

ORIGINAL  
INVESTIGATION

## Evaluation of Prognostic Factors for Survival in Stage I Non-small Cell Lung Carcinoma

Fatih Gürler, Ömer Önal, Ömer Faruk Demir

## ABSTRACT

**Objective:** Surgical resection is currently considered the most appropriate treatment option in early-stage lung cancer. However, surgical treatment of early-stage patients still results in different survival times. The aim of this study was to evaluate the effects of age, sex, smoking history, tumor size, localization, histopathologic type, and resection type on survival after surgically resected pathologic stage 1 non-small cell lung cancer (NSCLC).

**Materials and Methods:** Sixty consecutive patients who underwent surgical treatment between July 2006 and January 2011 for pathologic stage 1 primary lung cancer were included in this study.

**Results:** Fifty-five (91.7%) of the patients were males, and they were 46-88 (median, 64.4±8.5) years old. Age, sex, smoking history, histopathologic type, anatomical localization, stage, resection type, and postoperative complications did not affect survival rates. Patients with incomplete resection or metastases during the follow-up period had statistically significant decreased survival rates.

**Conclusions:** Staging according to anatomical markers in stage 1 NSCLC patients is not prognostically decisive. Therefore, we believe that staging in NSCLC may be accomplished according to not only anatomic indicatives but also molecular markers.

**Keywords:** Lung carcinoma, stage 1, prognosis, resection, survival

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## INTRODUCTION

Non-small cell lung cancer (NSCLC) includes 85% of all lung cancers, and surgical resection is the best treatment option for early-stage NSCLC (1). Although the 5-year survival rate is approximately 2%-3% in stage 4 NSCLC patients, it can be as high as 70% in completely resected stage 1 NSCLC patients (2). However, 30% of stage 1 NSCLC patients experience recurrence and mortality within 3 years due to micrometastasis at the time of surgery (3). Identifying prognostic factors of lung cancer, individually evaluating patients' prognosis, selecting the best treatment option, and defining new criteria for the classification of patients according to risk groups are thus very important for future studies (4). The aim of this study was to evaluate the effect of age, sex, smoking (pack-years), tumor size, localization, histopathologic type, and resection size on survival of surgically resected pathologic stage 1 NSCLC patients.

## MATERIALS and METHODS

Sixty consecutive patients who underwent surgical treatment between July 2006 and January 2011 for primary lung cancer (pathologic stage 1) were included in this study. Fifty-five (91.7%) of the patients were males. Age range was 46-88 (median, 64.4±8.5) years. The 7th TNM system was used for staging of NSCLC (5, 6). Mediastinal lymph node (LN) sampling was performed on all patients by video-mediastinoscopy. Pleural dissemination, LNs, and localization of the tumor were evaluated again during thoracotomy to determine the exact clinical stage of the patient. Postoperative symptoms, physical examination, chest radiography, and blood samples were evaluated every 3 months in the first 2 years and every 6 months thereafter. Local recurrence and metastasis were identified with thorax computed tomography, bone scintigraphy, abdominal ultrasonography, and positron emission tomography, and also with bronchoscopy if necessary. Recurrence, metastasis, and mortality rates were examined, and survey analyses were performed. Data on patient follow-up were obtained through hospital records. Deaths were identified by checking the mortality notification system in August 2015. Analyses were conducted in Statistical Packages for the Social Sciences (SPSS) version 21.0 (IBM Corp.; Armonk, NY, USA). Kaplan-Meier, log rank, and Cox regression analysis tests were used for statistical analyses, and p-values of <0.05 were considered significant. Informed consent forms were signed by all patients, and the study was approved by the ethics committee of the Erciyes University (No: 2015/150).

Department of Thoracic Surgery, Erciyes University Faculty of Medicine, Kayseri, Turkey

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## Correspondence

Ömer Önal,  
Department of Thoracic Surgery, Erciyes University Faculty of Medicine, Kayseri, Turkey  
Phone: 0 352 207 66 66  
e.mail:  
omeronal@erciyes.edu.tr

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## RESULTS

Forty-three (71.6%) of the patients had right-sided and 17 (28.3%) had left-sided lung cancer. Patient characteristics, prognostic fac-

tors, average survival times, and p-values are given in Table 1. Six (10%) of the patients had incomplete resections. The tumor was detected on the vascular margin in two patients and on the bronchial margin in four patients. Postoperative complications

**Table 1.** Patient characteristics, prognostic factors, average survival times, and p-values

Prognostic factors	Patient characteristics	n=60/(%)	Survival (months±SD)/(%)	p
Sex	Male	55 (91.7)	79.5±5.5	0.924
	Female	5 (8.3)	86.4±19.7	
Age	<65-year	30 (50)	73.8±6.0	0.885
	≥65-year	30 (50)	77.0±7.9	
Smoking history (Pack-years)	<20	26 (43)	5-year survival 69.2	0.896
	>20	34 (57)	5-year survival 67.6	
Histopathology	Epidermoid	31 (51.7)	5-year survival 69	0.115
	Adeno	21 (35)	5-year survival 67	
	Large cell	5 (8.3)		
	Adenosquamous	2 (3.3)		
	Sarcomatoid	1 (1.7)		
Anatomic location	Right	43 (71.7)	75.1±6.3	0.234
	Upper lobe	25 (41.7)	5-year survival 63	0.460
	Middle lobe	1 (1.7)		
	Intermediate	4 (6.6)		
	Lower lobe	13 (21.7)	5-year survival 43	0.985
	Left	17 (28.3)	82.4±6.0	
	Upper lobe	10 (16.6)	5-year survival 90	0.565
Resection type	Lower lobe	7 (11.7)	5-year survival 72	0.153
	Lobectomy	48 (80)	78.4±5.7	0.655
	Pneumonectomy	9 (15)	67.2±9.2	
	Bilobectomy	2 (3.3)		
R categories	Wedge	1 (1.7)		
	R0	54 (90)	81.7±5.5	
	R1	6 (10)	45.6±9.7	0.002
Postoperative complication	Absent	38 (63.3)	84.3±6.1	0.224
	Present	22 (36.7)	65.0±8.2	
Metastasis	Absent	49 (81.7)	87.9±5.4	0.003
	Present	11 (18.3)	43.7±7.6	
Pathologic stage	1A	25 (41.7)	83.1±7.386.5±12.074.3	0.539
	T1a	7 (11.7)	±7.463.3±5.563.3±5.5	
	T1b	18 (30)		
	1B	35 (58.3)		
	T2a	35 (58.3)		

SD: standard deviation

**Table 2.** Postoperative complications

Complications	(n=22)	Rate (36.7%)
Cardiac problems (arrhythmia hypotension, hypertension)	5	8.3
Expansion defect	5	8.3
Bleeding (Blood transfusion)	5	8.3
Empyema	2	3.3
Wound infection	1	1.7
Acute renal failure	1	1.7
Respiratory failure	1	1.7
Liver dysfunction, intra-abdominal fluid	1	1.7
Delirium	1	1.7

**Table 3.** Metastasis and local recurrences

Metastasis locations	(n=11)	Rate (18.3%)
Bone	4	6.6
Brain	2	3.3
Lung	1	1.7
Liver	1	1.7
Lymph node	1	1.7
Multi organ	2	3.3
Local recurrence	(n=2)	3.3

were observed in 22 patients (36.7%) (Table 2). Eleven (18.3%) patients had metastatic disease, and two (3.3%) patients had local recurrence in the follow-up period (Table 3). The average follow-up time was  $78.9 \pm 5.2$  months (2-106 months). In stage 1 NSCLC patients, the average survival time was  $78.9 \pm 5.21$  months with a 3-year survival rate of 72% and a 5-year survival rate of 69%. In stage 1a patients, the average survival time was  $83.1 \pm 7.3$  months, the 3-year survival rate was 84%, and the 5-year survival rate was 66%. In stage 1b patients, the average survival time was  $63.3 \pm 5.5$  months, the 3-year survival rate was 76%, and the 5-year survival rate was 72%. The average survival time for patients with T1a, T1b, and T2a tumors were  $86.5 \pm 12$ ,  $74.3 \pm 7.4$ , and  $63.3 \pm 5.5$  months, respectively. Patients with incomplete resection or metastases during the follow-up period had statistically significant decreased survival rates.

## DISCUSSION

Lung cancer is the most common cause of death due to cancer in both men and women, and several prognostic factors have been identified for non-small cell groups. Demographic characteristics of patients, smoking history, tumor histology, tumor stage, and genetic factors are all thought to influence prognosis. When the effect of age on survival rate was examined, patients aged <65 years had high survival rates (7-9). When based on different age groups, some studies reported no statistically significant differences, whereas others showed significant differences between survival and age

(10-16). In this study, no statistically significant effect was detected between patients aged <65 years and those aged >65 years when compared in terms of their survival rates ( $p=0.885$ ). Some studies that assessed the relationship between sex and survival reported that women have higher survival rates than men (7-11, 17). However, other studies, including ours, determined that sex had no effect on survival ( $p=0.924$ ) (14-16). Bryant et al. (18) stated that smoking history (>20 pack-years) was a negative prognostic factor in stage 1 NSCLC. Yoshino et al. (19) agreed with this opinion only for patients with stage 1 adenocarcinoma. Similar to the other publications in the literature, we found no statistically significant difference between smoking and survival (20-22). When studies on the relationship between histologic type and survival are reviewed, adenocarcinoma has lower survival rates (11, 13, 23). Chen et al. (24) reported no statistically significant differences in survival rate between adenocarcinoma and squamous cell carcinoma. Raymond et al. (25) stated that epidermoid carcinoma and bronchoalveolar type had higher survival rates than adenocarcinoma. In a study of 2,657 NSCLC patients, the univariate analysis showed that all histologic types except adenocarcinoma had low survival rates (26). In multivariate analysis, there were no significant differences among the histologic types. However, numerous studies have indicated that there is no statistically significant relationship between survival and histopathologic type (7-10, 14). Generally, study groups on thoracic oncology consider adenocarcinomas to have worse prognosis than epidermoid carcinomas. However, this was not sufficiently confirmed by studies comparing patients at the same stage. In this study, the 5-year survival rate was 69% for epidermoid carcinoma and 67% for adenocarcinoma, and no statistically significant difference was detected between the groups ( $p=0.115$ ). In a study on 12,349 NSCLC patients, it was reported that upper lobe tumors had lower survival rates than tumors in other locations (25). In another study, 261 patients with pathological stage 1 NSCLC underwent surgery. The central and peripheral tumors were compared in terms of survival, but no significant difference was detected (23). The surgical results of patients with NSCLC aged >80 showed no statistically significant difference in survival rates between right- and left-sided lung resections (10). In this study, there were no statistically significant differences in survival rates with the anatomical location of the tumor. Generally, patients with resected stage 1a NSCLC have higher survival rates than those at later stages of NSCLC. However, when stage 1 was considered in itself and compared between stage 1a (T1a/b) and stage 1b, different results were obtained (26). Two hundred and forty-nine patients diagnosed with early-stage NSCLC were included in a study to investigate the determinants of tumor recurrence after curative surgery. It was reported that stage 1a and T1aN0M0 patients had statistically significant differences when compared with other stages in terms of tumor recurrence (17). In another study, T1aN0M0 patients demonstrated statistically significant differences in survival rates compared with patients at other stages (including T1bN0M0) (14). There are also some publications reporting no statistically significant differences between T1aN0M0 and T1bN0M0 in terms of survival rates (7). Ziming Li et al. (9) published a study on survival rates of 325 NSCLC patients in pathological stage 1. They found no statistically significant differences between T1aN0M0 and T1bN0M0 stages. Shimada et al. (11) reported that in univariate analysis, T1aN0M0 and T1bN0M0

patients had no significant differences when compared in terms of survival rates ( $p=0.056$ ). However, in multivariate analysis, significant differences were found for the same comparison ( $p=0.045$ ). In our study, no statistically significant difference was detected in survival rates between stage 1a and stage 1b patients ( $p=0.539$ ).

When recent publications on the effect of resection type on survival rates were investigated, the primary finding was that lobectomy is associated with a better prognosis for stage 1 patients (27). Syed et al. (7) reported that lobectomy/bilobectomy resections were associated with better 5-year survival rates in NSCLC patients than segmentectomy/wedge resections were ( $p=0.032$ ). They detected no statistically significant difference in T1a patients. Christopher et al. (28) reported that segmentectomy has no significant difference in patients who can tolerate lobectomy in terms of respiratory reserve. But sub-lobar resections have lower survival rates in patients who can tolerate only segmentectomy. Lobectomy or bilobectomy was found to be superior to pneumonectomy in terms of survival rates in a series of 6,644 patients diagnosed with NSCLC ( $p=0.01$ ) (8). A study on the prognosis of stage 1 NSCLC patients stated that survival rates in the lobectomy or bilobectomy group were higher than those in the pneumonectomy group ( $p=0.021$ ) (9). There was no significant difference in terms of disease-free survival ( $p=0.2422$ ). In a multicenter study with 12,349 patients who underwent surgery with a diagnosis of early-stage NSCLC, it was reported that lobectomy had higher survival rates than other types of lung resections (25). In a study on 293 patients with stage 1 NSCLC, the risk of recurrence was investigated, and the results showed that patients who underwent anatomic resection had higher survival rates than those who underwent wedge resections (14). A study on recurrence rates of surgically treated stage 1a NSCLC patients found that there was no statistically significant difference in terms of survival between patients who underwent lobectomy and those who underwent bilobectomy or pneumonectomy ( $p=0.946$ ) (11).

The relationship between resection type and survival is associated with whether the resection is anatomic. In this study, anatomic resections were performed in all patients except one, and no statistically significant difference was detected between lobectomy and pneumonectomy in terms of survival ( $p=0.655$ ). In the literature, it is reported that patients with tumors on vascular or bronchial surgical margins have an increased recurrence rate and decreased 5-year survival rate (17, 29). Snijder et al. (30) examined the survival of stage 1 NSCLC patients with residual tumor on the bronchial resection margin. They reported that the 5-year survival rate was 58% in patients with carcinoma in situ on the surgical margin and received no adjuvant chemotherapy, 54% in patients who underwent complete resection, and 27.3% in patients with residual mucosal invasive carcinoma on the surgical margin ( $p=0.03$ ). Gebitekin et al. (31) reported a 5-year survival rate of 40.8% in stage 1 NSCLC patients with residual invasive tumor on the bronchial surgical margin. Hancock et al. (32) reported the surgical results of 54,512 patients diagnosed with NSCLC. They detected residual tumor on the surgical margin in 3,102 (5.7%) patients, and 1,688 (3.1%) of these patients had microscopic residual tumors (R1). In pathologic stage 1 patients, the 5-year survival rates were 37% in R1 and 62% in complete resections ( $p<0.0001$ ). Hofmann et al. (33) evaluated the R1 and macroscopic (R2) residual diseases in

596 patients. They found 26 (4.4%) patients with R1 and 12 (2%) with R2 residual diseases. In 21 of the 26 R1 patients, tumors remained on the bronchial surgical margin. The 5-year survival rate was 14% in R1 patients. In our study, 6 (10%) of the patients had incomplete resection. The residual tumor remained on the bronchial surgical margin in four patients and on the vascular surgical margin in two patients. Additional surgery could not be performed on two patients with residual tumor on the bronchial surgical margin because of the limited pulmonary reserve of patients. A statistically significant difference was detected between complete and incomplete resection groups in terms of survival ( $p=0.002$ ).

## CONCLUSION

In this study, we found that age, sex, smoking, histopathologic type, anatomic localization, stage, resection type, and postoperative complications did not affect survival rates. Patients with incomplete resection or metastases in the follow-up period had significantly lower survival rates. As seen in the literature, staging according to anatomical markers in stage 1 NSCLC patients is not very conclusive. Therefore, we believe that staging in NSCLC may be achieved according to not only anatomic indicatives but also according to molecular markers.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Erciyes University (No: 2015/150).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Conceived and designed the experiments or case: WFG., ÖÖ., ÖFD. Performed the experiments or case: FG., ÖÖ., ÖFD. Analyzed the data: FG., ÖÖ., ÖFD. Wrote the paper: FG., ÖÖ., ÖFD. All authors have read and approved the final manuscript.

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