

Research Article

## THE IMPACT OF LYMPHOVASCULAR INVASION ON PROGNOSIS AND SURVIVAL IN OPERATED LUNG CANCER PATIENTS

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### ABSTRACT

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**Aim:** Currently, patients who undergo surgery in the early stages of lung cancer are still at risk of recurrence or metastasis. Lymphovascular Invasion (LVI) is a key entity in terms of tumor dissemination and carries critical importance in influencing disease recurrence, lymph node metastasis, distant metastasis and disease-free survival. In this study, we investigated the relationship between LVI and clinical and histopathologic parameters in patients who underwent lung resection for primary lung cancer and evaluated its effect on prognosis and survival.

**Materials and Methods:** A total of 111 patients who underwent surgical resection in our clinic for lung cancer in a fourteen-year period were included in the study. All histopathological parameters of the resected surgical specimens were recorded. Data concerning demographic characteristics and life expectancy of the patients were obtained from archival records.

**Results:** Majority of cases (95.5%) were male patients with a mean ( $\pm$ SD) age of  $62.24 \pm 8.44$  years. Approximately 13% of the patients were alive. Most frequently (63.06%) lobectomies were performed. LVI was detected at a higher rate in patients with Squamous cell carcinomas ( $p=0.005$ ). The incidence of LVI increased as both T factor ( $p=0.029$ ) and N factor ( $p=0.000$ ) increased. There was no significant correlation between LVI and survival ( $p=0.916$ ).

**Conclusion:** LVI is the first step of tumor invasion and metastasis and correlates with recurrence and survival rates for some cancer types such as gynecologic and head and neck tumors. The presence of LVI could thus be used as an indicator to offer adjuvant therapies to patients with resected NSCLC.

**Keywords:** Non-small cell lung cancer; Surgical resection; Lymphovascular invasion; Metastasis; Survival; Prognosis

## INTRODUCTION

Despite many advances in imaging techniques and cancer treatment in recent years, lung cancer remains the leading cause of cancer-related mortality worldwide (1). Based on the literature data 5-year overall survival rate has been reported to be only 15%. The greatest increase in life expectancy in lung cancer patients has been detected in those with localized disease rather than those with regional or distant metastases (2,3). Although medical treatments have improved, the only curative treatment for lung cancer is still lung resection (4-6). Therefore, it is still appropriate to offer surgical treatment as a chance even to patients who are considered to have a high surgical risk. However, only 20-25% of lung cancer patients are diagnosed as operable (7).

In the light of advances in diagnostic and therapeutic methods, the most important prognostic factor in lung cancer is the stage of the tumor. The fact that tumor type and stage are the main factors determining the choice of treatment method forms the basis of the approach to lung cancer today. Staging is important in predicting the prognosis of patients diagnosed with lung cancer (4). In addition to the evaluation of the primary tumor, the extent of spread to thoracic and extrathoracic organs determines its resectability (4,6). However, the pathological stage is the most significant prognostic factor for survival post-resection, and it forms the basis of guideline recommendations for adjuvant therapies (4). Pathological TNM staging is based on the characteristics of the primary tumor (T), the degree of lymph node involvement (N) and the presence or absence of metastases (M). The combination of T, N and M, ie: TNM, is used to assign the final overall tumor stage (I-IV). Treatment options also vary according to the stage of the tumor (8).

Lymphovascular Invasion (LVI) is the invasion of tumor cells into blood vessels or lymphatic vessels and has been shown to be the first step in local recurrence and distant spread of the tumor (5,6). Since LVI plays a significant role in local recurrence, lymph node metastasis, distant metastasis and disease-free survival; therefore, it is considered to be an important prognostic indicator (9,10). Studies have shown that it independently predicts early recurrence following resection of Non-Small Cell Lung Cancer (NSCLC) (4,10). It has even been suggested that adjuvant therapies should be considered in the presence of LVI, even in those without lymph node involvement, as in some gynecologic and head and neck tumors (11,12). In patients with NSCLC, age, gender, resection type, tumor diameter, lymph node dissection and LVI have been

considered among the factors affecting survival (13), and LVI has been reported to play an important role in poor prognosis and tumor dissemination (4). In this study, we investigated the relationship between LVI and clinical and histopathologic parameters in patients who underwent lung resection for primary lung cancer within a period of fourteen years and evaluated its impact on prognosis and survival.

## MATERIALS AND METHODS

This retrospective study included 111 patients who underwent anatomical resection for lung cancer at the Department of Thoracic Surgery, Aydın Adnan Menderes University Faculty of Medicine, between 1998 and 2012. Routine preoperative examinations of our patients included anamnesis, physical examination, biochemical analyses, echocardiography, thoracic imaging, pulmonary function tests and arterial blood gas analysis. Patients with limited respiratory function reserves, cardiac ischemia or arrhythmia underwent more extensive investigations including lung perfusion scintigraphy, echocardiography, and coronary angiography.

Rigid or flexible bronchoscopy was performed in all patients preoperatively to evaluate endobronchial structures and/or lesions. Mediastinoscopy was performed before thoracotomy in the presence of mediastinal lymph nodes with a short axis larger than 1.5 cm on thoracic tomography or in the presence of malignant involvement of mediastinal lymph nodes on Positron Emission Tomography. All patients who underwent thoracotomy were intubated using double-lumen endobronchial tube with an appropriate caliber and operated under general anesthesia with the patient in the lateral decubitus position. Perioperatively administration of low-molecular- weight heparin was started against the risk of embolism. Treatment with a first generation cephalosporin (cefazolin sodium) was initiated as prophylactic antibiotherapy. Systematic mediastinal dissection was performed together with resection and surgical intrathoracic staging was completed. A single drain was placed in the thorax after pneumonectomy and, apical and basal thoracic drains were placed in other surgical resections. All hemodynamically stable patients with adequate respiratory effort were extubated in the operating room. Patients with borderline respiratory function and hypoxia or hypercapnia were intubated and taken to the intensive care unit.

The resection materials of the patients were examined in the medical pathology laboratory of our hospital. All

histopathological parameters (type of material, tumor localization, laterality, tumor size, bronchial surgical margin, visceral pleural involvement, LVI, lymph node involvement, pTNM staging) were recorded (Figure 1). Demographic data and life expectancy of the patients included in the study were determined based on the data obtained from archival records. Histopathological parameters were arranged according to the 2021 World Health Organization (WHO) classification of Lung Tumors (14), which is currently used in the categorization of lung resection materials, the pTNM classification of American Joint Committee on Cancer 8th Edition (AJCC) (8), and the College of American Pathologists Cancer Protocols (CAPCP) (15) guidelines, which we frequently use in reporting to ensure that all pathology reports contain the necessary data elements for patient treatment and follow-up.

**Table 1.** Demographic and clinicopathological data of the patients

| Parameters                                  |                  |
|---------------------------------------------|------------------|
| <b>Age, years (mean <math>\pm</math>SD)</b> | 62.24 $\pm$ 8.44 |
| <b>Gender, N(%)</b>                         |                  |
| Male                                        | 106(95.5)        |
| Female                                      | 5(4.5)           |
| <b>Resection type, N(%)</b>                 |                  |
| Lobectomy/Bilobectomy                       | 84 (75.67)       |
| Pneumonectomy                               | 25 (22.52)       |
| Others                                      | 2 (1.81)         |
| <b>Tumor type, N(%)</b>                     |                  |
| Adenocarcinoma                              | 34(30.6)         |
| Squamous cell carcinoma                     | 68(61.3)         |
| Others                                      | 9(8.1)           |
| <b>T factor, N(%)</b>                       |                  |
| T1                                          | 17 (15.3)        |
| T2                                          | 63 (56.8)        |
| T3                                          | 19 (17.1)        |
| T4                                          | 12 (10.8)        |
| <b>N factor, N(%)</b>                       |                  |
| N0                                          | 62 (55.9)        |
| N1                                          | 39 (35.1)        |
| N2                                          | 10 (9)           |
| <b>Stage, N(%)</b>                          |                  |
| I                                           | 40 (36)          |
| II                                          | 42 (37.8)        |
| III                                         | 28 (25.2)        |
| IV                                          | 1 (0.9)          |
| <b>Lymphovascular invasion, N(%)</b>        |                  |
| Present                                     | 81 (73)          |
| Absent                                      | 30 (27)          |
| <b>Visceral pleural invasion, N(%)</b>      |                  |
| Present                                     | 42 (37.8)        |
| Absent                                      | 69 (62.2)        |
| <b>Survival, N(%)</b>                       |                  |
| (-)                                         | 14 (12.6)        |
| (+)                                         | 97 (87.4)        |
| <b>Total</b>                                | 111 (100)        |

## Statistical analysis

Statistical analysis of the data was performed using SPSS statistical analysis software program, Chi-square test was used to comparatively evaluate tumor type vs LVI, gender vs LVI, LVI vs N, LVI vs tumoral invasion of visceral pleura. Mann-Whitney U Test was employed to compare LVI vs stage of the tumor, and LVI vs T. Independent samples t-test was utilized to compare LVI vs overall survival of the patients. All data were presented as mean $\pm$ standard deviation. The level of statistical significance was accepted as  $p \leq 0.05$ .

## RESULTS

Our study population (n=111) with a mean age of 62.24 $\pm$ 8.44 years mostly (95.5%) consisted of male patients. Approximately 13% of the patients were still alive and 87% of them exited. Table 1 shows the demographic and clinicopathologic data of the patients.

Anatomical resection was performed in all patients including pneumonectomy in 25 (22.52%), bilobectomy in 14 (12.61%), lobectomy in 70 (63.06%), and segmentectomy in 2 (1.81%) patients. The resection types and their detailed distribution are shown in Table 2.

**Table 2.** Types of anatomical resections performed in patients

| Types of surgery               | N   | %    |
|--------------------------------|-----|------|
| <b>Right upper lobectomy</b>   | 19  | 17.1 |
| <b>Right upper bilobectomy</b> | 4   | 3.60 |
| <b>Right lower lobectomy</b>   | 20  | 18   |
| <b>Right lower bilobectomy</b> | 10  | 9    |
| <b>Right pneumonectomy</b>     | 6   | 5.4  |
| <b>Left upper lobectomy</b>    | 16  | 14.4 |
| <b>Left lower lobectomy</b>    | 15  | 13.5 |
| <b>Left pneumonectomy</b>      | 19  | 17.1 |
| <b>Segmentectomy</b>           | 2   | 1.8  |
| <b>Total</b>                   | 111 | 100  |

Besides, LVI was more frequently detected in cases with Squamous cell carcinoma (SCC) ( $p=0.005$ ). When the relationship between LVI and stage of the cancer was evaluated, we noted that the incidence of LVI increased with increasing T factor ( $p=0.029$ ). LVI was observed in 58% of T1, but in 83.3% of T4 patients (Table 3). When the relationship between LVI and N factor was evaluated, it was observed that the incidence of LVI increased as the N

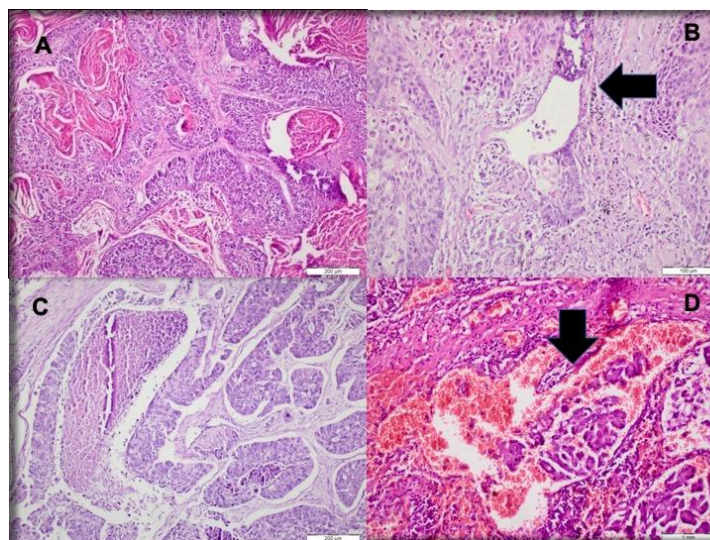


**Figure 1.** Photomicrographs of tumors with Squamous cell carcinoma (A, B) and Adenocarcinoma (C, D) morphology (H&E staining, X100 magnification) and examples of lymphovascular invasion (black arrows, H&E staining, X200 magnification)

factor increased ( $p=0.000$ ). A significant correlation was observed between stage of the cancer and LVI independent of tumor type. When LVI and stage of the cancer were compared, it was observed that LVI was more frequent as the stage of the cancer increased ( $p=0.005$ ). Besides, LVI was observed in 4 patients with stage IA, while in 20 patients with stage IIIA cancer (Table 3).

Survival in patients with LVI was not statistically significant according to the Kaplan-Meier test ( $p=0.916$ ). The effect of LVI on survival is shown in Figure 2.

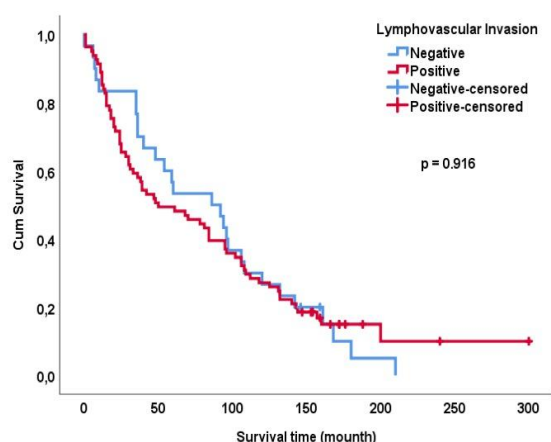


**Figure 2.** The effect of lymphovascular invasion on survival

## DISCUSSION

Lung cancer is the leading cause of cancer-related deaths. NSCLC, which accounts for approximately 85% of lung cancer cases, still disappointingly have short-term prognosis despite the currently advanced medical treatments (16). The etiology as well as the biological behavior of lung cancers is quite complex. Determining the causes and determinants of biological behavior is important in terms of treatment methods and prognosis (4,9). There are many studies on prognostic factors affecting survival in lung cancers and the three most important factors affecting prognosis are tumor type, tumor stage and patient performance status (17). Treatment options are evaluated considering the patients' histological diagnosis, general medical, and performance status, weight loss, clinical stage, of the disease and presence of co-morbidity. The dominant condition that determines the treatment of the disease is the stage of the tumor. However, performance status, weight loss and co-morbidity should also be considered. Surgery is the first treatment option in patients with good performance, weight loss and minimal comorbidity (18).

In surgical resections performed in lung cancer, segmentectomy is the minimal anatomical resection that can be performed on the lung. It is currently performed in T1 N0 cases with limited respiratory reserves (19). Okada et al. calculated a 5-year survival rate of 96.7% after segmentectomy for lesions smaller than 2 cm (20).

**Table 3.** Distribution of lymphovascular invasion according to clinicopathologic characteristics

| Criteria                               | Lymphovascular Invasion |              | P value |
|----------------------------------------|-------------------------|--------------|---------|
|                                        | Yes N(%)                | No N(%)      |         |
| <b>Age, years (mean±SD)</b>            | 61.90 ±8400             | 63.17± 8.655 | 0.486   |
| <b>Gender, N(%)</b>                    |                         |              |         |
| Male                                   | 78(73.6)                | 28(26.4)     | 0.520   |
| Female                                 | 3(60)                   | 2(40)        |         |
| <b>Tumor type, N(%)</b>                |                         |              |         |
| Adenocarcinoma                         | 19(55.9)                | 15(41,1)     | 0.005   |
| Squamous cell carcinoma                | 57(83.8)                | 11(16.2)     |         |
| Other                                  | 5(55.6)                 | 4(44.4)      |         |
| <b>T factor, N(%)</b>                  |                         |              |         |
| T1                                     | 10(58,8)                | 7(41,2)      | 0.029   |
| T2                                     | 44(69,8)                | 19(30,2)     |         |
| T3                                     | 17(89,5)                | 2(10,5)      |         |
| T4                                     | 10(83.3)                | 2(16,7)      |         |
| <b>N factor, N(%)</b>                  |                         |              |         |
| N0                                     | 35(56,5)                | 27(43.5)     | 0.000   |
| N1                                     | 36(93.3)                | 3(7.7)       |         |
| N2                                     | 10(100)                 | 0(0)         |         |
| <b>Stage, N(%)</b>                     |                         |              |         |
| I                                      | 20(24,6)                | 20(66)       | 0.005   |
| II                                     | 35(30,8)                | 7(33.3)      |         |
| III-I                                  | 26(32.9)                | 3(10)        |         |
| <b>Visceral pleural invasion, N(%)</b> |                         |              |         |
| Present                                | 33(40.7)                | 9(30)        | 0.349   |
| Absent                                 | 48(59.3)                | 21(70)       |         |
| <b>Survival</b>                        |                         |              |         |
| (-)                                    | 12(10.8)                | 2(1.8)       | 0.297   |
| (+)                                    | 69(62.2)                | 28(25.2)     |         |
| <b>Total</b>                           | 81(73)                  | 30(27)       |         |

Lobectomy is a common practice today and is the gold standard in early stage lung cancer (4). Treatment in patients with stage I and stage II NSCLC is primary resection. In stage III eligible patients, chemotherapy with a multimodal approach, chemoradiotherapy followed by surgical treatment can be applied (21). In cases where the tumor cannot be removed by lobectomy or sleeve resection, pneumonectomy may be required by removing the entire lung on one side. Pneumonectomy is frequently performed for central tumors located in the main bronchus, large proximal cancers extending beyond the fissure, tumors involving the interlobar vessels or lymph nodes, and invasion of the lymph nodes around the main bronchus (22). In a study evaluating the types of operations performed, pneumonectomy was reportedly carried out in 14.7%, bilobectomy in 13.7%, lobectomy in 70.6%, and segmentectomy 1.0% of the cases (23). Consistent with the literature data, lobectomy was the most common procedure performed in our study (63.06%).

GLOBOCAN data, which provides information about cancer statistics worldwide, and lung cancer statistical data of our country emphasize male gender predominance in lung cancer (24,25). The incidence of lung cancer increases with age and, peaks especially in the 6th and 7th decades of life (26). Accordingly, the predominance of male gender and a mean age of 62 years in the case series of our study were compatible with the literature data. The predominant histopathologic type in lung cancer varies greatly depending on smoking status, ethnicity and geographical location (27). When the distribution of lung cancer types in the population is analyzed, Squamous cell carcinoma (SCC) is the most common histologic type in Asian countries such as Korea and China, while Adenocarcinoma (ADC) is the most common type in the USA and Japan (28). In the literature, many studies have shown an increase in NSCLC cases in the last decade, especially in the prevalence of ADC (14, 29). Despite this increase in the prevalence of ADC, SCC remains the most

common tumor type in most countries including Türkiye (30). Supporting the tumor prevalence data in our country, we found a higher rate of SCC in our study compared to other studies.

Surgical resection with lymph node dissection constitutes the primary treatment for early-stage NSCLC. However, patients who undergo surgery at an early stage are still at risk for recurrence or metastasis. A high recurrence rate ranging from 24% to 73% has been reported in these patients (4-6). Adjuvant chemotherapy is given to patients with intrathoracic lymph node involvement and to those with large tumors without lymph node involvement. However, the survival benefit obtained from adjuvant chemotherapy after surgical treatment remains limited, ranging between 5% and 8% at 5 years postoperatively (4) which is thought to be due to the presence of cancer cells that migrated to the lymphovascular system before diagnosis and surgery (16). In these patients, new prognostic variables such as LVI need to be investigated and defined in order to both reduce the recurrence rate and to better classify those who are likely to benefit from adjuvant treatment.

Histopathologic parameters evaluated after examination of the resected material in NSCLC are very important in clinical follow-up, treatment and prognosis. In this context, the primary parameters that must be taken into consideration are as follows: tumor size, lymph node involvement, LVI and visceral pleural involvement (4,6,16). As a result of multivariate analyses including histological subtypes, tumor localization, gender, age and LVI, Gabor et al. found that LVI was an important prognostic factor in patients with NSCLC in whom the tumor was completely removed by surgical resection (31). Kawachi et al. investigated 402 early-stage NSCLC patients, and found pT factor, LVI and pleural invasion to be effective factors in terms of predicting one-year early-stage recurrence (32). Gao et al. also investigated important prognostic factors in 1826 patients with NSCLC who underwent complete resection of the cancerous tissue and reported that TNM staging and LVI were important prognostic factors (33). In the present study, the relationship of LVI, a significant factor in tumor dissemination, with other histopathological parameters was investigated, as well as its effect on survival and prognosis.

Limited number of studies have evaluated LVI status according to tumor subtype in NSCLC. One study reported an association between LVI and mortality or distant metastasis in patients with ADC, but not in SCC (4).

In another study including early stage NSCLC patients, no significant difference was found between ADC and SCC in terms of LVI ( $p=0.678$ ) (34). In a study from our country, the presence of LVI was reported more frequently in ADC (39.8%) rather than in SCC (28.8%), which is more common in our country. In this study, which involved 188 patients, the majority of cases were diagnosed with ADC (108, 57.4%) (35). In our study, LVI was detected at a significantly higher rate in SCC (83.8%), which is more common than ADC (55.3%). This situation may be due to the fact that the majority of cases included in our study were diagnosed with SCC.

One of the studies evaluating the relationship of LVI with clinicopathological parameters and survival indicated that LVI was strongly correlated with stage ( $p<0.001$ ), tumor size ( $p=0.004$ ) and recurrence ( $p<0.001$ ) and a significant decrease in recurrence-free and overall survival rates (34).

In another study, a correlation between LVI and lymph node and visceral pleural involvement was shown and LVI was associated with a worse overall survival in patients with resected NSCLC (4). In our study, a significant correlation was found between LVI and pT ( $p=0.029$ ), pN ( $p=0.000$ ) and stage ( $p=0.005$ ), and the frequency of LVI increased as the grade of these parameters increased. Contrary to some studies in the literature, no significant correlation was found between LVI and visceral pleural involvement ( $p=0.349$ ) and survival ( $p=0.916$ ). When examining the effect of LVI on survival, LVI was present in 71.1% of patients who survived. The effect of LVI on survival was not found to be statistically significant in these patients ( $p=0.297$ ). Based on the collective assessment of literature data, we can suggest that as a negative prognostic factor for metastasis and long-term survival especially in high-risk NSCLC patients. LVI induces tumor spread, and regional lymph node involvement (4,6,16,34,35). Although our findings show that survival is not statistically significantly worse in patients with LVI compared to those without, it is associated with tumor invasion and regional lymph node involvement. As a marker of the metastatic potential of the tumor, LVI can be used as a parameter in the evaluation of adjuvant therapies, especially when detected during histopathologic examination of the resection material in early stage NSCLC patients, even in the absence of lymph node involvement or overt metastasis (4). LVI is a key parameter for tumor dissemination and correlates with recurrence and survival rates for some cancer types such as gynecologic and head and neck tumors (5,11,12). Therefore, LVI is a promising area to be studied in future clinical trials on lung cancer and its use as a parameter

evaluating the efficacy of adjuvant therapy for eligible patient population according to this criterion may be considered.

## CONCLUSION

NSCLC is a malignancy with a poor prognosis and it is very well known that it is often associated with recurrence and metastasis. Individualized treatment combinations based on targeted therapy and immunotherapy in NSCLC have made great progress in the last decade. Therapies specifically targeting angiogenesis have made great progress and several drugs have been approved for clinical use. Favorable therapeutic effects have been achieved with the use of these drugs and the search for specific drugs targeting lymphangiogenesis has become a great potential (16). The combination of drugs targeting lymphangiogenesis with patient-specific treatment approaches based on targeted therapy and immunotherapy holds promise. LVI is a common metastasis route for NSCLC. In recent years, great progress has been made in research on neoplastic lymphangiogenesis in NSCLC. The results prove that LVI is an important prognostic factor for overall survival in NSCLC (16). As a result, in our study, we observed that LVI had no direct effect on survival. However, when evaluated together with pT, pN, tumor stage and tumor types, LVI was shown to exert an indirect effect on survival. LVI was found to be significantly more frequent in SCC's. In higher-grade and stage tumors, the incidence of LVI increases. While this increase is not statistically significant, survival rates do decrease. The presence of LVI could thus be used as an indicator to offer adjuvant therapies to patients with resected NSCLC.

This study has a number of limitations. First of all, it includes data from a single institution, which may affect its applicability to other patient populations. Secondly, adverse events that may affect survival during the prolonged follow-up period were not included in the analyses. Due to the restrictions imposed on the available data, the utilisation of multivariate statistical methods was not a viable option in the present study. The present study focuses on the relationship between LVI and clinical-pathological parameters, as well as survival. This scenario has the potential to compromise the capacity to identify all the variables that have a substantial impact on survival. Thirdly, we did not include data on smoking status, lung function, comorbidities of the patients and postoperative adjuvant therapy in the multivariate model that are known to influence survival in surgical patients undergoing lung resection. Some of these data were incomplete and

therefore unreliable because our hospital is providing healthcare services to a wide geographical region and some patients with missing data were referred from various regional hospitals to our hospital for surgical treatment of their lung cancer.

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## Authorship contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Salih Çokpınar, Serdar Şen, Nilgün Kanlıoğlu, Nesibe Kahraman Çetin, and Selda Şen. The first draft of the manuscript was written by Salih Çokpınar and Nesibe Kahraman Çetin. Finding and designing the topic of the project, statistics and control were carried out by Salih Çokpınar, Serdar Şen, Nesibe Kahraman Çetin, and İmran Kurt Ömürlü. All authors commented on previous versions of the manuscript, read and approved the final version of the manuscript.

## Data availability statement

All data used to support the findings of this study are included in the article.

## Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

## Ethics

This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (protocol no. 2024-228, Approval date: 2024/12/26). Individual consent for this retrospective analysis was waived.

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