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Title: What has changed in the surgical treatment strategies of non-small cell lung cancer in twenty years? A single centre experience

Short title: Changes in the surgical strategies of non-small cell lung cancer

Authors: Ahmet Üçvet, Soner Gürsoy, Serkan Yazgan

Instutions: Department of Thoracic Surgery, University of Health Sciences, Dr Suat Seren Chest Diseases and Surgery Medical Practice and Research Center, İzmir, Turkey

Address for correspondence: Ahmet Üçvet, Department of Thoracic Surgery, University of Health Sciences, Dr Suat Seren Chest Diseases and Surgery Medical Practice and Research Center, İzmir, Turkey

E-mail: ahmetucvet@hotmail.com

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Abstract

Objective*:* Non-small cell lung cancer (NSCLC) is a multifactorial disease and differences in surgical patient characteristics may develop over the years. The aim of this study is to evaluate the patients undergone curative surgical resection due to NSCLC in the last 20 years in our centre and analyze the changes by means of demographics, surgical strategies and histopathology.

Materials and Methods: In this retrospective single-center cohort study, 1995 patients, who had undergone lobectomy, bilobectomy, or pneumonectomy due to primary NSCLC between January 1997 and January 2017, were analyzed. Patients were divided into two groups; Group I is formed by the patients who were operated in the first ten years and Group II included the patients who were operated in the last ten years .

Results: 77% of the patients were operated in the last decade (458 vs 1537). Sleeve lobectomies performed in Group II reduced the rate of pneumonectomy from 37% to 20% (p<0.001) The rates of operated adenocarcinomas increased significantly during the study period, arising from 31.4% to 36.2% (p = 0.049). 30 and 90-day postoperative mortality rates

were 4.6% and 8.5% in Group I, whereas these rates were 4.1% and 5.7% in Group II, respectively (p = 0.69 and 0.037 respectively). When the groups were compared, the median and 5-year survival rates were 44.1 months (95% 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).

Conclusions: This study demonstrates an improvement in long-term outcome after lung cancer surgery with an increasing rate of surgery in the last decade. There was an increase in the female gender and adenocarcinoma histology. Pneumonectomy rate and postoperative N2 disease rates have decreased with advancing preoperative evaluation techniques and parenchyma-saving surgical methods. Postoperative mortality has decreased and survival has been lengthened.

Keywords: Non-small cell lung cancer, survival, mortality

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INTRODUCTION

Lung cancer is considered to be a public health problem due to ever-growing mortality figures all over the world. In many reports from different countries, lung cancer still ranks first among cancer-related deaths in both men and women [1-3]. This situation is not different in Turkey and according to 2014 results of Turkish unified database, new lung cancer detection rate is 52,5/100000 in men and 8,7/100000 in women [4]. Anatomic surgical resection and mediastinal lymph node dissection are the most effective methods for the treatment of early stage non-small cell lung cancer (NSCLC) [5,6]. Lobectomy and pneumonectomy are standard applications in patients who are scheduled for surgical resection. Success in surgical treatment depends on good selection of the patients and well-staging. In addition, performance and physiological status of the patients, as well as good evaluation of the pulmonary and cardiac functions are factors affecting early and late treatment outcomes. The number of studies that report a long-term follow-up and large patient series after NSCLC surgery is very low [7-9]. The objective was to review instutional strategies in the surgical treatment of NSCLC, and how this has changed over the last 20 years.

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MATERIALS and METHODS

The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki. 1995 patients, who had undergone lobectomy, bilobectomy, or pneumonectomy with mediastinal lymph node dissection due to primary NSCLC between January 1997 and January 2017, were included in the study. Patients' age, gender, operation method, operation type, 30 and 90-day postoperative mortalities, histopathology and survival rates were recorded. Patients were divided into two groups by ten years chronologically and the differences between the groups were evaluated. The patients operated on in the time period of January 1997 – January 2007 formed the Group I and the ones operated on in the time period of January 2007 – January 2017 Group II.

All of the patients had chest X-ray, biochemistry, and pulmonary function tests preoperatively and fiberoptic bronchoscopy were performed by the surgical team before the operation. Contrast-enhanced thoracic computerized tomography (CT) as well as brain scanning (Magnetic Resonance Imaging and/or CT) were performed in each patient and in the second ten-year period, positron emission tomography (PET-CT) was performed routinely. In the years when PET-CT had not been used yet, cranial CT / MRI, bone scintigraphy and abdominal CT were performed to scan distant metastases. Having an estimated postoperative

value of FEV1 greater than 800 mL or 40% was considered sufficient pulmonary function. Patients with restrictive pulmonary function test (PFT) underwent additional examinations such as ladder-climbing test and maximal oxygen consumption (VO_2max). Pulmonary functions of the patients over VO_2max 15 ml/kg/min were considered sufficient. Transbronchial fine needle aspiration biopsy (TFNAB) or mediastinoscopy and after 2011 endobronchial ultrasonography (EBUS) were performed on patients with clinical suspicion of N2 disease. Patients who had preoperative pathological N2 disease received neoadjuvant chemotherapy and/or radiotherapy. Re-staging was performed after treatment and downstaged patients underwent surgery. Suitable patients who did not have N2 disease peroperatively were scheduled for lobectomy or bilobectomy however, pneumonectomy was performed when necessary. In the postoperative period, the patients were checked through annual CT within the first three months in the first year and in the sixth month and later in the second year. Survival calculation was based on the time from the operation until the date of death.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 software program. The Fischer's exact test or Pearson's chi square test was used to determine the groups and age as well as size of tumor were determined by "T test". Survival analysis was carried out using the Kaplan-Meier method. All patients were included in the calculation of survival and all deaths were

considered. The groups were compared by log-rank method. Cox and logistic regression methods were used in multivariate analysis. The value of $p < 0.05$ was considered to be significant in the comparison.

RESULTS

77% of the patients were operated in the second ten-year period (458 vs 1537). The overall mean age was 60.5±8.9 (the age of 31-84) and the mean age of the operated patients in Group II was found to be higher (59.4 and 60.8 respectively; $p = 0.004$) (Table 1). In the last period, an increase of approximately 5% was detected in patients at the age of 60 and over concordantly. The overall rate of female patients was 9.2%, and male/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 ($p = 0.043$).

It was observed that sleeve resection had not been performed in Group I and 6.9% of the patients in Group II had undergone sleeve lobectomy. The rate of pneumonectomy decreased from 37% to 20% in the second ten-year period concordantly and the difference was found to be statistically significant ($p < 0.001$). Videothoracoscopic pulmonary resections that had not been performed in the first ten-year period have continuously increased in recent years, and the rate of its application was 21.8% in the last year of the study and 5.1% in the last ten-year. Histopathologically, the most frequent type of cancer was squamous cell

carcinoma with 55.4% (Table 2). However, in Group II, the rate of adenocarcinoma was found to increase almost significantly in comparison with non-adenocarcinoma histology (31.4% and 36.2% respectively; $p = 0.06$). It was found that in Group II, the rate of patients operated due to a tumor 3 cm and less was higher ($p = 0.003$) and the mean tumor size was smaller ($p = 0.002$) (Table 3). 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 postoperative N status, the rates of pathologic N2 disease (17.3% vs 13.9%) and skip N2 disease (8.3% vs 5.5%) decreased in Group II (Table 4).

While the overall rates of 30 and 90-day postoperative mortality were 4.2% and 6.3%, and both rates decreased in Group II; however, only the decrease in 90-day mortality rate was statistically significant ($p = 0.69$ and 0.037 respectively). In multivariate analysis, the groups were not determined as affective variables on 30 and 90-day mortality. When the study was completed, median survival was 63.1 months (95% CI, 55.6-70.6) and 5-year survival rate was 50.9% at the end of the follow-up period of 45.5±41.2 months for all patients (Fig. 1). When the groups were compared, the median and 5-year survival rates were 44.1 months (95% 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; and the difference was statistically significant ($p < 0.001$) (Fig. 2). In the Cox regression analysis, age, operation, neoadjuvant therapy, tumor size, nodal involvement,

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complete resection, as well as the groups were determined as variables affecting survival (Table 5).

DISCUSSION

Lung cancer ranks first among cancer-related deaths and comprises 12-16% of all cancers and 17.8-28% of all cancer-related deaths [10]. Lung cancer epidemiology has changed dramatically over the last 50 years. An increase in the number of lung cancer and adenocarcinoma has been observed in women [3,7]. On the other hand, especially in the last decade, diagnostic methods and opportunity to use these methods have improved. In addition, technical conditions and surgical skills and anesthesia management have also improved. In parallel with these developments, the number of patients who needed surgical treatment and undergone surgery had increased more than three times during the second ten-year period of our study. With the improvements in imaging techniques, it was seen that smaller tumors could be identified at an early and operable stage.

In our study, the ratio of male/female reduced from 13.8 to 9.1 between Group I and Group II. This may be attributed in particular to the distinct increase in smoking rates among women. It has been stated that the changes in the smoking habits of the society are the most important factor in the 3.7 times increase of the rate of female patients [11]. In another study from 2004 which examines 1403 patients diagnosed with primary lung cancer, it was

emphasized that the number of female patients had increased since the ratio of male/female was 10.9 in 1998, whereas it was 7.5 in 2004 [12].

The first aim of surgical treatment of NSCLC is to achieve complete resection. Accordingly, with the growing surgical experience during the second ten-year period, parenchyma-saving resections increased gradually and the rate of patients undergoing pneumonectomy reduced. However, due to the delayed symptoms of lung cancer, it was not possible to perform resections lesser than pneumonectomy in approximately 20% of the patients. This rate is even higher in other large series [9,13-15]. By virtue of advancing technology, minimally invasive anatomical resections have increased gradually and more than 20% of them were conducted by video-assisted thoracic surgery (VATS) in the recent year of the study period.

The rates of N2 disease detected by pathological examination have declined in Group II due to wider use of mediastinal staging methods, especially PET-CT, EBUS, and videomediastinoscopy. Although a reduction in the rates of postoperative adjuvant therapy was concomitantly expected, there was no obvious decrease due to the expansion of indications for adjuvant therapy and the development of treatment modalities with fewer side effects. It was found out that among the adjuvant therapy methods applied, chemotherapy had a tendency to increase.

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

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

The greatest advantage of surgical treatment is that it provides a higher survival rate than other treatment modalities does. In our study, it was observed that the overall survival

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rate in Group II had increased remarkably. 5-year survival rate was 42.9% in Group I and over 50% in Group II. This is not only a proof of the success in surgical treatments performed, but it may be also related to the substantial increase in the number of patients in Group II and accordingly increased surgical experience. In addition, we can say that tumor size is also an important prognostic factor among patient groups, based on previous reports and considering the statistically significant reduction in tumor size [18]. In a large retrospective cohort study which examines 2083 patients who underwent surgical resection for NSCLC, the overall 5-year survival rate was reported to be 46.8% [9]. In another study in which 2118 patients from 76 different hospitals were analyzed to investigate the impact of the number of patients on long-term survival, the survival outcomes were significantly better in hospitals with larger numbers of patients [8]. The time when this report was presented coincides with the first period of our study, and in this report, 5-year survival rate in hospitals with a large number of patients was found to be 44%, similar to our results. Another interesting result of the presented report is 30-day mortality. This rate is 3% in hospitals with a larger number of patients, while it is 6% in those having less patients. Based on all these data, we can speculate that mortal complications which may develop in surgical treatment of lung cancer can be prevented with a broader experience and good care.

There were some limitations. It was a retrospective study. The study groups were heterogeneous and this might have affected the results. Due to the study period of 20 years,

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treatment protocols for patients receiving neoadjuvant or adjuvant chemotherapy and radiotherapy were not fully available and specific evaluations could not be made. Since the staging system had been changed three times during the study period, survival analysis on the stages could not be performed.

In conclusion, the results of patients who underwent lobectomy or larger resection for NSCLC during the twenty-year period of the single thoracic surgery department were presented in this study. As a consequence of the increase of technical capacity, the diagnosis frequency of the disease has also increased. Accordingly, the number of patients operated has tripled in the last decade. An increase was observed in the number of female patients among the patients undergoing surgical treatment and in the histology of adenocarcinoma. Pneumonectomy rate and the rate of postoperative N2 disease detection have decreased with advancing preoperative evaluation techniques and parenchyma-saving surgical methods. We think that survival and postoperative mortality will be positively affected by the improvements in surgical and anesthetical techniques, and postoperative care as well as the diagnostic methods that allows to detect more patients in the early stage.

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	All	Group I	Group II	*p*

Table 1. The differences in patients characteristics and resection types between the goups.

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Mean age		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	**0.03**
Sex	Male	1812	90.8	427	93.2	1385	90.1	**0.04**
	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	**0.01**
Sleeve resection		106	5.3	-	-	106	6.9	-
VATS		79	4.0	-	-	79	5.1	-

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Bold values represent statistically significant outcomes

Table 2. The 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	
Non-adenocarcinoma	1294	64.9	314	68.6	980	63.8	0.06
NSCLC	22	1.1	8	1.7	14	0.9	
Squamous cell	1106	55.4	256	55.9	850	55.3	
Adenocarcinoma	701	35.1	144	31.4	557	36.2	**0.04**
Large cell	126	6.3	37	8.1	89	5.8	
Other	40	2	13	2.8	27	1.8	

Bold values represent statistically significant outcomes

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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 and smaller	864	43.3	170	37.1	694	45.2	**0.003**

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Larger than 3 cm	1131	56.7	288	62.9	843	54.8	
3-5 cm	696	34.9	163	35.6	533	34.7	
5-7 cm	291	14.6	89	19.4	202	13.1	**0.002**
Larger than 7 cm	144	7.2	36	7.9	108	7.0	

Bold values represent statistically significant outcomes

Table 4. The distribution of lymph node metastasis by groups.

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	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	

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Table 5. Univariate analysis and multivariate Cox regression analysis for overall survival in patients with non-small cell lung cancer.

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*p*	HR	95% CI	*p*
Group I and II	0.76	0.66-0.87	**< 0.001**	0.82	0.71-0.94	**0.006**
Gender	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**
Neo-adjuvant 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**

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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**

HR, hazard ratio; CI, confidence interval; Bold values represent statistically significant outcomes

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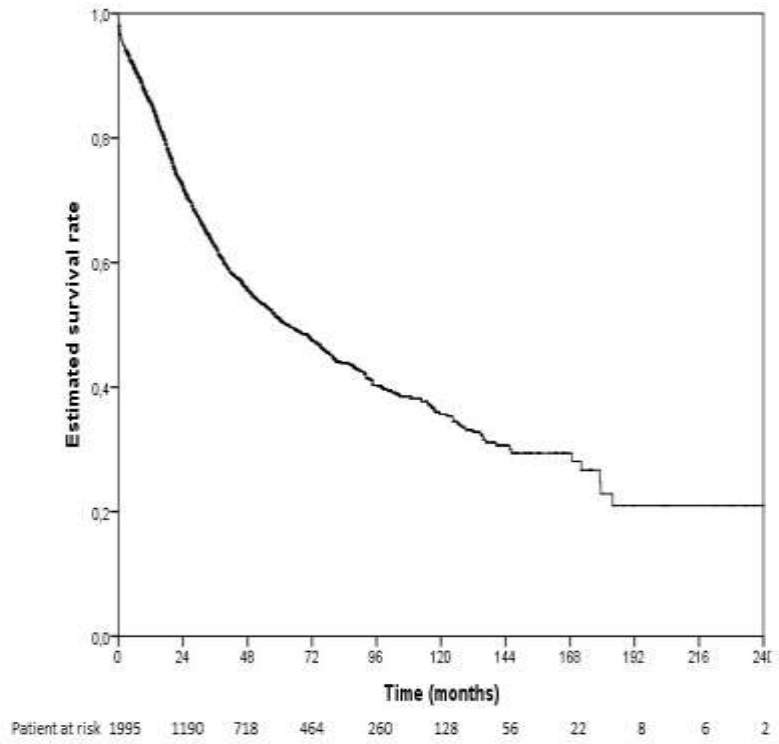

Fig. 1. Overall survival curve of all patients.

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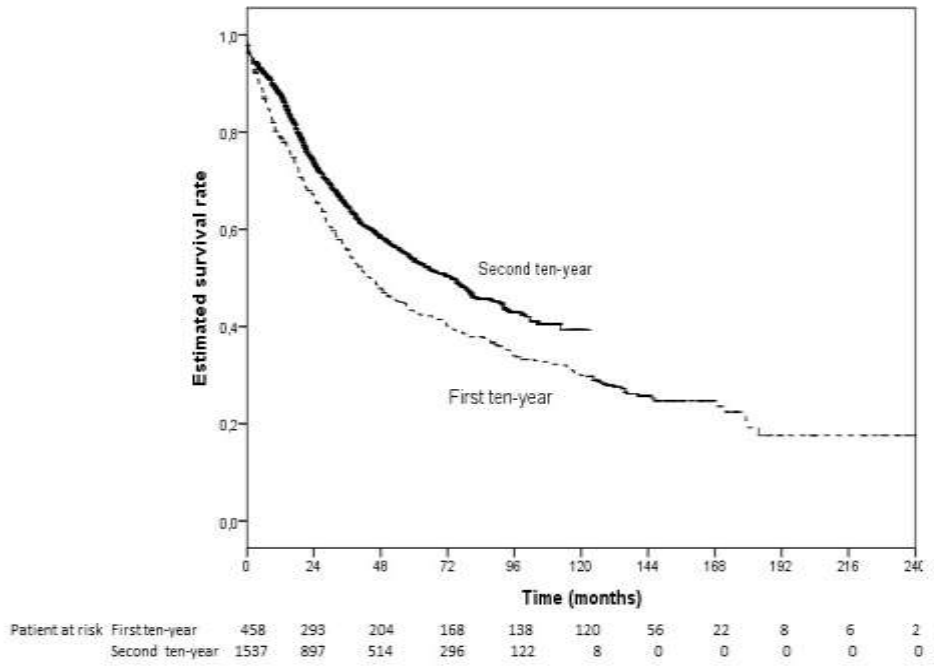

Fig. 2. Survival curves of the first ten-year (Group I) and the second ten-year (Group II) of the 20-year study period.

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