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The Survival Efficiency of Initial Surgical Treatment in Stage IIIa-N2 Positive Non-Small Cell Lung Cancer

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Abstract

Objective: The role of surgical treatment in the multimodal treatment of stage IIIA-N2 positive non-small cell lung cancer (NSCLC) patients is a matter of debate. We aim to investigate initial surgical treatment's survival efficiency in patients with IIIA N2 positive NSCLC**.**

Methods: The patients treated for stage IIIA N2 positive NSCLC in a single center between January 2009 and December 2014 were retrospectively analyzed. A total of 134 patients with 5 cm tumors in diameter or less and without involvements of the chest wall, mediastinal pleura, phrenic nerve, recurrent laryngeal nerve, pericardium, heart, diaphragm, vertebra, esophagus, large vessel invasion, and satellite nodule were detected. Of these patients, initial surgical treatment before chemoradiotherapy was performed in 72 (Group 1), while definitive concurrent chemoradiotherapy was performed in 62 patients (Group 2). Each patient's gender, age, physical performance status, tumors size, pathological diagnosis, lung resection types, and long-term survival data were evaluated.

Results: No statistically significant difference was found in patients' gender, physical performance, tumor size, and tumor histology. Survival rates were higher among patients aged ≤65 years and higher in Group 1 than Group 2. While one-, three, five-, and seven-year survival rates were detected as 86.1%, 62.5%, 41.6%, and 31% in Group 1, respectively, the rates were observed to be as 77.4%, 30.6%, 10.8%, and 6.7% in Group 2, respectively. However, no difference was seen between patients' survival rates with single and multiple ipsilateral mediastinal lymph node metastases.

Conclusion: Despite those advocating surgical treatment after neoadjuvant chemotherapy in treating stage IIIA N2 positive patients, others supporting surgical treatment should initially be performed. When conducted as the first step, surgical treatment achieves significant increases in survival.

Keywords: Non-small cell lung cancer, stage IIIA, N2 positive, survival**.**

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Introduction

Lung cancer is one of the leading causes of cancer-related deaths globally, and 80% of lung cancers are composed of non-small cell lung cancers (NSCLC). Additionally, almost 30% of NSCLC's are seen to be at a locally advanced stage at the time of diagnosis (1). The patients with locally advanced NSCLC are classified as stage III for the fundamental structure of the 8th TNM staging system: T for characteristics of the primary tumors, N for nodal involvement, and M for (distant) metastasis under the American Joint Commission on Cancer (AJCC) in the United States and the Union for International Cancer Control (UICC) internationally (2). Five-year survival for stage III NSCLC patients is 26% from diagnosis, and the patients at stage III constitute a very heterogeneous group (3). The presence of ipsilateral mediastinal lymph node positivity (N2 positive) independent of tumors diameter and local invasion causes the disease to be staged as III. The positivity of contralateral mediastinal lymph nodes also makes the disease be evaluated as stage III, regardless of tumors size and local invasion. Definitive concurrent chemoradiotherapy (CCRT) is recommended for stage III patients as the standard treatment (4). Although the surgical treatment after neoadjuvant chemotherapy and adjuvant chemoradiotherapy is recommended in some N2 positive patients under the National Comprehensive Cancer Network (NCCN) guidelines, the surgical treatment is not recommended the first-line modality for these patients (5). The present study aimed to evaluate the association of initial surgical treatment survival rates before chemotherapy and radiotherapy in the patients with stage IIIA N2 positive NSCLC compared to those receiving definitive CCRT.

Methods

This study was designed as a retrospective and observational study and approved by the local ethics committee (approval number: 2321/2021). An informed consent form was not obtained from the participants because of the study's retrospective design and the rendering of the patient information unrecognizable. All authors confirmed compliance with the World Medical Association Declaration of Helsinki on the ethical conduct of research involving human subjects.

The patients treated with initial surgical for stage III NSCLC in a single center between January 2009 and December 2014 were retrospectively analyzed. From the hospital records, 123 patients with the positivity of ipsilateral mediastinal lymph nodes (N2 positive) and undergoing surgical treatment were detected. Of 123 patients, 10 (8.1%) undergoing lung resection after neoadjuvant chemotherapy, four (3.3%) diagnosed with carcinoid tumor's, three (2.4%) with T4 tumor's, 18 (14.6%) with T3 tumors', 10 (8.1%) not receiving radiotherapy after lung resection, and six (4.9%) not receiving adjuvant chemotherapy were excluded from the study. Therefore, 72 (58.6%) patients treated with chemotherapy and radiotherapy following lung resection and systemic sampling of mediastinal lymph nodes were included in the study. These patients were classified as Group 1 in our study. In addition to 72 patients in Group 1, among those referred to the definitive CCRT due to N2 positivity within the pre-operative period, 62 patients with T1 and T2 tumor's and initially evaluated as respectable and operable were detected and included in the study as Group 2. As a result, of 134 patients constituting our study population, 72 (53.7%) received chemotherapy and radiotherapy after lung resection, and systemic lymph node sampling was classified as Group 1, 62 (44.3%) patients treated with definitive CCRT were put into Group 2. The patients were staged under the 8th edition of the Tumor-Node-Metastasis staging system (2). All patients (n=134) in the study were staged as stage IIIA. The follow-up period was determined to be between 60-132 months. The data of the patients were obtained from digital archive files of the hospital. Such characteristics as age, gender, date of diagnosis, pathological diagnosis, tumour location, types of pre-operative invasive mediastinal procedures, stage of the disease, and physical performance status were recorded. The patients' physical performance status was classified according to the performance status classification of Eastern Cooperative Oncology Group (ECOG) (6). The dates of the patients' deaths were also obtained from the Turkish Ministry of Health's death notification system.

Statistical analysis

The statistical analyses were carried out by using IBM SPSS Statistics for Windows, Version 22.0 (SPSS Inc., Chicago, IL, USA). The descriptive statistics of the study are presented with frequency and percentage for categorical variables and mean and standard deviations for numerical variables. Descriptive statistical methods (e.g. mean, standard deviation, median, frequency and ratio) and Shapiro-Wilks test, histogram and box plot graphics were used to evaluate the distribution of the variables. Independent group comparisons were made with the

chi-square test. The survival rates were calculated using the Kaplan-Meier method. The log-rank test evaluated the comparisons of survival curves between both groups. The effects of continuous and categorical variables on survival times were evaluated using the backward conditional method with the Cox proportional hazards regression model. The hazard ratios were estimated from the data. A $p \leq 0.05$ value was accepted to be statistically significant.

Results

Of 134 patients, 122 (91%) were male, and 12 (9%) were female. The mean age of the patients was found as 58.91±8.43 years. The findings concerning age, gender, size of tumours, number of N2 positive stations, pathological types, and physical performance status are given in Table 1. The histological investigation revealed that the most common tumours were evaluated as squamous cell carcinoma in 60 (44.7%) cases, adenocarcinoma in 51 (38%), not otherwise specified (NOS) in 14 cases (10.5%), adenosquamous tumours in 7 (5.2%) cases, and large cell carcinoma in two cases (1.6%). (Table 1)

Table 1. Baseline Characteristics of Patients

Variables	Group 1 n (%)	Group 2 n (%)	Total n (%)	P value*
Age (Years)				
≤65	59 (81.9)	49 (79)	108 (80.6)	p = 0.417
>65	13 (18.1)	13 (21)	26 (19.4)	
Gender				
Male	62 (86.1)	60 (96.7)	122 (91.0)	p = 0.029
Female	10 (13.9)	2 (3.3)	12 (9.0)	
Pathology				
Adenocarcinoma	34 (47.2)	17 (27.4)	51 (38.0)	p = 0.03
Squamous cell	31 (43.0)	29 (46.7)	60 (44.8)	
carcinoma	0	14 (22.6)	14 (10.5)	
NOS	7 (9.8)	2 (3.3)	9 (6.7)	
Others				
Metastatic mediastinal lymph node	48 (66.6)	43 (69.3)	91 (67.9)	p = 0.442
Single	24 (33.4)	19 (30.7)	43 (32.1)	
Multiple				
T status				
T1a (≤2 cm)	11 (15.3)	4 (6.4)	15 (11.2)	p = 0.413
T1b (>2cm, ≤3cm)	20 (27.8)	18 (29.0)	38 (28.3)	
T2a (>3cm, ≤4 cm)	21 (29.1)	37 (59.7)	58 (43.3)	
T2b (>4cm, ≤5 cm)	20 (27.8)	3 (4.9)	23 (17.2)	
ECOG performance status	68 (94.4)	60 (96.7)	128 (95.5)	p = 0.369
$ECOG_0$	4 (5.6)	2 (3.3)	6 (4.5)	
$ECOG_1$				

ECOG: Eastern Cooperative Oncology Group performance status, NOS: Not otherwise specified. *The distribution of the groups according to the categorical variables was analyzed with the chi-square test.

Of 72 patients in group 1, lobectomy was performed for 66 (91.6%), bilobectomy for four (5.5%), and pneumonectomy for two (2.9%) patients.

According to the Cox regression analysis, only the age (HR= 1.043, p<0.001) and the treatment groups (HR= 1.365, p<0.003) were statistically significant on survival. Gender, tumors histopathology, T status, and mediastinal lymph node metastasis (single/multiple) did not affect survival (Table 2)

When the patients in both groups were evaluated according to tumors diameter, the number of those with T1a, T1b, T2a, and T2b tumors' was 11 (15.3%), 20 (27.8%), 21 (29.1%), and 20 (27.8%) in Group 1, respectively. Even so, the number of those with the same tumours was detected as four (6.4%), 18 (29%), 37 (59.7), and 3 (4.9%) among Group 2 patients, respectively. No statistically significant difference was found between groups (p=0.91). (Table 2)

Table 2. Survival Analysis According to Categorical and Numeric Variables

	Hazard ratio	%95 CI*	p value
Gender	1.042	0.512-2.122	0.91
Age	1.043	1.017-1.070	**0.001****
Tumor histopathology	0.945	0.784-1.139	0.533
T status	1.011	0.840-1.217	0.91
N2 (Single/Multiple)	0.972	0.645-1.465	0.892
Treatment Group (Group1/2)	1.365	1.112-1.676	**0.003****

CI*: Confidence Interval

Of 134 patients, 106 (79.1%) deaths were detected, while 28 (20.9%) survived during the follow-up period as of 31st December 2019. When the survival rates were examined in both groups, median survival rates were 44 and 23 months for Groups 1 and 2, respectively. When the survival rates were evaluated by years, while one-, two-, three-, four-, and five-year survival rates were found as 86.1%, 73.6%, 63.5%, 48.6%, and 41.6% respectively for those in Group 1, the rates were calculated as 77.4%, 50%, 40.3%, 21%, and 10.3% for those in Group 2. The survival rates in Group 1 were determined to be statistically significantly higher than those in Group 2 (p<0.01). When the survival rates were examined in both genders, the average survival time was 44 months for men and 33 months for women. No statistically significant difference was found between both genders (p=0.91). (Table 2)

When the patients were divided into two groups as ≤65 years and >65 years of age, the average survival time was determined as 55.6 months among those aged ≤65 and 22.9 months among those aged >65. Based on the analyses of survival rates, a statistically significant difference was found in the survival rates of those aged ≤65 (p<0.01).

When the patients were divided into two groups as those with single N2 positive and multiple N2 positive, in light of the number of positive mediastinal lymph node stations, 91 (68%) patients were found to have single N2 positive. In contrast, 43 (32%) patients were found to be with multiple N2 positive. According to this criterion, while the mean survival rates were determined as 49.7 and 46 months for single and multiple N2 positive patients, respectively, the median survival times were calculated as 35 and 37 months. No statistically significant difference was found between those with single and multiple N2 positive (p=0.814). (Figure 1) (Table 2) However, when the survival rates of those with single and multiple N2 positive in Group 1 (n=72) were compared, the mean (median) survival times were determined as 63.5 months (median, 50 months) and 55.7 months (median, 37 months), respectively. No statistically significant difference was found between the patients with single and multiple N2 positive in Group 1 (p=0.581) regarding survival rates. (Table 3) Even so, when the survival rates of 62 patients with single and multiple N2 positive in Group 2 were compared, the mean (median) survival times were determined as 31.7 months (median, 23 months) and 32.8 months (median, 33 months), respectively. There was no statistically significant difference between single and multiple N2 positive patients in Group 2 regarding survival rates (p=0.743). (Table 3)

Table 3. Survival Analysis By Single and Multiple N2 Metastases

Survival Time Mean (Median) months			
	Single N2	**Multiple N2**	**P value**
Group 1	63.5 (50)	55.7 (37)	p = 0.581
Group 2	32.8 (33)	31.7 (23)	p = 0.743

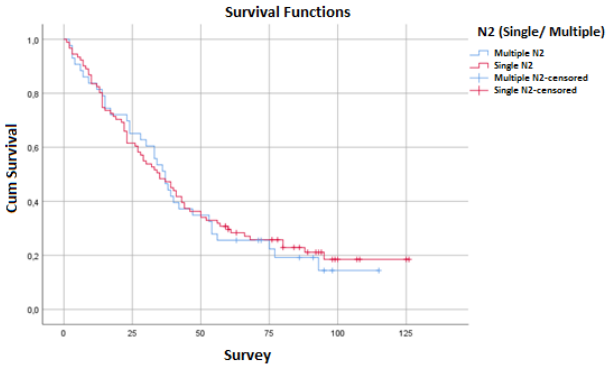

Figure 1. Analysis of survival by single and multiple mediastinal lymph node metastases

Discussion

The most critical factor determining the prognosis of NSCLC is the staging process of the disease (6). In a study, 25–30% of the patients with NSCLC were reported to be diagnosed at locally advanced stages (IIIA or IIIB). Postoperative 5-year survival rates were stated to range between 13 and 42.8% (7).

Stage III NSCLCs include a highly heterogeneous group of patients with differences in the extent and localization of the disease. Many aspects of the treatment of stage III N2 positive disease are controversial as the entities to be elucidated. The best-suggested therapy for most clinically evident N2 disease patients is definitive CCRT, using platinum-based chemotherapy plus radiotherapy. However, there is no consensus on the role of surgery in treating stage III (N2 positive) NSCLC patients. Despite definitive CCRT, survival rates require re-evaluating surgical treatment for such patients (8-10).

In previous studies, N2 positivity was the most important factor affecting prognosis negatively (11-13). Therefore, it is evident that determining the most appropriate treatment according to the stages of cancer, especially node metastasis is essential. When all patients were evaluated in our study, while the median survival time was determined as 35 months, the 5-year survival rate was 28.3 months.

The most appropriate treatment for the patients with stage IIIA N2 positive NSCLC remains controversial; however, a consensus is that utilizing a single treatment modality alone, whether surgery or radiotherapy, results in relatively low survival rates (14-17).

Definitive CCRT is recommended for those with stage IIIA (N2 positive) disease. However, surgical treatment following induction chemotherapy may also be utilized as an alternative therapy (5). In a study, overall survival (OS) was indicated better in

the patient's undergoing lobectomy than those receiving chemotherapy and radiotherapy alone (18). In other studies, postoperative radiotherapy and surgery alone were reported not to improve overall survival in the patients with IIIA N2 (positive) NSCLC, and lobectomy was stated to provide better long-term survival than pneumonectomy after induction chemotherapy, with no increase in postoperative complications or recurrence rates (19-21). In our study, the patients undergoing lung resection and systemic mediastinal lymph node sampling were considered to have no mediastinal lymph node metastasis in the pre-operative period; N2 positivity was detected intraoperative postoperative period, and so adjuvant chemoradiotherapy was performed in these patients. When the patients' survival times were examined, it was remarkable that the 5-year survival rates were like those of the patients undergoing lung resection+chemoradio therapy following neoadjuvant therapy.

Morbidity and mortality rates were determined according to the surgical resection types (20, 21). Accordingly, postoperative morbidity and mortality rates were higher in the patients undergoing neoadjuvant chemoradiotherapy after pneumonectomy than those treated with lobectomy (18). Our study demonstrated that the survival rates between the patients undergoing lobectomy and pneumonectomy were not different (p=0.635). We consider that the relatively low number of pneumonectomy patients included in the study may have affected our findings.

In the study performed it was reported that the 5-year survival rates for stages IA, IB, IIA, IIB, IIIA, IIIB, and IV in NSCLC were 82%, 66%, 52%, 47%, 36%, 19%, and 6%, respectively (20). The data released by the Japanese Lung Cancer Registry Center showed that the 5-year survival rates for stages IIA, IIB, and IIIA NSCLC were 61%, 47.4%, and 32.8%, respectively (21). In another study conducted by Cerfolio et al. (22) including similar findings to ours, the 5-year survival rate was reported to be 42% among stage IIIA N2 (positive) patients undergoing surgery after neoadjuvant treatment (22). Although surgical treatment was used as the first step of multimodal treatments in our study, our survival rates were similar to those undergoing surgery after neoadjuvant treatment reported in Cerfolio et al. (22). In our study, the 5-year survival rates were 41.6% and 10.3% in Group 1, and there was a statistically significant difference between the survival rates in Groups 1 and 2 (p<0.01). Our results indicate that combined treatments with initial surgical treatment and adjuvant chemoradiotherapy may have a higher chance for more prolonged survival in those with NSCLC. However, we consider that further studies are required to understand whether such a treatment modality can lengthen the survival rate in N2 positivity.

In the study by Misthos et al. (23) the patients with single N2 metastases were reported to have better survival rates than those with multiple N2 metastases in a relatively large group (23). There was no statistically significant difference between single and multiple N2 positive patients in our study regarding survival rates (p=0.814). When the patients in Group 1 were evaluated as single and multiple N2 positive, the mean survival times were found as 63 and 55 months, while the median survival times were calculated as 50 and 37 months, respectively. Although found to be high, the difference between the survival times was not statistically significant (p=0.581).

Conclusion

Current treatment modalities could not provide adequate survival for stage IIIA (N2 positive) NSCLC patients. Surgical treatment should be considered after neoadjuvant chemoradiotherapy and as the first step for stage IIIA N2 positive NSCLC patients' multimodal treatments. Despite the common belief that surgical treatment is not beneficial for those with multiple N2 metastases, we consider that better survival rates can be achieved in such patients, mostly when surgical treatment is performed as the first multimodal treatment step.

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References

1. Nicholson AG, Chansky K, Crowley J, Beyruti R, Kubota K, Turrisi A, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(3):300-311. doi:10.1016/j.jtho.2015.10.008
2. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10(12):1675-1684. doi:10.1097/JTO.0000000000000678
3. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64(4):252-271. doi:10.3322/caac.21235 .
4. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol. 2017;8(1):1-20. doi:10.5306/wjco.v8.i1.1
5. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 4.2016. J Natl Compr Canc Netw. 2016;14(3):255-264. doi:10.6004/jnccn.2016.0031
6. Hekimoglu B, Gulhan SSE, Akkas Y, Acar LN, Kaya S. Survival Analysis in N2 (+) Patients for Whom Surgical Resection Was Performed. Akd Med J. 2019; 5: 104-11. doi: 10.17954/amj.2018.1131
7. Hess LM, Smith D, Cui ZL, Montejano L, Liepa AM, Schelman W, et al. The relationship between Eastern Cooperative Oncology Group performance status and healthcare resource utilization among patients with advanced or metastatic colorectal, lung or gastric cancer. J Drug Assess. 2020;10(1):10-17. Published 2020 Dec 16. doi:10.1080/21556660.2020.1851504
8. Lee JG, Lee CY, Kim DJ, Chung KY, Park IK. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognosis analysis and staging assessment. Eur J Cardiothorac Surg. 2008;33(3):480-484. doi:10.1016/j.ejcts.2007.12.005
9. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial [published correction appears in Lancet. 2015 Sep 12;386(9998):1040]. Lancet. 2015;386(9998):1049-1056. doi:10.1016/S0140-6736(15)60294-X
10. Shah AA, Berry MF, Tzao C, Gandhi M, Worni M, Pietrobon R, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. Ann Thorac Surg. 2012;93(6):1807-1812. doi:10.1016/j.athoracsur.2012.03.018
11. Gurses A, Turna A, Bedirhan MA, Ozalp T, Kocaturk C, Demir A, et al. The value of mediastinoscopy in preoperative evaluation of mediastinal involvement in non-small-cell lung cancer patients with clinical NO disease. Thorac Cardiovasc Surg. 2002 Jun;50(3):174-7. doi: 10.1055/s-2002-32416. PMID: 12077692.
12. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol. 2008;3(8):819-831. doi:10.1097/JTO.0b013e31818020eb
13. Novaes FT, Cataneo DC, Ruiz Junior RL, Defaveri J, Michelin OC, Cataneo AJ. Lung cancer: histology, staging, treatment and survival. J Bras Pneumol. 2008;34(8):595-600. doi:10.1590/s1806-37132008000800009
14. Fernandes AT, Mitra N, Xanthopoulos E, Evans T, Stevenson J, Langer C. et al. The impact of extent and location of mediastinal lymph node involvement on survival in Stage III non-small cell lung cancer patients treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys. 2012;83(1):340-347. doi:10.1016/j.ijrobp.2011.05.070
15. Le Pechoux C, Arriagada R, Pignon JP. Need for new powered trials to assess the role of post-operative radiotherapy for stage III non-small cell lung cancer. Radiother Oncol. 2014;112(2):314-315. doi:10.1016/j.radonc.2014.05.015
16. Ma Q, Liu D, Guo Y, Shi B, Song Z, Tian Y. Surgical therapeutic strategy for non-small cell lung cancer with mediastinal lymph node metastasis (N2). Zhongguo Fei Ai Za Zhi. 2010;13(4):342-348. doi:10.3779/j.issn.1009-3419.2010.04.14

17. Katagiri Y, Jingu K, Yamamoto T, Matsushita H, Umezawa R, Ishikawa Y, et al. Differences in patterns of recurrence of squamous cell carcinoma and adenocarcinoma after radiotherapy for stage III non-small cell lung cancer. Jpn J Radiol. 2021;39(6):611-617. doi:10.1007/s11604-021-01091-y
18. Albain KS, Swann RS, Rusch VW, Turrisi AT 3rd, Shepherd FA, Smith C. et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379-386. doi:10.1016/S0140-6736(09)60737-6
19. Shi W, Zhang W, Sun H, Shao Y. Sleeve lobectomy versus pneumonectomy for non-small cell lung cancer: a meta-analysis. World J Surg Oncol. 2012;10:265. Published 2012 Dec 11. doi:10.1186/1477-7819-10-265
20. Tsiambas E, Ragos V, Lefas AY, Georgiannos SN, Grapsa D, Grapsa D. et al. Chromosome 7 deregulation in non-small cell lung carcinoma molecular landscape. J BUON. 2015;20(6):1635-1639.
21. Asamura H, Goya T, Koshiishi Y, Sohara Y, Eguchi K, Mori M, et al. A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol. 2008;3(1):46-52. doi:10.1097/JTO.0b013e31815e8577
22. Cerfolio RJ, Maniscalco L, Bryant AS. The treatment of patients with stage IIIA non-small cell lung cancer from N2 disease: who returns to the surgical arena and who survives. Ann Thorac Surg. 2008;86(3):912-920. doi:10.1016/j.athoracsur.2008.04.073
23. Misthos P, Sepsas E, Kokotsakis J, Skottis I, Lioulias A. The significance of one-station N2 disease in the prognosis of patients with nonsmall-cell lung cancer. Ann Thorac Surg. 2008;86(5):1626-1630. doi:10.1016/j.athoracsur.2008.07.076