Original Article

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Prognostic Factors of Operated Stage I Non-Small Cell Lung Cancers: A Tertiary Center Long-Term Outcomes

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Abstract

Aim: This study aimed to evaluate prognostic factors influencing survival in patients who underwent surgical resection of stage I non-small cell lung cancer (NSCLC) in our center.

Methods: A total of 472 patients with stage I NSCLC who were operated between January 2007 and November 2018 were retrospectively analyzed in the study. Patient data was collected using hospital database. The remaining patients were divided into 2 groups: patients younger than 65 years of age (group A) and those aged 65 and over (group B).

Results: The patient group comprised 80 women (16.9%) and 392 men (83.1%); 152 patients were aged 65 years or over (32.2%) and 320 patients were under 65 years of age (81.5%). The mean follow-up time was 51 months. The 5-year survival rate was 67.2% overall. Patients with stage IA1, IA2, IA3, and IB tumors had 5-year survival of 78.1%, 72.5%, 77.3%, and 56.7%, respectively (p=0.009). In multivariate analysis, advanced age (≥65 years), large cell carcinoma, left-sided surgery, and higher tumor stage were the most important prognostic factors associated with poorer survival.

Conclusion: Advanced age was determined to be an independent poor prognostic factor, and sub-group analyses showed that survival outcome was better with tumors smaller than 1 cm. Based on the results of our study, we believe that the classification of stage I group should be revised in the new edition of lung cancer staging.

Keywords: Survival rate, carcinoma, non-small-cell lung, prognosis

Introduction

Lung cancer is the most common adult cancer and the leading cause of cancer deaths worldwide and in Turkey. According to the most recent statistics from the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, the age-standardized incidence rate of lung cancer in Turkey was reported as 57.7 in 100000 men and 9.8 in 100000 women (1). Lung cancer patients over 75 years of age are especially challenging in terms of selecting a treatment protocol and approach. While the standard treatment approach recommended for early (stage I) lung cancer is surgical anatomic resection, older patients with advanced disease undergo surgery less frequently than younger patients (2). Despite reports of higher postoperative complication and mortality rates in this population, careful patient selection, preoperative multidisciplinary evaluation, and postoperative rehabilitation provide more moderate survival rates (3-7).

In the eighth edition of the tumor, node, metastasis (TNM) classification, stage I tumors are divided into 4 groups based on survival rates (stage IA1, IA2, IA3, and IB) (8). In previous studies, survival rates in the stage I sub group have varied depending on factors such as age, sex, and histological cell type. For early-stage tumors in all age groups, the consensus among many researchers is that survival rates with tumors smaller than 2 cm are better compared to the other groups (9-12).

Our aim in this study was to determine the impact of advanced age on survival in patients who underwent surgical resection of early non-small cell lung carcinoma

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(NSCLC) and evaluate the survival outcomes of stage I tumor subgroups.

Methods

Study Design

Data pertaining to patients who underwent surgery due to NSCLC between January 2007 and December 2018 were obtained from a prospective database and analyzed retrospectively. Patients whose data could not be accessed, who underwent sublobar (wedge) resection due to limited respiratory function, functional inoperable patients or were Stage I after neoadjuvant therapy were excluded from the study.

The remaining patients were divided into 2 groups: patients younger than 65 years of age (Group A) and those aged 65 and over (Group B). The ethics committee Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital and Helsinki approval for the study was obtained from the institutional review board (no: 2020-54).

Patient Selection

All patients underwent preoperative thoracic computed tomography (CT) for evaluation of primary disease, as well as positron emission tomography (PET/CT) and cranial magnetic resonance imaging for evaluation of distant metastasis. The pulmonary reserve was assessed by pulmonary function tests. The preoperative mediastinal staging was performed in accordance with the European Society of Thoracic Surgeons (ESTS) guidelines (13).

Postoperative Follow-up

Patient demographic data, mortality, histopathological characteristics, recurrence, and 5-year survival rates were analyzed. Age, histopathology, tumor Stage, and survival data were obtained from hospital records and the national survival database. Pathologic staging was performed according to the 8th edition of the TNM classification system.

Patients were followed up in collaboration with oncologists by physical examination and thoracic CT every 3 months for the first 2 years, every 6 months from years 2 to 5, and once a year thereafter. An oncologist was present during all postoperative examinations.

Statistical Analysis

The patients' demographic and clinical data were evaluated using descriptive statistics. Relationships between categorical data were evaluated using chi-square (χ^2) or Fisher's Exact test. Student's t and Mann-Whitney U tests were used for comparisons of continuous variables. Survival was evaluated using Kaplan-Meier analysis, and log-rank analysis was performed to compare factors. A $p<0.05$ was considered statistically significant. All tests were performed on SPSS version 22 (IBM Corp., Armonk, NY) statistical software.

Results

A total of 472 NSCLC patients were included in the study. The patient Group included 80 women (16.9%) and 392 men (83.1%). The mean age of the patients was 60.53±8.35 (r=26-84) years. One hundred fifty two patients were aged 65 years or over (32.2%) and 320 patients were under 65 years of age (81.5%). Left resection was performed in 190 patients (40.3%), right resection in 282 patients (59.7%). The histologic type was adenocarcinoma in 247 patients (52.3%), squamous cell carcinoma in 205 patients (43.4%), and large-cell carcinoma and adenosquamous cell carcinoma in 20 patients (4.2%). A mean of 17.57±9.08 lymph nodes were removed. The comparison of demographic and histopathological characteristics between the <65 and ≥65 age groups is shown in Table 1.

Nine patients (1.9%) died in the first 90 days. The mean follow-up time was 51 months. The mean survival time was 126 months and the 5-year survival rate was 67.2%. In the univariate analysis, the 5-year survival rate was 55.2% for patients over the age of 65, while this rate was 72% in patients younger than 65 ($p<0.001$). The 5-year survival rate in right-sided resections was 70.1% ($p=0.024$). In terms of histopathology, survival time was significantly longer in squamous cell carcinoma than for other types ($p<0.05$) (Figure 1). The poorest 5-year survival (33.2%) was seen in patients with large-cell and adenosquamous cell carcinomas. Five-year survival rates for patients with Stage IA1, IA2, IA3, and IB tumors were 78.1%, 72.5%, 77.3%, and 56.7%, respectively ($p=0.009$). Patients with tumors 2 cm or smaller had a 5-year survival rate of 76.4% ($p=0.004$ vs. tumors >2 cm) (Figure 2).

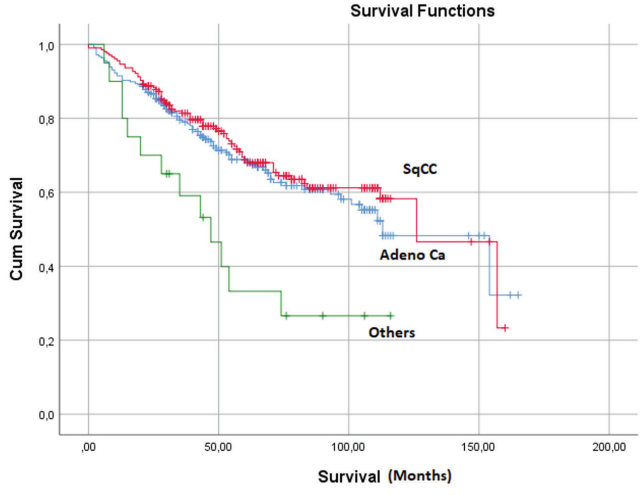

Figure 1. Kaplan-Meier curve of histopathological stage

In multivariate analysis, age ≥65 years, left-sided resection, large cell and adenosquamous cell cancers, and Stage IB tumors were found to be poor prognostic factors. Table 2 presents the analyses of factors affecting mortality.

Discussion

Based on the Stage-based survival data obtained in our study, we recommend that Stage I tumors be divided into those <1 cm and those between 1 and 4 cm. On the 8th edition of the TNM classification for lung cancer, Goldstraw et al. (8) divided Stage I lung cancer tumors into 4 subgroups according to their differences in survival. They determined a statistically significant difference in survival between the groups, with 5-year survival rates of 92% for Stage IA1, 83% for IA2, 77% for IA3, and 68% in IB tumors (8). Aokage et al. (14) also reported 5-year survival rates in the Stage I subGroup as 95% in IA1, 84% in IA2, 76% in IA3, and 65% in IB. Stage IA1 had significantly better survival than the other groups, but there were no significant differences among the Stage IA2, IA3, and IB groups in terms of survival outcomes. Similar to the study by Aokage et al. (14), multivariate analysis in our study revealed a statistically significant difference in survival between Stage 1A1 and 1B but no differences between Stage IB and the other groups. Our survival results different from some of publications in the literature, this is due to the performance status of the patients.

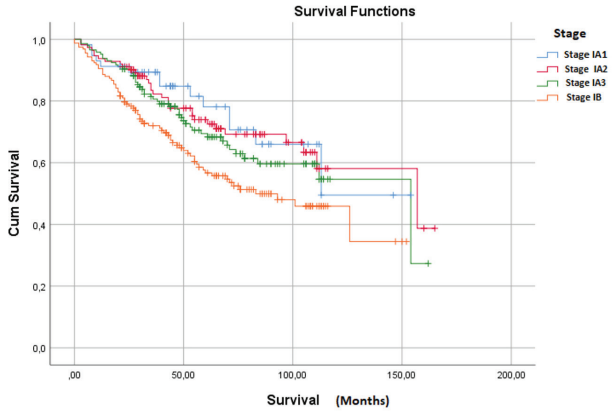

Figure 2. Kaplan-Meier Curve of Stage

Although surgery is considered the gold standard treatment approach in early-stage lung cancer (Stage I-IIA), surgical outcomes in geriatric patients differ compared to those of younger patients. Studies have shown that geriatric patients have poorer survival outcomes compared with younger patients, with this being mainly attributed to

Table 1. Comparison of the demographic and clinical characteristics of the patients by age group

Variable		Group A (<65 years)		Group B (≥65 years)		p
		n	%	n	%	
Sex	Male	264	82.5	128	84.2	0.643
	Female	56	17.5	24	15.8	
Age, years (mean ± SD)		56.10±5.77		69.86±4.26		0.001*
Resection	Segmentectomy	3	0.9	4	2.6	0.111
	Lobectomy	292	91.3	142	93.4	
	Pneumonectomy	25	7.8	6	3.6	
Resection side	Right	191	59.7	91	59.9	0.970
	Left	129	40.3	61	40.1	
Operation	Standard	298	93.1	141	92.8	0.885
	Sleeve	22	6.9	11	7.2	
Histopathology	Adenocarcinoma	168	52.5	79	52	0.753
	Squamous cell carcinoma	137	42.8	68	44.7	
	Other	15	4.7	5	3.3	
Tumor size, cm (mean ± SD)		2.54±0.99		2.54±0.91		0.908
Stage	1A1	40	12.5	17	11.2	0.928
	1A2	74	23.1	38	25	
	1A3	97	30.3	48	31.6	
	1B	109	34.1	49	32.2	
Lymph nodes removed		17.49±8.65		17.70±9.95		0.837

Chi-square tests was used in this table
SD: Standard deviation, * indicate statistical significance (p<0.05)

Table 2. Factors affecting survival

Variables		5-year survival (%)	Median survival (months)	95% CI	Univariate	Multivariate	
					p	HR (95% CI)	p
Age, years	<65	72	154	100-207	0.001	1.92 (1.38-2.65)	<0.001*
	≥65	55.2	98	40-101			
Sex	Male	66	103	89-136	0.157	-	
	Female	71	90	80-100			
Side	Right	70.1	154	100-207	0.024	1.37 (1-1.8)	0.047*
	Left	62.8	97	69-124			
Resection	Lobectomy	67.3	126	95-156	0.334	-	
	Pneumonectomy	61.5	84	64-103			
Histopathology	Adenocarcinoma	68.9	113	87-138	0.004	-	0.001
	SqCC	81.4	126	97-154		0.77 (0.5-1.0)	0.125
	Other	33.2	47	27-66		2.58 (1.4-4.6)	0.002*
TNM Stage (8^{th} ed)	1A1	78.1	113	91-129	0.009	0.57 (0.39-0.38)	0.004*
	1A2	72.5	157	79-234		2288 (0-2.96)	0.836
	1A3	77.3	154	70-237		2022 (0-2.62)	0.840
	1B	56.7	83	56-109		-	0.036
Tumor size	<2 cm	76.4	157	99-214	0.004	481 (0-6.23)	0.822
	>2 cm	62	112	84-139			
Resection type	Standard	67.1	154	95-212	0.992	-	
	Sleeve	69.3	126	47-204			

Kaplan-Meier Survival test was used in this table
CI: Confidence interval, HR: Hazard ratio, SqCC: Squamous cell carcinoma, TNM: Tumor, node, metastasis, * indicate statistical significance (p<0.05)

age-related tissue fragility, physiological changes (reduced performance and respiratory capacity), and surgical risks (11,15-20). Park et al. (3) observed a major difference in survival between geriatric and young patients (5-year survival of 69% vs. 91%, respectively). Differences in 5-year survival between older and younger patients were also reported by Goodgame et al. (21) (52% vs. 67%) and Sigel et al. (22) (63.5% vs. 69.2%). Consistent with the literature, postoperative 5-year survival was poorer among geriatric patients in our study when compared with the younger patient Group (55.2% vs. 72%).

In contrast to other studies in the literature, Cerfolio and Bryant (23) found that 5-year survival was better in their geriatric patient Group than the young patient Group (78% vs. 69%). The differences among these studies may be related to the retrospective design of most studies, differences in the selection of patients for surgical resection, and variation between surgical protocols [sublobar resection (wedge resection, segmentectomy), lobar resection] among clinics. In addition, older age has been associated with poorer survival outcomes even within the geriatric population. In a study conducted in the US, patients over 80 years of age had a 5-year survival rate below 40% (24).

Stereotactic body radiotherapy (SBRT) has been increasingly used in the treatment of geriatric patients with early-stage NSCLC in recent years. However, although SBRT significantly improved survival outcomes in patients who were considered inoperable and those who refused surgical treatment or in clinics that revised the treatment protocol for this patient group, the success rate is still much lower when compared with surgery (16,25). Ruiter et al. (16) compared patients who underwent surgery and those who had SBRT and reported a 5-year overall survival of 62% in the surgery group and 29% in the SBRT group. Successful outcomes have been achieved with SBRT in primary local control of the disease. For example, in the radiation therapy oncology Group 0236 trial, the 3-year primary disease control rate was reported to be 97.6%, and the 3-year survival rate was 55.8% (26). Despite the lower toxicity and better early-stage mortality and survival outcomes reported with SBRT, it has not been able to replace surgery in terms of long-term survival. Of course, the overall performance status, inoperability criteria, and respiratory capacity of patients who underwent SBRT should not be overlooked. When patients who undergo surgery are evaluated in terms of these criteria, they have considerable advantages. In our clinic, we operate on all

patients who have performance capacity amenable to surgery. We expect the ongoing randomized prospective studies on this subject (VALOR, POSTILV) to yield more objective results.

Evaluation of the effect of surgical resection type on survival has produced different results. When the survival rates of lobectomy and pneumonectomy patients in our study were compared, the lobectomy Group had a higher survival rate but the difference was not statistically significant (p=0.334). Similarly, in our previous series we observed no difference in survival between geriatric patients who underwent lobectomy, segmentectomy, and pneumonectomy groups. Additionally, no significant differences in long-term survival and recurrence rates were reported in studies comparing sublobar and lobar resections in early-stage geriatric populations (4). In one such study conducted by Fiorelli et al. (27), the 5-year survival rate among 239 patients was 60.5% in the lobar resection Group and 45% in sublobar resection group, but the difference was found not to be statistically significant (p=0.1). Dell'Amore (28) also reported no difference in survival between lobectomy and sublobar resection patients (p=0.6). However, some authors argue that pneumonectomy adversely affects mortality and long-term survival outcomes compared to other resection types (29-31). In the study by Goodgame et al. (21), the pneumonectomy Group had the highest rate of perioperative mortality. In addition, the pneumonectomy Group exhibited significant differences in terms of recurrence and overall survival (p=0.0003, p=0.043, respectively). It was argued that survival rates were low because pneumonectomy increases perioperative mortality and considerably increases the rate of postoperative complications in geriatric patients. We believe that the discrepant results of these studies can be attributed to factors such as surgical technique and surgeon experience, differences in preoperative evaluation, heterogeneous patient groups, postoperative rehabilitation, the method of selecting suitable candidates for the resection types, and neoadjuvant/adjuvant treatment protocols.

Most survival studies in the early-stage NSCLC geriatric patient population have reported better histopathological outcomes in the adenocarcinoma Group (11,32,33). In their study of 1116 patients, Ganti et al. (34) detected a significant difference in survival in the adenocarcinoma group. A multivariate analysis conducted by Bei et al. (11) showed adenocarcinoma to be an independent factor of better prognosis in early-stage octogenarians. Hino et al. (35) included all Stage groups in their evaluation and determined that patients with adenocarcinoma had a significantly higher survival rate than the other groups (p=0.016). In other studies, similar survival outcomes were reported in all histopathology groups (adenocarcinoma, squamous cell carcinoma, large-cell) [Dell'Amore et al. (28), 2014; Razi et al. (36), 2016]. In contrast to these studies, multivariate analysis in our study indicated that the large-cell and adenosquamous cell Group had the poorest prognosis in terms of overall survival. There was no statistically significant difference between adenocarcinoma and squamous cell carcinoma.

Study Limitations

Potential sources of bias in this study include the retrospective study design and the smaller proportion of women in the study sample. Furthermore, the operations included in the analysis were performed by different surgeons, and the patients' performance status was not evaluated. Another shortcoming of this study is that disease-free survival was not calculated for these patients.

Conclusion

Advanced age is an important prognostic factor in stage I lung cancer. Early-stage large-cell and adenosquamous cancer have the worst prognosis. There was no difference in survival between adenocarcinoma and squamous cell carcinoma in this study. Based on our results, we believe that revision of the Stage I classification is warranted in the next edition of the TNM staging. However, more comprehensive multi-center studies on this subject are still needed.

Authorship Contributions

Concept: M.V.D., C.B.S., A.A., S.E., M.E., A.O., M.M., Design: M.V.D., C.B.S., V.E., C.A., Data Collection or Processing: M.V.D., C.B.S., V.E., C.A., A.A., S.E., M.E., A.O., M.M., Analysis or Interpretation: M.V.D., C.B.S., Literature Search: M.V.D., C.B.S., A.O., M.M., Writing: M.V.D., C.B.S., A.O., M.M.,

Conflict of Interest: No conflict of interest was declared by the authors.

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