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Middle lobe tumors and lymphovascular invasion as independent predictors of recurrence-free survival in stage I NSCLC

Mustafa Akyıl[1*] and Serkan Bayram[1]

Abstract

Background Recurrence and metastases are prevalent in lung cancer, contributing to a concerning rate of treatment failure. As a result, there is a pressing need for multivariate analyses of prognostic utility in non-small cell lung cancer (NSCLC). This study reports on the factors influencing metastasis and recurrence-free survival (RFS) in patients with clinical stage I NSCLC who have undergone anatomic lung resection.

Methods This study included patients diagnosed with stage I NSCLC who received surgical treatment at our institution between January 2016 and December 2022. A careful examination was conducted of the patients' demographic, clinical, radiological, and histopathological data. The prognostic value of the recorded parameters was assessed according to recurrence and/or metastasis, considering RFS during follow-up assessments.

Results Among the 616 patients included in this study, the average age was 63 ± 8.9 years, with 506 (82.1%) of patients being male. During a median follow-up period of 50.4 ± 23.7 months (ranging from 1 to 89 months), 79 patients (12.8%) experienced recurrence or metastasis, while 41 patients (6.7%) died. Multivariate analysis showed no significant differences ($p > 0.05$) regarding recurrence or metastasis development when considering demographic characteristics, tumor size, operation forms, histopathologic types involved, perineural and visceral pleural invasion status, and aspects of oncological treatment. Conversely, the presence of lymphovascular invasion ($p < 0.003$) and tumor localization in the middle node ($p < 0.045$) emerged as significant predictors of RFS.

Conclusion In patients with early-stage NSCLC, the presence of lymphovascular invasion and localization of the tumor in the middle lobe are independent predictors of RFS.

Keywords Lung cancer, Lymphovascular invasion, Middle lobe

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases, with only about 30% of these patients receiving an early diagnosis [1]. Despite advances in surgical techniques and adjuvant therapies, the rates of recurrence or metastasis within the first five years post-surgery remain concerningly high, ranging between 30% and 55% [2]. This underscores the critical need for insights into early-stage prognostic factors in order to improve follow-up strategies and ultimately, treatment outcomes.

The impact of tumor localization on survival in early-stage NSCLC remains controversial. One study by Kuo et al. shows that tumors located in the lower lobe are associated with poorer survival outcomes compared to those in the upper and middle lobes for stage IA and IB NSCLC [3]. Furthermore, a meta-analysis by Lee et al., involving 35,570 patients, found that tumors located in the upper lobe were linked to improved five-year survival rates compared to those in other lobes [4]. Although the middle lobe has been studied less frequently, it has distinct lymphatic drainage patterns involving the right peribronchial, right paratracheal, and subcarinal nodes, which may contribute to higher rates of lymph node metastasis and a poorer prognosis relative to other lobes [5, 6].

Lymphovascular invasion (LVI) is another critical prognostic factor in NSCLC and is often associated with adverse outcomes. Theoretically, LVI represents the presence of micrometastatic tumor cells within the vascular or lymphatic systems, enabling the spread of these cells to lymph nodes and distant organs. Sung et al. demonstrate that LVI significantly diminishes five-year RFS rates and increases the risk of nodal and distant metastases in T1-2N0 NSCLC patients [7]. Moreover, multiple studies have consistently identified LVI as an independent negative prognostic factor for both overall survival (OR) and RFS [8, 9].

Materials and methods

This study is a retrospective, single-center, observational study. It was designed in a teaching and research hospital recognized as a reference facility for chest diseases and thoracic surgery. Subjects were selected from daily operation notes, which are regularly reviewed by a thoracic surgery fellow in conjunction with a leading thoracic surgeon. This study focused on patients who underwent anatomic lung resection at our institution and were pathologically classified as stage I NSCLC [10]. Patients who died within the first month of their operation or those who were unable to maintain regular follow-up were excluded from the analysis, as illustrated in Fig. 1, which depicts a flowchart of the patients.

Organization of the thoracic surgery clinic and operations

In our hospital, surgery councils are responsible for all operation decisions and treatment management policies. These councils are composed primarily of thoracic surgeons, specialists in thoracic diseases, professors, and residents. Regular participants also include specialists from oncology, radiology, radiation oncology,

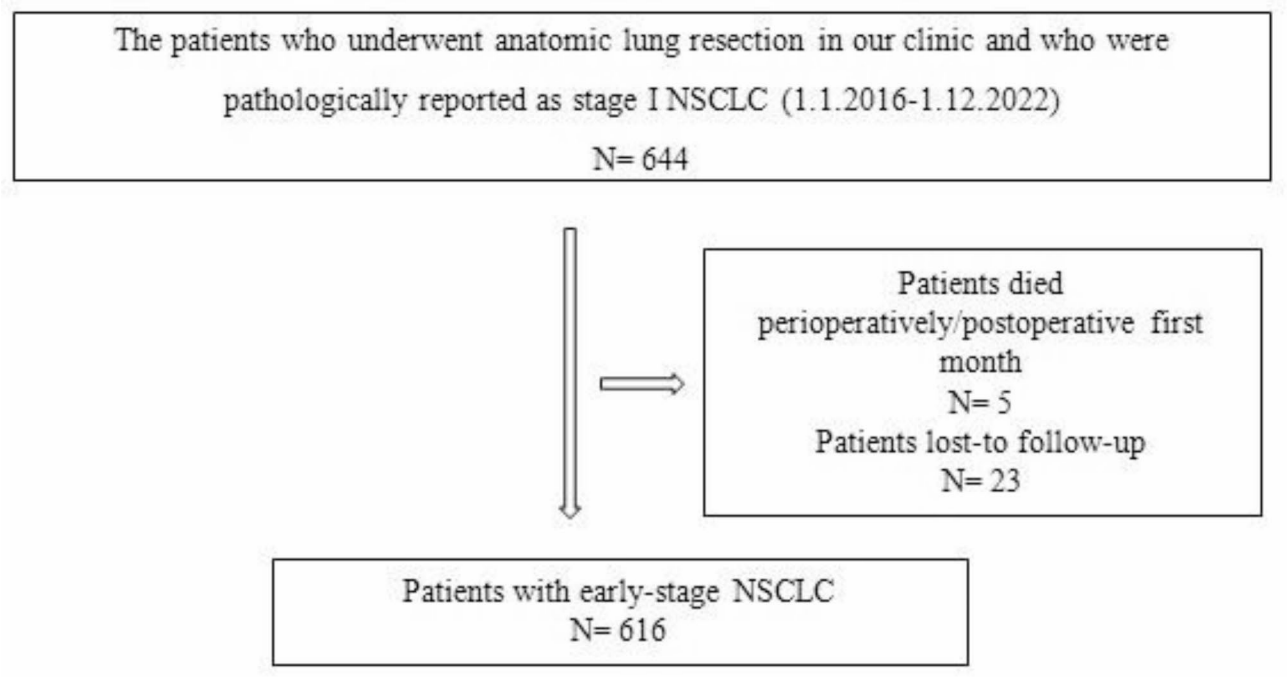

Fig. 1 Flowchart of the patients

nuclear medicine, and pathology. Consequently, operations are carried out by collaborative teams consisting of professors, specialists, and thoracic surgery residents. Follow-up care for some discharged patients is similarly determined by the council. In early-stage cases, patients are referred to the oncology department while continuing follow-up in our clinic. This protocol allows us to remain actively involved in the treatment trajectory of our diagnosed patients.

Recorded parameters

The parameters recorded in this study included PET-CT reports and the primary tumor's FDG involvement. We examined several values in the pathology reports including tumor size, tumor length, tumor extent, perineural invasion (PNI), visceral pleural invasion (VPI), lymphovascular invasion (LVI), and tumor subtype. Patients were classified into stages according to the TNM 8 classification [10].

Post-operative follow-up notes were reviewed to assess survival status as well as the presence of recurrence or metastasis. We investigated the cause of death for any patients who died following surgery but before follow-up in our clinic. Based on the presence of recurrence, patients were categorized into two groups: those with relapse and those without. Patients experiencing recurrence were further subdivided into two subgroups based on the primary tumor site. Recurrences that occurred in the same hemithorax, mediastinum or pleura were defined as local recurrences, while recurrences at all other sites were considered distant metastases [8]. In addition, RFS analysis was performed, incorporating patients who died without developing any metastases [8].

Statistical analysis

Statistical analyses were performed using the $\chi 2$ test, Fisher's exact test, or Student's ttest, as appropriate. RFS and OS were evaluated using the Kaplan–Meier method. RFS was defined as the time from surgery to recurrence, death, or the date of the last follow-up. OS was similarly defined as the time from surgery to death or the last follow-up, with the later being censored if the patient was still alive.

Results yielding a p-value of less than 0.15 in the univariate analysis were subsequently included in a multivariate analysis. For predicting RFS, analysis was carried out using the Cox proportional hazard univariate model. Multivariate analyses were also based on Cox's proportional hazards model.

All statistical analyses were performed using Statistical Analysis System version 9.1 (SAS Institute, Inc., Cary, NC, USA), and a p-value of less than 0.05 was considered statistically significant.

Results

Our study included 616 patients with a mean age of 63.6 ± 8.9 years; notably, 506 patients (82%) were male. The most prevalent site for tumor occurrence was the right upper lobe, accounting for 36% of cases. The mean tumor size measured 2.5 ± 1 (range: 0.5-4) cm and the average maximum standardized uptake value (SUVmax) was 7.8 ± 4.9 (NA-19). Our review of patient files indicated that 370 (60%) of patients underwent video-assisted thoracoscopic surgery, while 246 (40%) of patients underwent thoracotomy. Lobectomy emerged as the most frequently performed operation, constituting 91% of all operations. Post-operative complications were observed in only 8 (1.3%) patients.

Histopathological evaluation revealed that 333 patients (54%) were diagnosed with adenocarcinoma and 266 patients (43%) were diagnosed with squamous cell carcinoma. Additionally, PNI was documented in 42 patients (6.8%), LVI was observed in 60 patients (9.7%), and VPI was recorded in 154 patients (25%). According to pathological staging, 366 patients (59.4%) were classified with stage IA and 250 patients (40.6%) with stage IB (Table 1).

Oncological treatment was administered to 154 patients (25%). The reasons for instituting oncological therapy included VPI in 107 patients, vascular invasion (VI) in 29 patients, malignant differential tumor in 5 patients, and other unspecified causes in the remaining 13 patients. The overall median follow-up duration was 50.4 ± 23.7 months (range: 1–89 months), with surviving patients exhibiting an average follow-up duration of 52.2 ± 22.7 months (range: 13–89 months). During the period studied, 41 patients (6.7%) died.

Within the follow-up period, 79 (12.8%) patients developed recurrence and metastasis (Table 2). Relapse was recorded at a median time of 32 ± 24 months. Conversely, patients who did not experience relapse had a median follow-up period of 52 ± 23 months. RFS analysis was conducted by including the 27 patients who died without known metastasis (Table 3).

Evaluation of demographic characteristics, tumor size, surgical approaches, histopathological types, and incidence of perineural and visceral pleura alongside oncological treatment data, revealed no significant difference in RFS ($p > 0.05$). Univariate analysis revealed that tumors located in the right middle lobe ($p < 0.0001$) and the precense of lymphovascular invasion ($p = 0.001$) were significantly correlated with RFS (Table 4). Furthermore, other potential factors of limited significance ($p < 0.15$), such as age, tumors in the left upper lobe, squamous cell carcinoma, and T staging, did not demonstrate significant correlation. Nevertheless, middle lobe tumors (HR:1.143, CI: 1.049–1.093, $p = 0.023$) and lymphovascular invasion (HR:1.829, CI: 1.116–2.998, $p = 0.017$) were identified as independent correlates of RFS (Table 4) (Figs. 2 and 3).

Table 1 General characteristics of whole study population and of patients with recorded recurrence and/or metastasis

	Study population (*N* = 616, %)	**Relapse (*N* = 79, 12.8%)**
Age (year)	63.6 ± 8.9	63.4 ± 8.7
Gender		
Male	506 (82.1)	69 (87.3)
Female	110 (17.9)	10 (12.7)
Tumor localization		
RUL	222 (36)	32 (40.5)
RML	32 (5.2)	11 (13.9)
RLL	98 (15.9)	13 (16.4)
LUL	164 (26.6)	16 (20.2)
LLL	100 (16.2)	7 (8.9)
Tumor length (average cm)	2.5 ± 1 (0.6-4)	2.6 ± 1 (0.9-4)
PET SUVmax (average cm)	7.8 ± 4.9	8.5 ± 5.1
Operation type		
Segmentectomy	13 (2.1)	1 (1.3)
Lobectomy	560 (90.9)	73 (92.3)
Bilobectomy	13 (2.1)	1 (1.3)
Pneumonectomy	23 (3.7)	3 (3.8)
Sleeve resection	7 (1.1)	1 (1.3)
Operation		
VATS	370 (60)	46 (58)
Thoractomy	246 (40)	33 (42)
Complication		
Yes	8 (1.3)	1 (1.3)
No	608 (98.7)	78 (98.7)
Pathological Stage		
IA	366 (59.4)	45 (57)
IB	250 (40.6)	34 (43)
T factor		
T1a	69 (11.2)	11 (13.9)
T1b	166 (26.9)	18 (22.7)
T1c	129 (20.9)	15 (18.9)
T2a	252 (40.9)	35 (44.5)
Visceral pleural invasion		
Yes	154 (25)	17 (21.6)
No	462 (75)	62 (78.4)
Perineural invasion		
Yes	42 (6.8)	7 (8.9)
No	574 (93.2)	72 (91.1)
Lymphovascular invasion		
Yes	60 (9.7)	18 (22.8)
No	556 (90.3)	61 (77.2)
Chemotherapy		
Yes	154 (25)	28 (35.5)
No	462 (75)	51 (64.5)
Tumor histology		
Adenocarcinoma	333 (54)	45 (56.9)
SCC	266 (43.2)	33 (41.7)
Other	17 (2.8)	1 (1.4)
Adenocarcinoma subtype		
Pre-invasive	5 (1.5)	1 (2.4)
Minimal invasive	25 (7.5)	4 (8.8)
İnvasive	261 (78.4)	35 (77.7)
Other	42 (12.6)	5 (11.1)

Table 1 (continued)

	Study population (*N* = 616, %)	Relapse (*N* = 79, 12.8%)
Mortality		
Yes	41 (6.7)	14 (17.8)
No	575 (93.3)	65 (82.2)

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RML, middle lobe; RLL, right lower lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; VATS, video-assisted thoracoscopic surgery

Table 2 Relapse and Metastasis Localizations

Relapse localisation	N (*N* = 79, 12.8%)
Bone	12 (15.1)
Brain	12 (15.1)
Mediastinal lymph nodes	11 (13.9)
Parietal pleura	10 (12.6)
Local recurrence	10 (12.6)
RUL	6 (7.5)
LLL	4 (5.1)
LUL	3 (3.9)
RLL	3 (3.9)
Liver	3 (3.9)
Axillary lymph node	2 (2.5)
RML	2 (2.5)
Adrenal gland	1 (1.3)

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RML, middle lobe; RLL, right lower lobe; RUL

Table 3 Relapse-free survival status and percentages*

	Relapse–free Survival (*N* / Total)	%
6 months	14/616	0.022
1-year	2/616	0.003
1–2 year	8 /531	0.015
2–3 year	10/445	0.022
3–4 year	10/384	0.026
4–5 year	17/294	0.057
> 5 years	45/ 285	0.157

*Numbers and percentages are given with recorded patients vs. no censored patients

Discussion

Lung cancer is the leading cause of cancer-related death and is the most commonly diagnosed cancer type in males. In females, while the incidence rates are comparatively lower, lung cancer is second only to breast cancer in terms of both incidence and mortality [11]. Approximately 80% of lung cancers are categorized as NSCLC, with adenocarcinoma being the predominant subtype [1]. Despite the poor survival rate and high fatality associated with lung cancer, accurately diagnosing lung cancer at an early phase remains a challenge. Often, lung cancer is not detected as a standalone suspicion; rather, it is identified incidentally through clinical findings arising from various symptoms and diseases [12]. Patients diagnosed with early-stage NSCLC typically undergo complete lung resection. Data collected from the first five years post-surgery indicate that 30–55% of these patients experience recurrence, while survival rates following intervention ranges from 50 to 90% [13, 14].

Several clinical studies demonstrate that tumor location does not significantly impact survival in NSCLC patients with pathological stages I and II [15, 16]. Kuo et al. conducted a comparative analysis of early-stage IA and IB tumors located in the lower lobe versus those in the upper and middle lobes, concluding that the lower-lobe tumors are associated with poorer survival outcomes [3]. In a meta-analysis involving 35,570 patients, Lee and colleagues observe a higher 5-year survival rate in upper lobe tumors compared to those in other lobes [4]. In line with these findings, the incidence of nodal upstaging has been documented to be more pronounced in upper lobe tumors than in their lower lobe counterparts.

There is comparatively limited literature addressing middle lobe tumors. Our study specifically aims to explore lung cancer dynamics when tumors are located in the middle lobe. The infrequency of middle lobe tumor detection accounts for the scarcity of research on this subject. In an analysis by Handa Y et al. regarding middle lobe tumors, 82 out of 711 patients were found to have tumors localized in the middle lobe [6]. However, other studies have reported lower prevalence rates; for example, Mazza et al. found that middle lobe tumors constituted only 6% of tumors in an analysis of 808 patients [17]. Similarly, Rivera et al., in their study on right lung tumors, reported that middle lobe tumors represented merely 6.5% of 3,234 patients diagnosed with right-sided tumors [18]. In our study, we identified middle lobe tumors in 5.4% of the cohort.

The middle lobe's lymphatic drainage encompasses the right peribronchial, right paratracheal, periesophageal, and subcarinal nodes. Middle lobe tumors thus contains peribronchial lymph nodes in approximately half of all patients [5]. A middle lobe tumor may extend vascularly and invade earlier fissures due to its small size and the proximity of the other two lobes [18]. This anatomy may explain why many studies confirm a higher rate of lymph node metastasis and poorer prognosis in the right middle lobe compared to tumors detected in other lobes [6, 11]. Nevertheless, it is important to note that exceptions exist.

Table 4 Univariate and multivariate regression analysis for recurrence-free survival

	Univariate			Multivariate		
	HR	**CI (95%)**	***P***	**HR**	**CI (95%)**	***P***
Gender	0.707	0.387-0.1.293	0.261			
Age (year)	1.017	0.996–1.039	0.117	1.018	0.997–1.040	0.098
Tumor localization	0.867	0.764–0.984	**0.027**			
RUL and others	1.159	0.784–1.714	0.459	1.413	1.049–1.903	**0.023**
RML and others	1.660	1.262–2.182	**< 0.0001**	0.901	0.797–1.015	0.087
RLL and others	1.031	0.867–1.225	0.733			
LUL and others	0.890	0.791–1.001	0.062			
LLL and others	0.922	0.814–1.045	0.202			
Tumor length (average cm)	1.108	0.907–1.353	0.315			
PET SUVmax (average cm)	1.013	0.975–1.052	0.512			
Pathological Stage IA vs. IB	1.262	0.862–1.849	0.231			
T factor	1.143	0.956–1.366	0.143	1.090	0.908–1.310	0.355
T1a and others	0.698	0.373–1.307	0.261			
T1b and others	0.954	0.762–1.194	0.679			
T1c and others	0.982	0.832–1.159	0.826			
T2a and others	1.067	0.970–1.173	0.184			
Visceral pleural invasion	1.066	0.679–1.673	0.783			
Perineural invasion	1.511	0.787–2.898	0.215			
Lymphovascular invasion	2.156	1.364–2.418	**0.001**	1.829	1.116–2.998	**0.017**
Tumor histology Adenocarcinoma, SCC, other	0.745	0.518–1.072	0.113			
Tumor histology	1.326	0.901–1.951	0.152	0.882	0.724–1.3074	0.212
Adenocarcinoma and others	0.667	0.667–1.049	0.122			
SCC Other	0.894	0.736–1.085	0.256			

LLL: left lower lobe; LUL: left upper lobe; RML: middle lobe; RLL: right lower lobe; RUL: right upper lobe; SCC: squamous cell carcinoma; VATS: video-assisted thoracoscopic surgery

Miura et al. reported no significant difference in survival between patients with a middle lobe tumor and those with tumors located in other lobes [19]. In their study on the prognostic significance of tumor sites in T1-2 NSCLC patients, Whitson and colleagues reported that the middle lobectomy group experienced higher cancer-related mortality, although OS was similar across groups [16]. Our study identified middle lobe tumor location as a significant factor for RFS ($p < 0{,}045$). However, only 32 patients (5.2%) presented with middle-lobe tumors. Although this percentage may seem small relative to the overall patient population, we believe it suggests a focal point for multicenter studies involving larger cohorts.

Mazza et al. focused their investigation solely on right-lung tumors due to differences in lymph node dissection during left-lung tumor surgeries. Their findings indicated that advanced and aggressive right middle lobe tumors had lower survival rates when compared to upper and lower lobectomies of the right lung. In light of the improved survival rates associated with T1 and well-differentiated middle lobe tumors, they advocate for the standard approach of middle lobectomy [17].

In a study examining different surgical modalities in 861 patients with middle lobe tumor stage IA, Lv et al. found no significant difference in survival rates between the lobectomy and segmentectomy groups for tumors less than or equal to 1 cm, while those with tumors ranging from 1 to 2 cm exhibited better survival in the lobectomy group [20]. On the other hand, Lin et al. conducted a subgroup analysis based on tumor size, revealing similar prognostic results for lobectomy and segmentectomy across the patient groups (≤ 1, 1–2 and 2–3; for all, $p > 0.05$) [21]. The discrepancies between these two studies could be explained by the distinct patient populations studied, as Lv et al. excluded patients receiving adjuvant therapy while Lin et al. included such patients. Additional research suppports this explanation, indicating that adjuvant therapy influences postoperative prognosis for stage IA NSCLC patients [22, 23].

The prevalence of LVI presence in pathology samples of NSCLC ranges between 5% and 40% [24, 25]. LVI is conceptually understood as a distortion indicative of the stealth presence of micro-metastatic tumor cells within the circulatory system. These hidden cells are believed to cause metastases in lymph nodes and distant body parts. In an investigation of T1-2N0 NSCLC, Sung et al. included 381 patients who underwent resection. The study found a significant decrease in 5-year RFS in the presence of LVI, alongside an increased risk of lymph node and distant recurrence [7]. Numerous studies

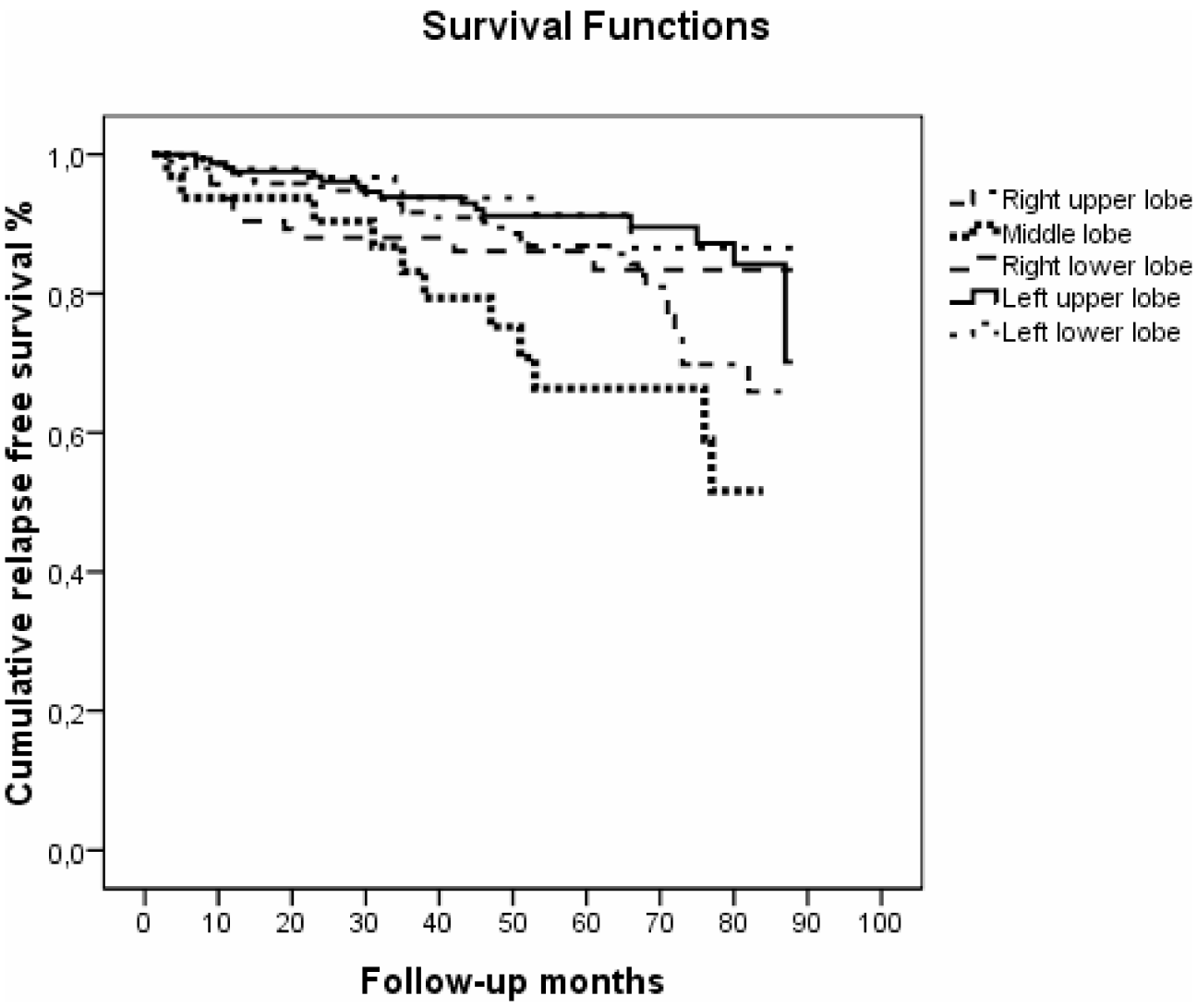

Fig. 2 Kaplan-Meier curve for relapse free-survival based on tumor localizations

demonstrate that LVI presence is a negative prognostic factor for both RFS and OS [8, 9, 26–28]. Furthermore, a meta-analysis focusing on early-stage NSCLC patients who underwent surgical resection revealed that VI presence indicates poor prognostic outcomes [29]. Our findigs align with this body of literature, reinforcing the significance of LVI presence ($p < 0.003$) in relation to recurrence and metastic progression.

Another research has explored the prognostic significance of LVI. Tsuchiya et al. conductied a comparison between stage IA NSCLC patients with LVI and those with non-LVI stage IB NSCLC, concluding that the prognostic outcomes for both cohorts was comparable [30]. Similarly, Cai et al. observed that within their group of stage I lung resection patients, those with stage IA NSCLC with LVI exhibited similar survival rates to those with stage IB NSCLC. They proposed that LVI could be a non-dimensional T definer which elevates stage IA diseases to stage IB [31]. Tumors of larger size are also acknowledged to be more likely to recur. Both VPI and tumor size are incorporated into the T category in TNM staging guidelines [9, 10]. The TNM classification system has redefined the T staging factor for patients with VPI, elevating it from T1 to T2a and advancing stage tumor from IA to IB [32]. A group of scientists have also recommended addition of LVI into T stage classification [33].

The National Comprehensive Cancer Network (NCCN) Guidelines emphasize the importance of implementing a regular follow-up strategy for stage IA patients with LVI [34]. However, studies focusing on the potential for improving the survival rate of patients with stage IB NSCLC, it is recommended that those exhibiting high-risk factors should be considered for adjuvant chemotherapy [35]. Evidence indicates that systemic adjuvant therapy yields improved survival outcomes for stage IB NSCLC patients with LVI and VPI compared to regular

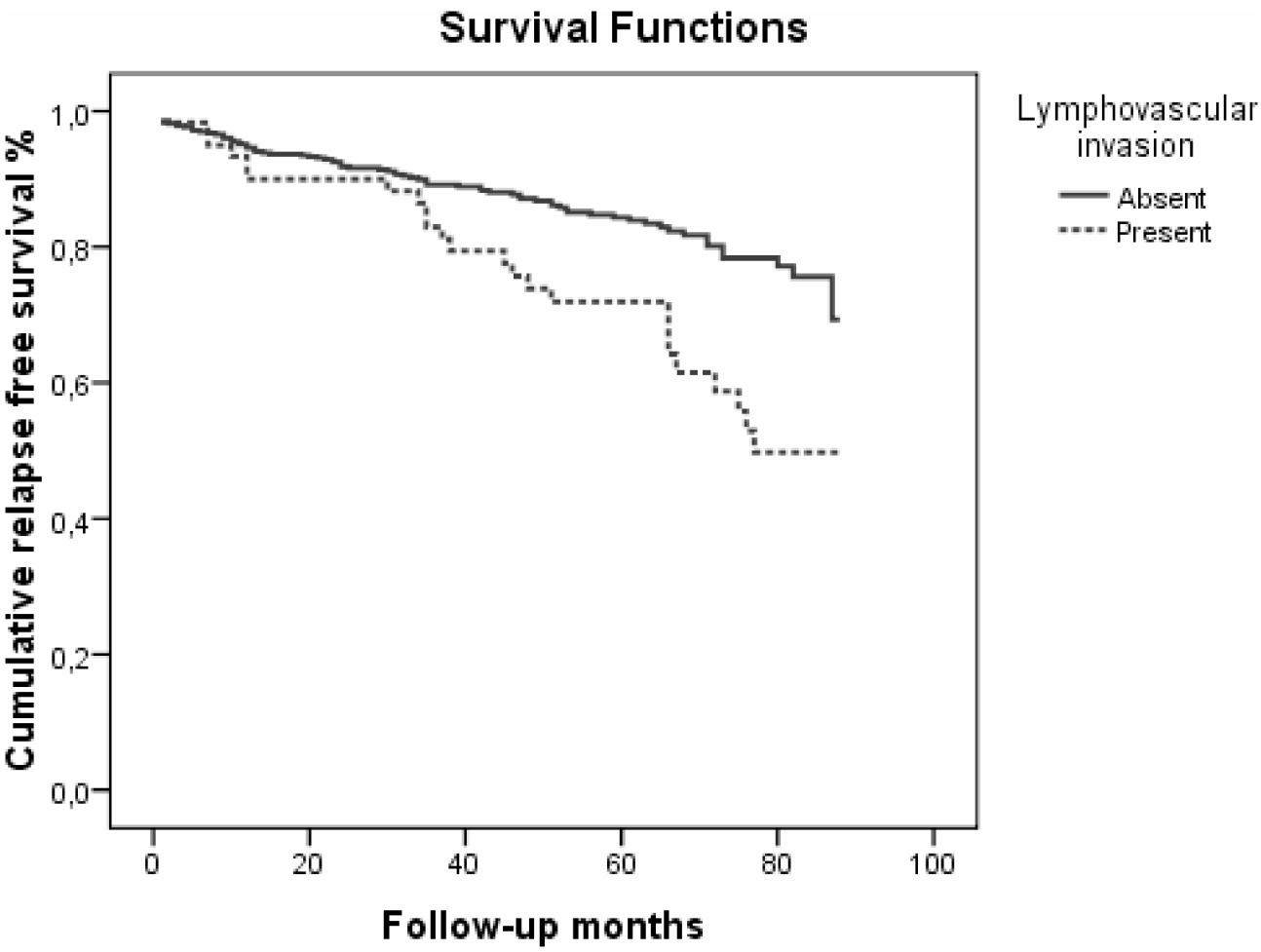

Fig. 3 Kaplan-Meier curve for relapse free-survival based on lymphovascular invasion

follow-up alone [8, 36]. Although Sung et al. noted that adjuvant therapy increased the 5-year RFS from 39.8 to 77.1%, the difference did not achieve statistical significance ($p = 0.054$). Nevertheless, it is pertinent to compare this 5-year disease free survival rate of 77.1% with the 74.4% rate observed in patients without LVI to highlight the implications for LVI-survival association [7].

Our study does have limitations due to its retrospective, single-center design. Additionally, the proportion of patients with middle-lobe tumors is relatively small. Still, the rates observed in our study align with existing literature. A notable strength of this study lies in its execution within a specialized thoracic surgery clinic at a dedicated specialty hospital, which enabled thorough patient monitoring and provided a patient population large enough for statistical analysis.

In conclusion, our findings indicate that the presence of LVI and the location of tumors in the middle-lobe are both independent risk factors for RFS in patients with early-stage NSCLC. We advocate for additional studies, especially with multi-center designs, to establish the prognostic significance of LVI presence, potentially establishing it as a critical factor within the TNM staging system, similar to VPI. Furthermore, our results suggest that adjuvant therapy could be a pivotal intervention for early NSCLC cases with LVI, acknowledging the presence of LVI as a high-risk factor. Regarding middle lobe tumor location, we posit that multi-center clinical research with larger cohorts could yield deeper insights on the binary analysis of middle lobe tumors and LVI as discussed here.

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Author contributions
Contributions: Conception and design, administrative support, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript: All authors.

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Data availability
The datasets used and/or analysed during the current study available from thecorresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Süreyyapaşa Chest Disease and Thoracic Surgery Training and Research Hospital Ethics Committee (2024-21/01.08.2024). Due to the retrospective nature of the study, the obligation to obtain informed consent was waived by the Ethics Committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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