Factors Affecting Survival in Early–Stage Lung Cancer other than Subtype and Stage

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ABSTRACT

Objective: Main factors affecting survival in lung cancer are known to be histopathological subtype and stage. In this study, we aimed to uncover factors affecting long-term outcomes in early-stage lung cancer treated with thoracoscopic anatomical resection.

Methods: The study took place between 2006 and 2018. A total of 204 patients who underwent thoracoscopic anatomical resection were evaluated retrospectively. Preoperative, perioperative, and postoperative parameters were evaluated, and their influence on survival was analyzed. Preoperative parameters, age, gender, and respiratory function tests — diffusing capacity of the lungs for carbon monoxide (DLCO) — are evaluated. Perioperative parameters included the type of anatomical resection and conversion to open thoracotomy. Postoperative parameters included major and minor complications, duration of hospital stay.

Results: A total of 204 patients were included in the study. The 5-year survival rate was 76.5%. Age 65 or younger is related to better 5-year survival (80.6% vs. 67.7%, p=0.008). Five-year survival of patients with a DLCO value greater than 80% is 83.2%, and it is 51.1% for a DLCO value equal to or lower than 80% (p=0.001). Hospital stay for 4 days or less is related to better 5-year survival (86% vs 69%, p=0.017).

Conclusion: In our study, it was determined that age, preoperative DLCO value, duration of hospital stay, and postoperative complication development were statistically significant in survival. However, conversion to open thoracotomy and the difference between segmentectomy and lobectomy did not have a specific effect on survival.

INTRODUCTION

Among all malignancies, lung cancer is one of the deadliest.[1] Surgery is the primary treatment option in early-stage lung cancer. However, the incidence of early-stage tumors is increasing due to advancing technology, making minimally invasive surgery a subject to overriding innovations. The use of minimally invasive methods in early-stage lung cancer is on the rise.

It has been shown that the 5-year survival in early-stage lung cancer is up to 94%,[2] while the overall 5-year survival of lung cancer stands at 23.6%.[3] However, there are other factors that affect survival in early-stage lung cancer beyond stage and histopathological subtype.

In our study, the effects of preoperative, perioperative, and postoperative parameters on survival were investigated by retrospectively collecting patients who were operated on for early-stage lung cancer. Preoperative determinant factors include age, gender, forced expiratory volume in 1 second (FEV1) value, and DLCO value. Perioperative parameters include conversion to open thoracotomy, and the type of anatomical resection such as segmentectomy of lobectomy. Postoperative parameters include major complications, minor complications, and duration of hospital stay.

MATERIALS AND METHODS

Selection of Patients

After excluding benign lesions, secondary lung carcinomas, and bronchiectasis, 204 patients who underwent video-assisted thoracoscopic surgery (VATS) anatomical resec-

Table 1. Preoperative determinant factors

	Minimum	Maximum	Mean
Age	23	82	60.9±9.7
FEV1 (ml)	1030	4570	2440±705
FEV1%	%43	%146	%90.9±21.5
DLCO%	% 42	%163	%91.8±24.3
Radiological tumor size (mm)	8	90	25.5±12.1
Sex	Male: 141 (69%)	Female: 63 (31%)	
Side	Right: 120 (84%)	Left: 84 (16%)	
Preoperative tissue diagnosis	Absent: 35 (17%)	Present: 169 (83%)	

DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: Forced expiratory volume in 1 second.

tion for primary lung cancer between 2006 and 2018 were investigated retrospectively. Preoperative, perioperative, and postoperative factors were evaluated, and their influence on survival was analyzed.

Patients who met the inclusion criteria were those diagnosed with primary lung carcinoma via bronchoscopy/ EBUS (Endobronchial Ultrasound) or TTFNB (Transthoracic Fine Needle Biopsy), patients operated on for a solitary pulmonary nodule and who underwent VATS anatomical resection after frozen section work-up, patients with no proven N2 disease and who did not receive neoadjuvant therapy, and patients with no suspected distant metastases via whole-body magnetic resonance imaging (MRI) or Positron Emission Tomography/Computed Tomography (PET/CT). In order to form a homogenous group, only patients who underwent thoracoscopic resection rather than open thoracotomy were included.

Ethical Considerations

This study is approved by the Ethics Committee of our Faculty by number 1347. The study procedure was prepared in accordance with the guidelines and regulations of The Code of Ethics of the World Medical Association (Declaration of Helsinki). In the study, the confidentiality of the patients was guaranteed. A detailed informed consent form was obtained from the patients prior to the operation.

Statistical Analysis

Student's T-test was preferred for parametric values, and the Mann-Whitney U test was preferred for non-parametric values for the comparison of continuous variables. The Kaplan-Meier method was used to calculate OS. Statistical significance was determined by the log-rank test. P values below 0.05 were considered to be statistically significant. Statistical analyses were performed with SPSS (Statistical Program for Social Sciences 25.0; IBM Corporation, Armonk, NY, USA).

I. Preoperative Determinant Factors

Preoperative parameters include age, gender, FEV1, and DLCO values. Preoperative parameters are shown in detail in Table 1.

II. Perioperative Determinant Factors

Segmentectomy, lobectomy, and pneumonectomy were performed on 34 (16.7%), 168 (82.8%), and 1 patient, respectively. A total of 12 patients underwent conversion. Of the 168 lobectomy procedures, 8 were VATS bronchial sleeve lobectomies.

Table 2. Distribution and rates of each complication

Complication	Number (n)	Percentage (%)
ARDS	4	2%
Chylothorax requiring re-operation	2	1%
Prolonged air leak requiring re-operation	10	4.9%
Hemorrhage requiring re-operation	1	0.5%
Atelectasis requiring bronchoscopy	4	2%
Empyema	3	1.5%
Pneumonia	30	14.7%
Atrial fibrillation	14	6.9%
Chylothorax not requiring re-operation	3	1.5%
Major Complications	24 (11.8%)	
Minor Complications	47 (23.0%)	

ARDS: Acute respiratory distress syndrome.

Table 3. Definitive histopathological diagnoses of patients

Histopathological Subtype	Count (n)	Percentage (%)
Adenocarcinoma	108	52.9
Squamous Cell Carcinoma	62	30.4
Carcinoid Tumors	18	8.8
Adenosquamous Carcinoma	8	3.9
Large Cell Carcinoma	2	1
Pleomorphic Carcinoma	3	1.5
Large Cell Neuroendocrine Tumor	3	1.5

III. Postoperative Determinant Factors

Of the 204 patients, 65% were complication-free. Complications were analyzed according to the Clavien-Dindo Classification. Atrial fibrillation, pneumonia, and chylothorax treated with a non-surgical approach belong to Clavien-Dindo grade II. Acute respiratory distress syndrome (ARDS) belongs to Clavien-Dindo grade IV. Chylothorax requiring re-operation and prolonged air leak requiring re-operation belong to Clavien-Dindo grade IIIb. Atelectasis requiring bronchoscopy and empyema belong to Clavien-Dindo grade IIIa. Complications listed as grade II or less are grouped as minor complications. Complications listed as Clavien-Dindo grade III or higher are grouped as major complications. The distribution and rates of each complication are depicted in Table 2.

Mean drainage duration was 5.87±5.3 (range:2-48) days and mean hospital stay was 7.29±5.6 (range:2-48) days.

Definitive histopathological diagnoses of patients are given in Table 3. Seven (3.7%) patients were stage IA1, 43 (23.0%) were IA2, 38 (20.3%) were IA3, 48 (25.7%) were IB, 7 (3.7%) were IIA, 26 (12.7%) were IIB, 15 (7.4%) were IIIA, and 3 (1.6%) were IVA.

RESULTS

I. Preoperative Parameters and Survival

Mean survival of whole group was calculated as 107±4.5 months and 5-year survival was 76.5%. Effects of preoperative parameters on survival are expressed in Table 4.

II. Perioperative Parameters and Survival

We had to convert to thoracotomy in 12 patients due to reasons like hemorrhage and adhesions. Mean survival of patients converted to open surgery was 94±17 months, and mean survival of patients whose operations were completed with VATS was 94±4 months. Their 5-year survival rates are 90.0% and 74.2% respectively. Difference between these groups were not statistically significant (p=0.595). Conversion to open surgery did not have any effect on long term survival as the mean survivals of each group were similar. Among these 12 patients, 1 patient experienced a major complication.

Thirty-four (16.7%) patients underwent segmentectomy and 168 (82.4%) patients underwent lobectomy. For segmentectomies, 5 year survival was 74%, mean survival was 94±9 months and for lebectomies 5 year survival was 76% and mean survival was 106±5 months. Difference was not

Table 4. Preoperative parameters and Survival

Preoperative parameters	5-year survival	p value
Gender		
Male	73.6%	0.103
Female	84.0%	
Age		
≤65	80.6%	0.008
>65	67.7%	
FEV1		
≤80%	66.1%	0.063
>80%	80.1%	
DLCO		
≤80%	51.1%	0.001
>80%	83.2%	

DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: forced expiratory volume in 1 second.
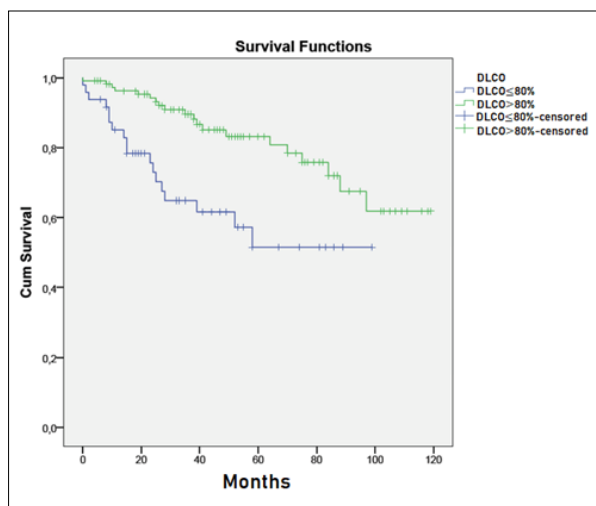
Figure 1. Cumulative survival probability of two groups differentiated by DLCO.

statistically significant (p=0.775) (Figure 1).

III. Postoperative Parameters and Survival

Mortality was observed at 48 patients (23.5%). Postoperative mortality occurred at 4 (2%) patients.

After excluding operative mortalities and comparing patients with or without major or minor complications, it is determined that patients who developed major complications had significantly worse survival (p=0.013). For patients who experienced major complications, 5-year survival was %67.3 and mean survival was 71±10 months, whereas they were 76.2% and 106±4 monthsfor patients discharged without a major complication (p=0.013). Survival of patients who developed minor complications were also studied and similar results were encountered. Five-year survival of these patients were 66.8% and mean survival was 76±5.4 months. On the other hand patients who did not experience any minor complications had a 5 year survival of 79.7% and mean survival of 113±5. This difference was statistically significant (p=0.044).

Mean hospital stay was 7.2±5.6 days. Among whole group, 35.8% was discharged at postoperative day 4 or earlier. Staying only for 4 days or less was related with significantly better survival (86% vs 69%, p=0.017)

DISCUSSION

In this study, we investigated the factors affecting survival for early-stage lung cancer, excluding tumor stage and histopathological subtype. No significant survival difference was observed between the segmentectomy group and the lobectomy group. Segmentectomy, being a parenchymal-sparing surgery compared to lobectomy, is often preferred for patients with small tumors and limited respiratory function.

Our study indicates that a hospital stay of four days or fewer is significantly associated with better survival. The

mean length of hospital stay for the patients in our study aligns with those reported in the current literature.[4] However, we are not aware of any studies in the literature reviews that clearly display and compare survival rates based on postoperative hospital stay lengths. Our study provides valuable insights into survival outcomes related to the length of stay.

The length of hospital stay and the occurrence of postoperative complications appear to be interrelated factors. Despite a reduction in postoperative complication rates due to advancements in technology and increased experience with minimally invasive surgery, rates are still around 30%.[5] Pneumonia emerged as the most common postoperative complication in our study. Mei et al. also identified pneumonia as the most common postoperative complication but did not discuss its impact on survival.[6] In line with our findings, Naada et al. observed that the occurrence of postoperative complications is linked to poorer survival outcomes.[7] Wang et al. highlighted that the 5-year survival rate for patients who developed a major complication is 66.6%, while it is 80.9% for those without major complications. They emphasized the statistical significance of this disparity and noted that any postoperative major complication is an indicator of poor prognosis.[8] Contrary to these studies, our research categorizes complications into major and minor, demonstrating that even minor complications adversely affect prognosis, akin to major complications.

Age is a prominent factor influencing survival in lung cancer. Our study indicates that patients aged 65 or younger fare better than their older counterparts, likely due to reduced performance, respiratory capacity, increased tissue fragility, and a propensity for thrombosis.[9,10] Nonetheless, surgical intervention in early-stage lung cancer can yield promising results for patients of advanced age.[11,12]

We observed that diminished preoperative respiratory function correlates with poorer prognosis. Although survival rate differences according to FEV1 values approach but do not achieve statistical significance, these differences are significant when considering DLCO values. Thus, DLCO is considered a more reliable indicator of respiratory function than FEV1. Berry et al. have similarly reported that a low FEV1 value does not significantly impact prognosis,[13] while low DLCO values are associated with a marked difference in outcomes.[14] Galata et al. also found that both preoperative FEV1 and DLCO values significantly influence survival, with DLCO serving as a more predictive measure than FEV1.[15]

With the advancement of technology and surgeons' increasing proficiency with minimally invasive techniques, the scope for such surgeries widens, while contraindications and related complications diminish.[16] Although opinions vary regarding the impact of conversion to open surgery on survival, a definitive consensus remains elusive.[17] A contributing factor to this debate is the enhanced capability to manage complications that may necessitate perioperative conversion, mitigating their impact on sur-

vival outcomes. Hence, a timely and well-executed thoracotomy should not be deemed a failure.[18] Our study demonstrates that patients who underwent conversion did not experience survival rates different from those whose operations were completed thoracoscopically. This is consistent with Park et al., who reported comparable survival and recurrence rates between patients requiring conversion and those managed solely with thoracoscopy. [19] Additionally, Sezen et al. contend that unexpected conversions do not significantly adversely affect long-term survival.[20] Common causes for unanticipated thoracotomy include reduced vascular elasticity due to aging, surgical experience, pleural adhesions, and mediastinal and hilar lymph node metastases.[21]

Limitations

This study presents several limitations. Firstly, the retrospective nature of the study may introduce potential bias. However, it is fortunate that patient records are meticulously maintained. Secondly, the sample size of this study is relatively small. Thirdly, the absence of recurrence-free survival data is another limitation of this study.

Conclusion

This study indicates that age, preoperative DLCO values, the presence of major or minor complications, and the duration of postoperative hospital stays are significant prognostic factors in early-stage lung cancer. Gender, preoperative FEV1 values, conversion to open thoracotomy, and the type of anatomical resection do not appear to significantly impact the prognosis in early-stage lung cancer. Further studies with larger sample sizes are warranted to corroborate the findings reported in this study.

Ethics Committee Approval

This study approved by the Istanbul University Istanbul Medical Faculty Ethics Committee (Date: 10.11.2017, Decision No: 1347).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.Ö., S.D., M.K.; Design: A.T., B.Ö., R.D.; Supervision: M.K., B.Ö., R.D.; Materials: S.E., B.C.; Data: S.E., S.D., B.Ö.; Analysis: S.E., S.D., A.T.; Literature search: B.Ç., R.D., A.T.; Writing: B.Ç., S.D.; Critical revision: R.D., A.T., M.K.

Conflict of Interest

None declared.

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Akciğer Kanserinde Histopatolojik Alt Tip ve Evre Dışında Prognoza Etki Eden Faktörler

Amaç: Akciğer kanserinde sağ kalımı etkileyen temel faktörlerin histopatolojik alt tip ve evre olduğu bilinmektedir. Bu çalışmada torakoskopik anatomik rezeksiyonla tedavi edilen erken evre akciğer kanserinde uzun dönem sonuçları etkileyen faktörleri ortaya çıkarmayı amaçladık.

Gereç ve Yöntem: Çalışma 2006-2018 yılları arasında gerçekleştirildi. Torakoskopik anatomik rezeksiyon uygulanan toplam 204 hasta retrospektif olarak değerlendirildi. Ameliyat öncesi, ameliyat sırası ve ameliyat sonrası parametreler değerlendirilerek sağ kalıma etkileri analiz edildi. Ameliyat öncesi parametreler, yaş, cinsiyet ve solunum fonksiyon testleri – akciğerlerin karbon monoksit (DLCO) kapasitesi idi. Perioperatif parametreler anatomik rezeksiyon tipi ve açık torakotomiye geçiş idi. Ameliyat sonrası parametreler majör ve minör komplikasyonlar, hastanede kalış süresi idi.

Bulgular: Çalışmaya toplam 204 hasta dahil edildi. Hastaların 5 yıllık sağkalımı %76,5 idi. 65 yaşında veya daha genç olan hataların sağkalımları daha iyi bulundu (%80.6 ve %67.7, p=0.008). DLCO değeri %80'in üzerinde olan hastaların 5 yıllık sağ kalımı %83,2 iken, DLCO değeri %80'e eşit veya daha düşük olan hastaların 5 yıllık sağ kalımı %51,1 olarak tespit edildi (p=0.001). Hastanede 4 gün veya daha az kalış, daha iyi 5 yıllık sağkalım ile ilişkili olduğu görüldü (%86 ve %69, p=0.017).

Sonuç: Çalışmamızda yaş, ameliyat öncesi DLCO değeri, hastanede kalış süresi, ameliyat sonrası komplikasyon gelişiminin sağkalım üzerinde istatistiksel olarak anlamlı olduğu belirlendi. Ancak açık torakotomiye geçiş ve segmentektomi-lobektomi arasındaki farkın sağkalım üzerine spesifik bir etkisi olmadığı görüldü.

Anahtar Sözcükler: Akciğer kanseri; lobektomi; sağkalım.