasing long-term survival.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AK, OY, AT; Veri toplama: MÜ, KK, AT; Veri analizi ve yorumlama: İS, EE, MÜ; Yazı taslağı: OY, AK; İçeriğin eleştirel incelenmesi: OY, AK; Son onay ve sorumluluk: OY, AK, EE, İS, MÜ, AT, KK; Teknik ve malzeme desteği: İS, EE; Süpervizyon: EE, KK, AT; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Bolu Abant İzzet Baysal Üniversitesi Klinik Araştırmalar Etik Kurulundan 02.02.2021 tarih ve 2021/30 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar bu makale ile bağlantılı olarak çıkar çatışması ilan etmediler ve açıklanan materyal başka bir yerde yayınlanmak üzere yayınlanmadı veya değerlendirilmedi.
Finansal Destek: Yazarlar bu makalenin araştırılması ve/veya yazarlığı için maddi destek almamışlardır.
Yazarın Notu: Bu çalışma Bolu Abant İzzet Baysal Üniversitesi'nde yapılmıştır.

Author Contributions: Concept/Design : AK, OY, AT; Data acquisition: MÜ, KK, AT; Data analysis and interpretation: İS, EE, MÜ; Drafting manuscript: OY, AK; Critical revision of manuscript: OY, AK; Final approval and accountability: OY, AK, EE, İS, MÜ, AT, KK; Technical or material support: İS, EE; Supervision: EE, KK, AT; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee with the decision dated 02.02.2021 and numbered 2021/30.
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors declared no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.
Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.
Acknowledgement: This study was conducted at Bolu Abant Izzet Baysal University.

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