Original Article

Changes in the Surgical Treatment Strategies for Nonsmall Cell Lung Cancer in the Past 20 Years: A Single-Center Experience

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Abstract

OBJECTIVES: Nonsmall cell lung cancer (NSCLC) is a multifactorial disease, and differences in the characteristics of surgical patients may develop over the years. This study aimed to evaluate the patients who underwent curative surgical resection for NSCLC in the past 20 years at our center and analyze the changes in the treatment strategies based on demographics, surgical strategies, and histopathology.

MATERIALS AND METHODS: In this retrospective single-center cohort study, 1995 patients who had undergone lobectomy, bilobectomy, or pneumonectomy for primary NSCLC from January 1997 to January 2017 were analyzed. Patients were divided into two groups: Group I included patients operated in the first 10 years and Group II included patients operated in the last 10 years.

RESULTS: Overall, 77% of patients were operated in the last 10 years (458 vs. 1537 patients). Sleeve lobectomies performed in Group II reduced the rate of pneumonectomy from 37% to 20% (p<0.001). The operation rates for adenocarcinomas increased significantly during the study period, increasing from 31.4% to 36.2% (p=0.049). The 30- and 90-day postoperative mortality rates were 4.6% and 8.5% in Group I and 4.1% and 5.7% in Group II, respectively (p=0.69 and p=0.037, respectively). When the groups were compared, the median and 5-year survival rates were 44.1 months (95% confidence interval [CI], 35.6–52.6) and 42.9% in Group I and 73.6 months (95% CI, 63.3–83.9) and 53.9% in Group II, respectively (p<0.001).

CONCLUSION: This study demonstrates an improvement in long-term outcomes following lung cancer surgery with an increasing rate of surgical procedures in the last 10 years. There was an increase in the proportion of females affected and the rate of adenocarcinoma. However, the pneumonectomy and postoperative N2 disease rates have decreased with advancing preoperative evaluation techniques and parenchyma-saving surgical methods. Postoperative mortality has decreased, and the survival rate has increased.

KEYWORDS: Nonsmall cell lung cancer, prognosis, surgical treatment

INTRODUCTION

Lung cancer is considered a public health problem owing to its ever-growing mortality rates worldwide. Several reports from different countries have reported that lung cancer is the leading cause of all cancer-related deaths in both men and women [1-3]. Similar observations have been noted in Turkey; according to the results of a Turkish unified database in 2014, the detection rate of new lung cancer was 52.5/100,000 individuals in men and 8.7/100,000 individuals in women [4]. Anatomic surgical resection and mediastinal lymph node dissection are the most effective methods for treating early-stage nonsmall cell lung cancer (NSCLC) [5, 6]. Lobectomy and pneumonectomy are the standard procedures for patients scheduled to undergo surgical resection. Success in surgical treatment depends on appropriate patient selection and cancer staging. In addition, the performance and physiological status of patients, as well as appropriate evaluation of pulmonary and cardiac functions, are factors affecting early and late treatment outcomes. However, only few studies have reported the long-term follow-ups details in large patient series following surgery for NSCLC [7-9]. Therefore, the present study reviewed institutional surgical treatment strategies for NSCLC and the changes in these strategies over the past 20 years.

MATERIALS AND METHODS

The study's ethics committee approval was provided by Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital's institutional review board (03.09.2018-9910) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was not obtained from the patients due to the retrospective nature of the study

design. A total of 1995 patients who underwent lobectomy, bilobectomy, or pneumonectomy with a mediastinal lymph node dissection for primary NSCLC from January 1997 to January 2017 were included in the study. Patients' age, sex, operation method, operation type, 30- and 90-day postoperative mortalities, histopathology, and survival rates were recorded. Patients were divided into two groups each covering 10 years chronologically, and all variables between the groups were evaluated. Patients operated from January 1997 to January 2007 were included in Group I, and those operated from January 2007 to January 2017 were included in Group II.

Preoperative chest radiography, biochemistry tests, and pulmonary function tests were completed in all the patients, and fiberoptic bronchoscopy was performed by the surgical team preoperatively. Contrast-enhanced thoracic computed tomography (CT) and brain magnetic resonance imaging and/or CT were performed in all the patients, and positron emission tomography–CT (PET–CT) was routinely performed in the second 10-year period. In the first 10 years where PET–CT was not performed, cranial CT/MRI, bone scintigraphy, and abdominal CT were performed to scan distant metastases. Sufficient pulmonary function was defined as having an estimated postoperative forced expiratory volume in 1 second (FEV_1) value of >800 mL or 40%. Patients with restrictive pulmonary function tests underwent additional examinations such as the ladder-climbing test and maximal oxygen consumption (VO_2 max). Sufficient pulmonary function was defined as having >VO_2 max value of 15 mL/kg/min. Transbronchial fine-needle aspiration biopsy or mediastinoscopy and endobronchial ultrasonography (EBUS) were performed before and after 2011, respectively, in patients with clinical suspicion of N2 disease. Patients with pathological N2 diseases preoperatively received neoadjuvant chemotherapy and/or radiotherapy. Restaging was performed after treatment, and patients who were downstaged underwent surgery. Suitable patients who did not have N2 diseases preoperatively were scheduled for lobectomy or bilobectomy; however, pneumonectomy was performed when necessary. Postoperatively, the patients underwent CT examinations every three months for the first year and six months for the second year and then annual follow-up. Survival was calculated based on the time from the operation until the date of death.

MAIN POINTS

- The rate of pneumonectomy and postoperative N2 disease has decreased with the advances in thoracic surgery over the past decade.

- Both postoperative mortality has decreased and overall survival has increased after lung cancer surgery over the past decade.

- The overall 5-year survival rate is over 50% for surgically treated non-small cell lung cancer.

- The finding that women had a higher incidence of surgically treated non-small cell lung cancer than men over the past decade. Also, the rate of adenocarcinoma increased during this period.

- Surgical treatment is increasing rapidly for non-small cell lung cancer.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 20.0 software program (SPSS IBM Corp.; Armonk, NY, USA). Fischer's exact test or Pearson's chi-squared test was used to analyze the groups and age, and the t-test was used to determine the tumor size. A survival analysis was performed using the Kaplan–Meier method. Survival was defined as the time from surgery to death any cause or last follow up. The groups were compared using the log-rank method. Cox and logistic regression methods were used for multivariate analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

Overall, 77% of the patients were operated in the last 10-year period (458 vs. 1537 patients). The overall mean age was 60.5±8.9 years (range: 31–84), and the mean age of the operated patients was higher in Group II than in Group I (59.4 and 60.8 years, respectively; p=0.004) (Table 1). In the last 10-year period, the proportion of patients aged ≥60 years increased by approximately 5%. The overall incidence rate was 9.2% in females, and the male-to-female ratio was 13.8 in Group I and 9.1 in Group II; the increase in the proportion of female patients was statistically significant (p=0.043).

Sleeve resection has not been performed in Group I, whereas 6.9% of the patients in Group II underwent sleeve lobectomy. The rate of pneumonectomy decreased significantly from 37% to 20% in the last 10-year period (p<0.001). The frequency of video thoracoscopic pulmonary resections, which were not performed in the first 10-year period, has been increasing in the recent years, and the frequency rate was 21.8% in the last year of the study (ie 2016) and 5.1% in the last 10 years. Histopathologically, the most frequent type of cancer was squamous cell cancer at 55.4% in the whole study period (Table 2). However, the incidence rate of adenocarcinoma increased almost significantly in comparison with the incidence rate of nonadenocarcinoma (31.4% and 36.2%, respectively; p=0.06) in Group II. The proportion of patients operated for tumors of ≤3 cm was higher in Group II than in Group I (p=0.003), whereas the mean tumor size was smaller (p=0.002) (Table 3). The complete resection rate was 95.6% in Group I and 96.7% in Group II. Although there was no significant difference between the groups in terms of a postoperative N status, the incidence rates of pathological N2 diseases (17.3% vs. 13.9%) and skip N2 diseases (8.3% vs. 5.5%) decreased in Group II (Table 4).

The overall 30- and 90-day postoperative mortality rates were 4.2% and 6.3%, respectively, and although, these rates decreased in Group II, only the decrease in the 90-day mortality rate was statistically significant (p=0.69 and p=0.037, respectively). In a multivariate analysis, the groups were not identified as factors affecting the 30- and 90-day mortality. When the study was completed, the median survival duration was 63.1 months (95% confidence interval [CI], 55.6–70.6), and the 5-year survival rate was 50.9% at the end of the follow-up period of 45.5±41.2 months for all the patients (Figure 1). When the groups were compared, the median and 5-year survival rates were 44.1 months (95% CI, 35.6–52.6)

Table 1. Differences in patient characteristics and resection types between the groups

		Total		Group I		Group II		p
Mean age (years)		60.5±8.9		59.4±9.6		60.8±8.7		**0.004**
		n	**%**	**n**	**%**	**n**	**%**	
Overall		1995	100	458	100	1537	100	-
Result	Dead	995	47.9	326	71.2	629	40.9	**0.001**
	Alive	1040	52.1	132	28.8	908	59.1	
30-day postoperative mortality		84	4.2	21	4.6	63	4.1	0.69
90-day postoperative mortality		126	6.3	39	8.5	87	5.7	**0.037**
Sex	Male	1812	90.8	427	93.2	1385	90.1	0.043
	Female	183	9.2	31	6.8	152	9.9	
Side	Right	1106	55.4	265	57.9	841	54.7	0.24
	Left	889	44.6	193	42.1	696	45.3	
Operation	Lobectomy	1328	66.6	249	54.4	1079	70.2	**0.001**
	Bilobectomy	184	9.2	37	8.1	147	9.6	
	Pneumonectomy	483	24.2	172	37.6	311	20.2	
Complete resection		1924	96.4	438	95.6	1486	96.7	0.31
Chest wall resection		166	8.3	51	11.2	115	7.5	**0.016**
Sleeve resection		106	5.3	-	-	106	6.9	-
VATS		79	4.0	-	-	79	5.1	-

Values set in bold represent statistically significant outcomes
VATS: video-assisted thoracic surgery

Table 2. Distribution of histopathological diagnoses by groups

	Total		Group I		Group II		
Histopathology	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Adenocarcinoma	701	35.1	144	31.4	557	36.2	0.06
Nonadenocarcinoma	1294	64.9	314	68.6	980	63.8	
Nonsmall cell lung cancer	22	1.1	8	1.7	14	0.9	**0.049**
Squamous cell cancer	1106	55.4	256	55.9	850	55.3	
Adenocarcinoma	701	35.1	144	31.4	557	36.2	
Large cell cancer	126	6.3	37	8.1	89	5.8	
Other	40	2	13	2.8	27	1.8	

Values set in bold represent statistically significant outcomes

Table 3. Analysis of the groups according to tumor size

	Total		Group I		Group II		
Size	**Number**	**Rate**	**Number**	**Rate**	**Number**	**Rate**	**p**
Mean	4.0±2.1		4.2±2.2		3.9±2.1		**0.002**
≤3 cm	864	43.3	170	37.1	694	45.2	**0.003**
>3 cm	1131	56.7	288	62.9	843	54.8	
3–5 cm	696	34.9	163	35.6	533	34.7	**0.002**
5–7 cm	291	14.6	89	19.4	202	13.1	
>7 cm	144	7.2	36	7.9	108	7.0	

Values set in bold represent statistically significant outcomes

Table 4. Distribution of lymph node metastasis by groups

|	Total		Group I		Group II		
N status	Number	Rate	Number	Rate	Number	Rate	p
N0	1390	69.7	312	68.1	1078	70.1	0.18
N1	313	15.7	67	14.6	246	16.0	
N2	292	14.6	79	17.3	213	13.9	
N0-1	1703	85.4	379	82.7	1324	86.1	0.08
N2	292	14.6	79	17.3	213	13.9	

Table 5. Univariate analysis and multivariate Cox regression analysis of overall survival in patients with nonsmall cell lung cancer

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	p	HR	95% CI	p
Groups I and II	0.76	0.66–0.87	**<0.001**	0.82	0.71–0.94	**0.006**
Sex	0.78	0.61–0.99	**0.04**	0.79	0.61–1.02	0.07
Age	1.64	1.44–1.87	**<0.001**	1.76	1.54–2.01	**<0.001**
Operation	1.45	1.26–1.66	**<0.001**	1.32	1.14–1.54	**<0.001**
Neoadjuvant treatment	1.15	0.99–1.35	0.07	1.16	0.99–1.36	0.07
Histopathology	1.04	0.91–1.19	0.53	1.21	1.05–1.39	**0.009**
Tumor size	1.43	1.26–1.64	**<0.001**	1.33	1.14–1.54	**<0.001**
Nodal status	2.34	2.00–2.74	**<0.001**	2.19	1.86–2.58	**<0.001**
Complete resection	2.26	1.70–3.02	**<0.001**	2.21	1.65–2.96	**<0.001**

Values set in bold represent statistically significant outcomes
HR: hazard ratio; CI: confidence interval
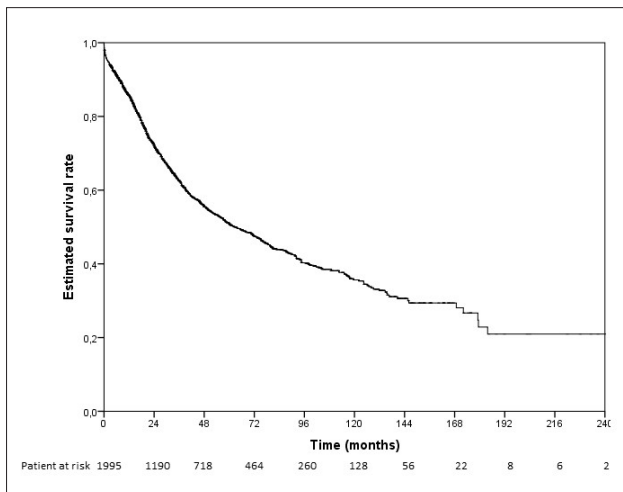
Figure 1. Overall survival curve of all patients
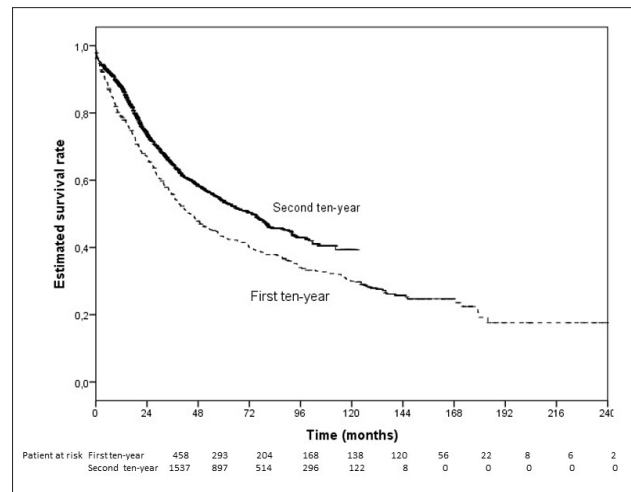
Figure 2. Survival curves for the first 10-year period (Group I) and the last 10-year period (Group II) of the 20-year study period

and 42.9% in Group I, respectively, and 73.6 months (95% CI, 63.3–83.9) and 53.9% in Group II, respectively, and the differences were statistically significant (p<0.001) (Figure 2). The Cox regression analysis revealed that age, surgical procedure, neoadjuvant therapy, tumor size, nodal involvement, and complete resection as well as the groups were determined as factors affecting survival (Table 5).

DISCUSSION

The patients who underwent curative surgical resection for NSCLC in the last 20 years were divided into two groups of ten years and the changes in the process were compared. Total number of patients, female gender, incidence of adenocarcinoma, mean age and survival time increased in the second decade. On the other hand, pneumonectomy and 30 and 90 days mortality rates decreased. Sleeve resection and VATS have been used at an increasing rate in the second decade.

Lung cancer is the leading cause of deaths among all cancer-related deaths, accounting for 12%–16% of all the cancers and 17.8%–28% of all cancer-related deaths [10]. Lung cancer epidemiology has drastically changed over the past

50 years. An increase in the number of lung cancer and adenocarcinoma cases has been observed in women [3, 7]. Conversely, the diagnostic methods have improved and the opportunity to use these methods has increased mainly in the last decade. In addition, technical conditions, surgical skills, and anesthesia management have also improved. Consistent with these developments, the number of patients who needed surgical treatment and underwent surgery increased by 3-fold during the last 10-year period of our study. With improvements in imaging techniques, smaller tumors could be identified at an early and operable stage.

In our study, the male-to-female ratio reduced from 13.8 to 9.1 when comparing Groups I and II. This may be mainly attributed to the distinct increase in smoking rates among women. It has been stated that the changes in smoking habits constitute the most important factor in the 3.7-fold increase in the proportion of female patients [11]. Another study in 2004 examined 1403 patients diagnosed with primary lung cancer and emphasized that the number of female patients increased since 1998 when the male-to-female ratio was 10.9; this ratio was 7.5 in 2004 [12].

The primary aim of surgical treatment for NSCLC is to achieve complete resection. Accordingly, with the increasing surgical experience during the last 10-year period, parenchyma-saving resections have gradually increased, whereas the proportion of patients undergoing pneumonectomy has reduced. However, it was not possible to perform resections smaller than pneumonectomy in approximately 20% of the patients because of the delayed symptoms of lung cancer. This rate was even higher in other large series [9,13-15]. By virtue of advancing technologies, the number of minimally invasive anatomical resections was gradually increased, and more than 20% of them were conducted using video-assisted thoracic surgery in the recent years of the study period.

The incidence rates of N2 disease detected by pathological examinations decreased in Group II because of the wider use of mediastinal staging methods, especially PET–CT, EBUS, and video mediastinoscopy. Although a decrease in the rates of postoperative adjuvant therapy was expected, there was no obvious decrease due to the expansion of indications for adjuvant therapy and the development of new chemotherapy agents and radiotherapy techniques with fewer side effects. Among the adjuvant therapy methods, the rate of chemotherapy tended to increase.

It is known that the proportion of squamous cell cancer was higher among cases of NSCLCs in the past, but the rate of adenocarcinoma has increased over time, and it has reached and even outnumbered the rate of squamous cell cancer in developed countries [3, 16]. In our study, the incidence rate of adenocarcinoma increased by approximately 5% in Group II.

In this study, we found out that the 30- and 90-day postoperative mortality rates had reduced over the years; in particular, the decrease in the 90-day mortality was significant. In 1537 patients who underwent lobectomy and a larger anatomic lung resection for NSCLC, the 30- and 90-day mortality rates were 4.1% and 5.7%, respectively, in the last decade. This can be attributed to the use of minimally invasive surgical methods, a reduction in pneumonectomy rates due to performing parenchyma-saving surgeries more frequently, and improvements in postoperative care. A large multi-institutional study reported that the 30-day mortality rate following major pulmonary resections in 3516 patients was 5.2%. In addition, the 30-day mortality was reported to be 4.0% in patients undergoing lobectomy and 11.5% in those undergoing pneumonectomy [17]. Considering the findings of this large multi-institutional study and those of the present study, we believe that mortality rates will decline over the years owing to the decreased need for pneumonectomy.

The greatest advantage of surgical treatment is that it provides a higher survival rate than other treatment modalities. In our study, the overall survival rate in Group II had remarkably increased. The 5-year survival rate was 42.9% in Group I and >50% in Group II. This is not only a proof of the successful performance of surgical treatments but is also related to the substantial increase in the number of patients in Group II and eventually in surgical experience. In addition, we believe that tumor size is also an important prognostic factor among the patient groups based on a previous report [18] and considering the statistically significant reduction in tumor size in the present study. A large retrospective cohort study examined 2083 patients who underwent surgical resection for NSCLC and reported an overall 5-year survival rate of 46.8% [9]. In another study that examined 2118 patients at 76 different hospitals to investigate the impact of the number of patients on long-term survival, the survival outcomes were significantly better at hospitals with a larger number of patients [8]. The time when this report [8] was presented coincides with the first 10-year period of our study, and similar to the results of our study, the 5-year survival rate at hospitals with a large number of patients was 44% in this previous study. Another interesting finding of this report [8] is the 30-day mortality of 3% at hospitals with a larger number of patients and 6% at hospitals with a smaller number of patients. Based on these data, we speculate that fatal complications that can develop during surgical treatment for lung cancer are prevented with a broader experience and good care.

The present study has some limitations. First, it is retrospective in nature. Second, the study groups were heterogeneous, and this might have affected the results. Third, owing to the study duration of 20 years, the treatment protocols for patients receiving neoadjuvant or adjuvant chemotherapy and radiotherapy were not fully available, and therefore, specific evaluations could not be made. Finally, because the staging system was changed three times during the study period, survival analysis based on the stages could not be performed.

In conclusion, this study investigated patients who underwent lobectomy or larger resection for NSCLC during the 20-year period at a single thoracic surgery department. As a consequence of the increase in technical capacity, the diagnosis frequency of the disease has also increased. Accordingly, the number of patients who underwent surgery has tripled in the last decade. There was an increase in the number of female patients among the patients undergoing surgical treatment and the incidence of adenocarcinoma. The pneumonectomy

and postoperative N2 disease detection rates have decreased with advancing preoperative evaluation techniques and parenchyma-saving surgical methods. We believe that overall survival and postoperative mortality is positively affected by improvements in surgical and anesthetic techniques and postoperative care as well as diagnostic methods that allow detecting relatively more patients at the early stage.

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