ORIGINAL ARTICLE

COMPARISON OF PROGNOSTIC FACTORS IN PATIENTS WITH LUNG CANCER OPERATED AFTER NEOADJUVANT TREATMENT

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Abstract

Aim: *Lung cancer is the leading cause of cancer-related deaths worldwide. The most favorable treatment option for early-stage non-small cell lung cancer is surgical resection. In locally advanced lung cancer, surgery can be performed as part of multimodal treatment regimens. In this study, we aimed to investigate the survival outcomes and prognostic factors of non-small cell lung cancers operated on after neoadjuvant treatment.*

Methods*: The data of patients who were operated on after neoadjuvant treatment in our clinic between 2012 and 2022 were collected. Data were analyzed according to age, gender, complete resection, applied treatment regimen, operation type, presence of viable tumor, histopathology, N status, tumor diameter, and presence of progression.*

Results: *A total of 96 patients were included in the study. There were 9 female (9.4%) and 87 male (90.6%) patients. The mean age was 65.2 ± 8.3. Median overall survival was 41 months (15.7-66.2), and 5-year overall survival was 42.4%. Poor prognostic factors for overall survival in our study are being older than 65 years (p=0.02), tumor progressing despite treatment (p=0.008), tumor diameter greater than 2.65 cm (p=0.01), incomplete resection (p=0.002), and tumor stage higher than stage I according to TNM classification 8th edition (p=0.02). There was no significant correlation between survival and gender, tumor histopathology, neoadjuvant treatment protocol, presence of viable tumor, presence of persistent N2, and type of surgery performed (p>0.05)*

Conclusion: *When planning surgery after neoadjuvant treatment in locally advanced lung cancer, there are some parameters to take into consideration which are age, tumor diameter after treatment, complete resectability, and the presence of diameter progression despite treatment.*

Keywords: *Neoadjuvant, non-small cell lung cancer, pulmonary resection, survival*

INTRODUCTION

According to WHO (World Health Organization)-GLOBOCAN 2020 data, lung cancer ranks first among cancer cases in men and third in women in the world [1]. After staging and preoperative evaluation, the most appropriate treatment option for early-stage non-small cell lung cancer is surgical resection [2]. There is no single treatment option for locally advanced non-small cell lung cancer. Today, with multimodal treatment approaches, 5-year OS has increased to 19-45% [3]. For patients with locally advanced lung cancer who are planning for surgery, neoadjuvant therapy is the preoperative treatment aimed to provide local and systemic control of the disease. Treatment can be planned as isolated chemotherapy, isolated radiotherapy, or chemoradiation. Nowadays, tyrosine kinase inhibitors and immunotherapy have also been added to this group as neoadjuvant therapy options with acceptable success in terms of overall survival and disease-free survival [4-5]. With neoadjuvant treatment, systemic control and reduction in tumor size can be achieved, and an increase in complete resection rates can be detected [6]. Although various treatment regimens have been shown to have a positive effect on survival, there are also studies showing that operative complications increase in the patient group for whom surgery is planned after neoadjuvant treatment [7]. In this study, we aimed to investigate the survival outcomes and prognostic factors of patients with non-small cell lung

cancer who were operated on after neoadjuvant treatment in our clinic.

MATERIALS AND METHODS

Following the ethics committee's approval, the data of patients who underwent surgery for lung cancer in our clinic between February 2012 and June 2022 was retrospectively examined. Patients who were operated after neoadjuvant treatment for NSCLC were included in the study. Patients whose follow-up records were not available, whose indication for neoadjuvant treatment could not be determined, those using tyrosine kinase inhibitors, and who did not undergo appropriate lymph node dissection, according to the IASLC guideline, were not included in the study. Analyses were performed with Statistical Package for the Social Sciences software (version 25.0, USA). Categorical variables were given as n and %; numerical variables were given as mean/standard deviation for normal distributions, and median and distribution (minimum-maximum) for skewed distributions. Distribution normality in numerical data was determined by histogram and Kolmogorov-Smirnov methods. Overall Survival times of the patients were calculated in months. The date of diagnosis was taken as the starting point for the overall survival of the patients. For deceased patients, the date of death and for living patients, the date of data collection was taken as the end date. Overall survival was calculated by the Kaplan-Meier method, and survival between groups was calculated by Log-Rank and Cox-regression methods. The cut-off value of tumor diameter associated with survival in pathological staging was determined by Receiver Operating Characteristic (ROC) analysis. Studies were performed with a 95% confidence interval. The significance between neoadjuvant treatment type (only chemotherapy or chemo-radiotherapy) and complications was investigated using Pearson's chi-square or Fisher's exact test according to the expected count. A two-sided p-value was calculated; $p<0.05$ was considered statistically significant.

RESULTS

A total of 96 patients who met the inclusion criteria were included in the study. There were 9 female (9.4%) and 87 male (90.6%) patients. The mean age was 65.2 ± 8.3. The most common histopathological subtype was squamous cell carcinoma in 56 (58.3%) patients. There was a neoadjuvant indication due to mediastinal, chest wall, carinal or atrial invasion in 43 patients (44.8%) and N2 station metastasis in 42 patients (43.8%). The most applied neoadjuvant treatment protocol was isolated chemotherapy in 60 patients (62.5%). According to TNM classification 8th edition, the most common clinical stage before neoadjuvant treatment was stage IIIA in 52 patients (54.2%), and the most frequently detected stage in the pathological staging after surgery was stage IIB in 36 patients (37.5%). With neoadjuvant treatment, tumor regression was detected in 66 patients (68.8%), while there was no change in 27 patients (28.1%). Progression was detected in 3 patients (3.1%). With ROC analysis, the cut-off value for significant tumor diameter in pathological staging was determined as 2.65 cm (Figure 1). When high and low diameter groups were determined according to this value, there were 47 patients (49%) in the high group and 49 patients (51%) in the low group. In pre-treatment clinical staging, the median tumor diameter was 5 cm (range: 1.5-14), and in postsurgical pathological staging, it was 2.5 cm (range: 0-15) cm. Lung resections performed were lobectomy in 63 patients (65.6%). Clinicopathological characteristics of the patients included in the study are given in tables 1-3. The average follow-up period in our study was 34.2 months. Median OS was 41 months (Range: 15.7-66.2), 5-year OS was 42.4% (Figure 2). Poor prognostic factors for OS; being older than 65 years ($p=0.02$, Figure 3), tumor progressing despite treatment ($p=0.008$, Figure 4), tumor diameter measured at pathological restaging being larger than 2.65 cm ($p=0.01$, Figure 5), incomplete resection ($p=0.002$, Figure 6), tumor re-stage was higher than stage I according to 8th TNM staging ($p=0.02$, Figure 7). There was no significant correlation between OS and gender, tumor histopathology, neoadjuvant treatment protocol, presence of viable tumor, presence of persistent N2, and type of surgery performed ($p>0.05$) (Table 1-4). The postoperative complication rates in patients receiving neoadjuvant chemotherapy and chemoradiotherapy were 40% and 65.7%, respectively, and were statistically significant ($p=0.01$).

DISCUSSION

In this study, we demonstrated advanced age, incomplete resection, tumor progression despite neoadjuvant treatment, high pathological stage, and high pathological tumor diameter were significantly poor prognostic in patients who underwent lung resection after neoadjuvant treatment.

In the literature, there are various opinions regarding the prognostic effect of gender in studies examining lung cancer cases operated on after neoadjuvant treatment. In the study conducted by Karaman et al., which included patients receiving neoadjuvant treatment for NSCLC during the COVID-19 pandemic, gender was not seen as a factor that significantly affected overall survival [8]. Although survival was found to be worse in male patients in our study, the difference between the groups was not statistically significant, consistent with the literature.

In some studies, the age factor has been reported as an important prognostic factor in patients undergoing lung cancer surgery. While Furrer et al. reported that age was a significant poor prognostic factor in terms of OS in lung resection series performed after neoadjuvant treatment, there are also studies in the literature reporting that age is not associated with mortality and long-term

survival and that it is safe even in octogenarian patients [10-11]. According to the results of our study, overall survival was significantly worse in lung resection performed after neoadjuvant treatment in patients older than 65 years of age. Due to possible postoperative complications and poor long-term OS, age can be assumed as an important predictor in patient selection.

When studies examining the relationship between OS and NSCLC-histopathological subtypes were examined, the general opinion was that histopathology did not have a significant correlation with survival. In the study published by Corsini in 2021 examining the relationship between neoadjuvant treatment and lung cancer, it was observed that the histopathological subtype did not make a statistically significant difference in survival [11]. Although Melek et al. stated in their study that the predominant histopathology in patients who achieved a complete pathological response after neoadjuvant treatment was squamous cell carcinoma, they did not find a statistically significant difference [12]. As a result of our study, it was determined that survival after surgery in adenocarcinoma histopathology was better than others, but the difference was not statistically significant. This result shows that the NSCLC subtype is not an important marker in patient selection for surgical planning after neoadjuvant therapy.

In our study, survival was found to be significantly poorer in patients with progression despite neoadjuvant treatment. It has been reported in the literature that progression occurs in 10% of patients after neoadjuvant chemotherapy, and this is associated with tumor aggressiveness [13]. The progression rate in our series is 3%, which is lower than the rate stated in the literature. Local progression in terms of diameter and invasion was observed in 3 patients in our series, and the patients were operated on to prevent possible progression and inoperability due to chemotherapy resistance. However, our results showed that OS after surgery is significantly poorer in patients who progress with induction therapy, and the tumor is quite aggressive in these patients, and this should be taken into consideration when selecting patients.

Whereas previously, concurrent irradiation with induction chemotherapy may have been a preferred option for resectable locally advanced NSCLC, the current National Comprehensive Cancer Network (NCCN) guideline (version 3.25) recommends neoadjuvant radiotherapy only for specific conditions such as Pancoast tumors [14]. It is also possible to come across opinions in the literature stating that neoadjuvant radiotherapy increases operative complications and does not have a positive effect on survival. Mortality after neoadjuvant chemotherapy varies between 2.5-8%. With the addition of neoadjuvant radiotherapy to the treatment, this rate changes to 0-23%. In the study conducted by Martin et al., mortality was found to be 3.8% in the neoadjuvant treatment group, and this rate was found to be similar to studies in which cases did not receive neoadjuvant treatment [15]. In our study, survival was worse in the neoadjuvant chemoradiotherapy group compared to the group that received only induction chemotherapy; but it was not statistically significant. This situation can be interpreted as neoadjuvant radiotherapy not affecting survival and chemotherapy alone will be sufficient. At the same time, neoadjuvant radiotherapy complicates intraoperative manipulations and increases the risk of postoperative complications. Considering these findings, it can be concluded that the combination of chemotherapy and radiotherapy is not superior to chemotherapy alone.

Some factors associated with survival have been reported for pathological staging after neoadjuvant therapy. One of these is the belief that the absence of viable tumor cells in the specimen is associated with good survival. Hellman et al. reported the detection of <10% viable tumor cells in pathological examination as a major pathological response and emphasized that this was associated with good survival [16]. Junker et al. reported that OS was 14 months and 36 months in patients with viable tumors above and below 10%, respectively in their study, including 40 cases that underwent lung resection after neoadjuvant chemoradiotherapy, and found that this difference was statistically significant [17]. In our study, although the mean OS was minimally higher in those without viable tumors, the difference was not statistically significant.

There are few studies showing the correlation between tumor diameter in pathological staging and survival in patients receiving neoadjuvant therapy. In a study conducted by Fırat et al. on 112 patients diagnosed with stage III NSCLC and receiving only radiotherapy, it was reported that a tumor size of 7 cm and above was not a poor prognostic factor for survival [18]. However, since resectable T4N0 and T4N1 patients are candidates for direct surgery, this group of patients is quite small. In our study, the cut-off value of tumor diameter that would affect survival in pathological restaging was determined to be 2.65 cm, and survival was found to be significantly worse in tumors larger than this diameter. Our result here is consistent with the significantly better survival found in patients with tumor regression after neoadjuvant treatment and can be interpreted as tumors with larger diameters despite treatment being more aggressive.

The relationship between pathological restaging and survival in patients undergoing surgery after neoadjuvant therapy is an intriguing topic. In their multivariate analysis, Zens et al. created a prognostic score for this condition and found survival to be significantly worse in the high rTNM stage [19]. Akyıl et al. reported that survival was significantly worse in the stages in relation to the rT and rN factors [20]. In a retrospective study by Melek et al., patients who received and did not receive neoadjuvant treatment were compared. The authors found a significant difference in survival between pathological stages in the neoadjuvant group and claimed

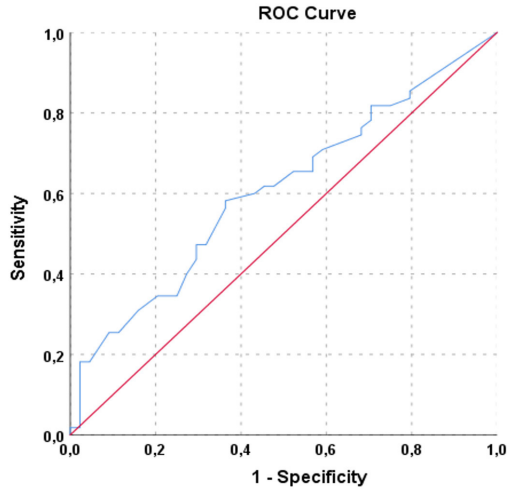

Figure 1 *The ROC curve for tumor diameter detected in pathological staging.*

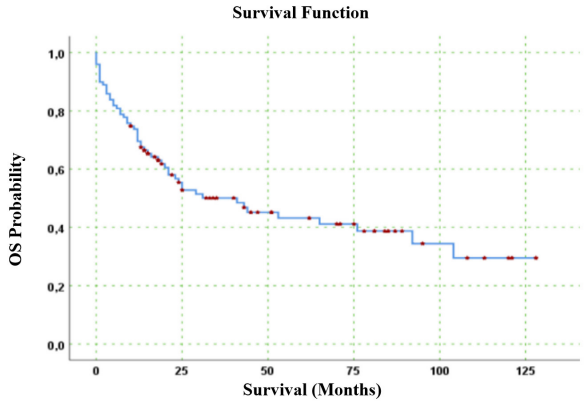

Figure 2 *The Kaplan–Meier curve of overall survival.*

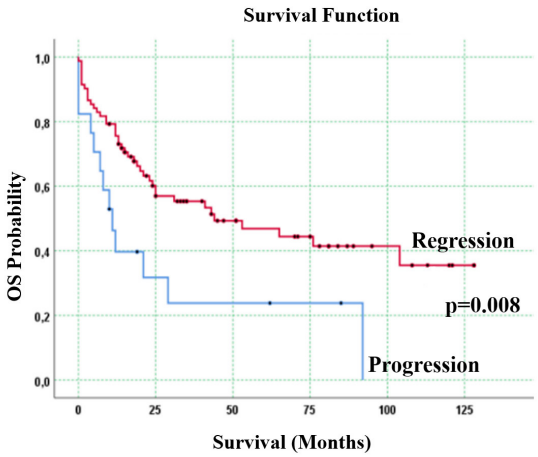

Figure 4 *The progressive tumor, despite neoadjuvant therapy, is a significantly worse prognostic factor (p=0.008).*

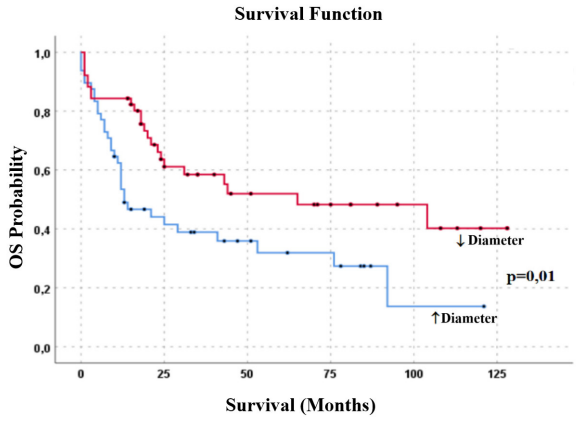

Figure 5 *Tumor diameter measured in pathologically larger than 2.65 cm is a poor prognostic factor (p=0.01).*

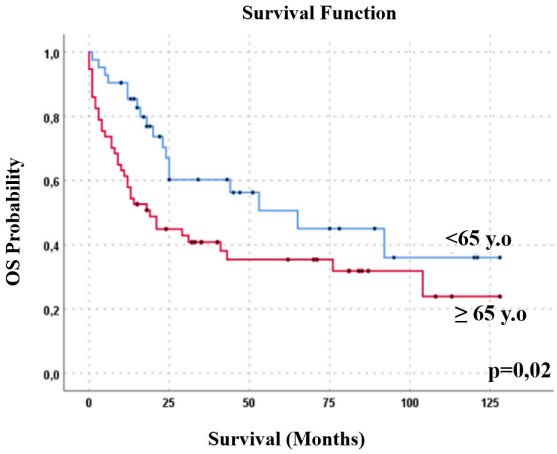

Figure 3 *Advanced age (≥ 65 years old) is a worse prognostic factor (p=0.02).*

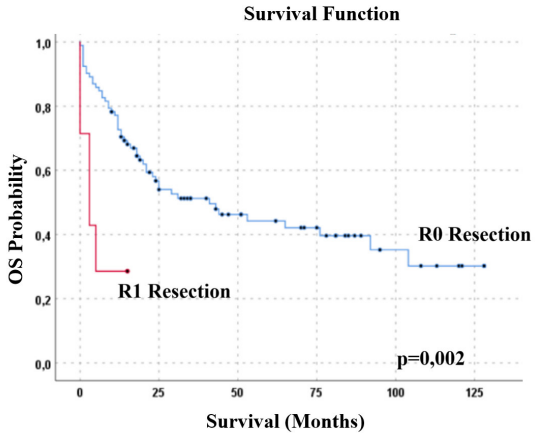

Figure 6 *Incomplete resection is a poor prognostic factor. (p=0.002).*

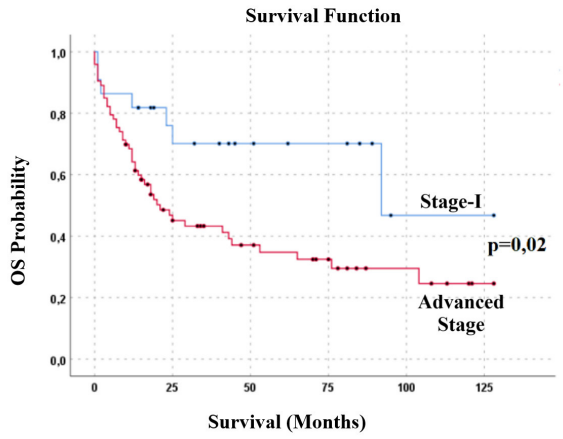

Figure 7 *In restaging, tumor stage higher than Stage 1 according to the 8th TNM is a poor prognostic factor (p=0.02).*

Table 1 **The numerical variables of patients included in the study, N=96**

Variables	Values
Age (years) (Mean with SD)	65.2 ± 8.3
Pretreatment tumor diameter (cm), Median (min-max)	5 (1.5-14)
Posttreatment tumor diameter (cm), Median (min-max)	2.5 (0-15)
Dose of RT (Gy), Median (min-max)	60 (45-65)
Cycles of CT, Median (min-max)	3 (2-9)
Pretreatment SUV-max of mass, Median (min-max)	13.3 (2.6-31.9)
Posttreatment SUV-max of mass, Median (min-max)	3.2 (0-6.3)

Abbreviations: CT: Chemotherapy, RT: Radiotherapy, SD: Standard Deviation, SUV-max: Maximum Standard Uptake Value.

that patients without viable tumors had similar survival to early-stage patients who did not require neoadjuvant therapy [12]. In our study, patients were divided into two groups as early (stage 0-I) and advanced (> Stage I), and the median OS and 5-year OS were significantly higher in the patients with early pathological stages of cancer. In our study, the fact that posttreatment tumor diameter was a more significant prognostic factor than the presence of persistent N2 and viable tumor may be interpreted as the local effect of the tumor is important in terms of survival. The relationship between the type of resection performed after neoadjuvant treatment and survival has been examined in various publications. In lung resection studies performed after neoadjuvant therapy, Furrer et al. reported that extended resection did not adversely affect survival and even provided better complete resection [9]. Brunswicker et al. reported that neoadjuvant therapy was significantly associated with 90-day and 1-year mortality in patients with pneumonectomy but found that it had no significant prognostic effect on long-term survival [21]. In the article published by Broderick, it was reported that there was no significant difference between other groups in terms of operative mortality and overall survival in patients who underwent pneumonectomy after neoadjuvant treatment [22]. In our study, the best median OS was in the lobectomy group, while the worst survival was in the sublobar resections, and no significantly worse prognostic effect of pneumonectomy was detected. Our result may indicate that sublobar resections negatively affect survival in patients receiving neoadjuvant therapy, and this should be taken into account in surgical planning. It is a known entity that incomplete resections are associated with poor survival in pulmonary resections performed for NSCLC, whether neoadjuvant therapy is received. In the study conducted by Collaud et al., it was shown that peribronchial involvement and lymph node infiltration are more common in advanced-stage disease, and although microscopic incomplete (R1) resection is associated with this condition, R1 resection is associated with poor survival even in the early-stage [23]. In a study, Riquet et al. stated that the 5-year OS in the R1 resection group that received neoadjuvant treatment was 19.8% [24]. In our series, survival was significantly worse in the R1 resection group, consistent with the literature. Our result may indicate surgery should be avoided whenever an R0 resection cannot be guaranteed after neoadjuvant therapy.

The limitations of our study were as follows: it is a retrospective and single-centered study and included a small number of cases. Another limitation was that the pathology results were not standard, and some results were reported as viable or not viable cells, but the percentage of viable tumor cells was not given. Therefore, subgroups such as complete pathological response, major pathological response, or partial response could not be determined, and two groups were created due to the presence or absence of viable cells. In addition, some patients received neoadjuvant radiotherapy at another center. Although patients with uncertain dose information are excluded from the study, the fact that the device and delivery techniques used for radiotherapy are not standard can be seen as a disadvantage. Another limitation was that molecular studies could not be performed on all patients, and related prognostic groups could not be created since older patients were predominant in the study.

Table 2 **Characteristics of patients included in the study, N=96**

Variables		n	%
Gender	Male	87	90.6
	Female	9	9.4
Tumor Histopathology	Adeno CA	33	34.4
	Squamous Cell CA	56	58.3
	Large Cell CA	3	3.1
	Pleomorphic CA	1	1.0
	Combined Large Cell CA	2	2.1
	LCNEC	1	1.0
Posttreatment Tumor Diameter	≥2.65 cm	47	49.0
	<2.65 cm	49	51.0
Neoadjuvant Therapy Indication	Lymph Node Metastasis	42	43.8
	Invasion	43	44.8
	Combined	11	11.5
Neoadjuvant Treatment Protocol			
	CT	60	62.5
	CRT	36	37.5
Adjuvant Therapy	CT	28	29.2
	CRT	16	16.7
	CT+ Cranial Irradiation	6	6.3
	CT+ Adrenal Gland Irradiation	1	1.0
	RT	3	3.1
	No	42	43.8
Pretreatment Tumor Stage (8th TNM)	II-B	22	22.9
	III-A	52	54.2
	III-B	19	19.8
	IV-A	3	3.1
Posttreatment Pathological Tumor Stage	I-A	18	18.8
	I-B	4	4.2
	II-A	10	10.4
	II-B	36	37.5
	III-A	20	20.8
	III-B	4	4.2
	0*	4	4.2
Change of the Tumor Stage After Neoadjuvant Therapy	No	27	28.1
	Progression	3	3.1
	Regression	66	68.8
Postoperative Complications** No		49	51
Yes		47	49
	30 Day Mortality	4	4.2
	PAL	21	21.9
	Bleeding***	3	3.1
	Chylothorax	2	2.1
	CSF Leak	1	1.0
	Pneumonia	6	6.3
	BPF	6	6.3
	Atrial Fibrillation	9	9.4
	Acute Kidney Injury	11	11.5
	Empyema	8	8.3
	PTE	1	1.0
	VCP	2	2.1
	Prolonged ICU stay	6	6.3

Abbreviations: CA: Carcinoma, CSF: Cerebro Spinal Fluid. CT: Chemotherapy, CRT: Chemoradiotherapy, ICU: Intensive Care Unit, LCNEC: Large Cell Neuroendocrine Carcinoma, PAL: Prolonged Air Leak, PTE: Pulmonary Thromboembolism, RT: Radiotherapy, VCP: Vocal Cord Paralysis, Explanations: *Viable tumor and tumor bed were not detected histopathological examination. * Postoperative complications were determined by higher than grade 2 according to the Clavien–Dindo classification.
**Represents bleeding requiring revision.

Table 3 **Surgical Procedures Applied, N=96**

Variables	n	%
Left pneumonectomy	19	19.8
Right upper lobectomy	14	14.6
Left upper lobectomy	12	12.5
Right lower lobectomy	5	5.2
Left lower lobectomy	4	4.2
Bilobectomy inferior	2	2.1
Bilobectomy superior	1	1.0
Right pneumonectomy	7	7.3
Left pneumonectomy with aortic resection	1	1.0
Left pneumonectomy with chest wall resection	1	1.0
Left upper lobectomy with arterioplasty	1	1.0
Left Upper Lobectomy with aortic resection	1	1.0
Left upper lobectomy with vertebra resection	1	1.0
Left upper sleeve resection with arterioplasty	1	1.0
Left extended pneumonectomy	2	2.1
Left upper lobectomy with chest wall resection	2	2.1
Right upper lobectomy with subclavian artery resection	2	2.1
Left S6 segmentectomy	2	2.1
Right upper sleeve lobectomy	8	8.3
Right upper lobectomy with chest wall resection	6	6.3
Left upper lobe wedge resection	1	1.0
Right lower sleeve resection	1	1.0
Right lower lobectomy with esophagectomy	1	1.0
Right upper lobectomy with vertebra resection	1	1.0

Table 4 **The results of survival analyses and p values according to some variables, N=96**

Variables		n	%	Median Survival (months)	CI-95%	p-value
Gender						
	Male	87	90.6	25	0-56.3	0.4
	Female	9	9.4	44	24.9-63.0	
Age (years old)						
	<65	41	42.7	65	18.4-111.5	0.02
	≥65	55	57.3	19	9.9-28.0	
Progression Status						
	Progression	3	3.1	11	5.9-16.0	0.008
	Regression	66	68.8	44	6.5-81.4	
Histopathology						
	Adeno CA	35	36.5	43	8.4-77.5	
	Squamous Cell CA	54	56.2	31	0-67.7	0.3
	Other	7	7.3	8	2.8-13.1	
Indication of Neoadjuvant Therapy						
	Lymph Node Metastasis	42	43.8	41	12.7-69.2	
	Invasion	43	44.8	44	7.4-80.5	0.3
	Combined	11	11.4	16	13.4-18.5	
Treatment Protocol						
	CT	60	62.5	41	15.2-66.7	0.3
	CRT	36	37.5	25	0-51.1	
Viable Tumor						
	No	4	4.2	31	7.2-50.7	0.5
	Yes	92	95.8	29	-	
Posttreatment Tumor Diameter						
	≥2.65 cm	47	49	13	5.1-20.8	0.01
	<2,65 cm	49	51	65	0-130.1	
Complete Resection						
	R0	89	92.7	41	15.7-66.2	0.002
	R1	7	7.3	3	0-6.8	
Pathological Stage						
	Stage 0-I	26	27.1	92	-	0.02
	Stage II-III	70	72.9	21	9.5-12.4	
Persistent N2						
	Yes	22	22.9	25	0-54.1	0.2
	No	74	77.1	41	0-83.7	
Surgery						
	Lobectomy	63	65.6	53	0-146.8	
	Pneumonectomy	30	31.3	25	4.5-45.4	0.09
	Limited Resection	3	3.1	12	0-25.2	

Abbreviations: CA: Carcinoma, CI: Confidence Interval, CT: Chemotherapy, CRT: Chemoradiotherapy

CONCLUSION

When planning surgery after neoadjuvant treatment in locally advanced NSCLC; age, tumor diameter after treatment, complete resectability, and the presence of tumor progression after induction therapy should be taken into consideration. Additionally, although not statistically significant, the result that survival is worse in sublobar resections should be taken into consideration in preoperative evaluation. Our results need to be supported by multicenter prospective studies.

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