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Original Article / Özgün Makale

The effect of the number of dissected lymph nodes on survival in patients operated on for T_{1a}-T_{2a} N_0 non-small cell lung cancer

T_{1a}-T_{2a} N_0 küçük hücreli dışı akciğer kanseri nedeni ile ameliyat edilmiş hastalarda diseke edilen lenf nodu sayısının sağkalım üzerine etkisi

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ABSTRACT

Background: This study aims to investigate the effect of the number of dissected lymph nodes on survival in patients operated on for T_{1a}-T_{2a} N_0 non-small cell lung cancer.

Methods: The medical records and follow-up data of patients operated on for non-small cell lung cancer between January 2005 and December 2009 were analyzed retrospectively. One hundred and forty-one patients (128 males, 13 females; mean age 63±8.7 years; range 37 to 82 years) who did not receive neoadjuvant treatment, with pathological stage of $T_{1a}N_0M_0$, $T_{1b}N_0M_0$, and $T_{2a}N_0M_0$ (stage I according to seventh edition of tumor-node-metastasis classification of malignant tumors), and who were performed lobectomy or pneumonectomy and mediastinal lymph node dissection were included in this study. The significance between the total number of dissected lymph nodes from both N_1 and N_2 stations and the survival of the patients were evaluated. The patients were divided into two groups: Group A included the patients having less than nine lymph nodes dissected, whereas group B included the patients with nine or more dissected nodes. Survival rates of the two groups were compared.

Results: The survival rate was lower in group A compared to that of group B and the difference was statistically significant. The multivariate Cox regression analysis demonstrated that the number of dissected lymph nodes (in addition to age, gender, T stage, type of resection, and histopathologic subtype) was an independent prognostic factor.

Conclusion: The number of lymph nodes dissected effects survival in non-small cell lung cancer in patients with stage T_{1a}-T_2 N_0. Surgeons should make an effort to dissect as many lymph nodes as possible during lung cancer surgery.

Keywords: Lung cancer; lymph node; surgery; survival.

ÖZ

Amaç: Bu çalışmada T_{1a}-T_{2a} N_0 küçük hücreli dışı akciğer kanseri nedeni ile ameliyat edilmiş hastalarda diseke edilen lenf nodu sayısının sağkalım üzerine etkisi araştırıldı.

Çalışma planı: Ocak 2005 ve Aralık 2009 tarihleri arasında küçük hücreli dışı akciğer kanseri nedeni ile ameliyat edilmiş hastaların tıbbi kayıtları ve izlem verileri retrospektif olarak incelendi. Neoadjuvan tedavi almamış, patolojik evresi $T_{1a}N_0M_0$, $T_{1b}N_0M_0$ ve $T_{2a}N_0M_0$ (malign tümörlerin tümör-nodül-metastaz sınıflandırmasının yedinci edisyonuna göre evre I) olan, lobektomi veya pnömonektomi ile mediastinal lenf nodu diseksiyonu uygulanmış 141 hasta (128 males, 13 females; mean age 63±8.7 years; range 37 to 82 years) çalışmaya dahil edildi. N_1 ve N_2 istasyonlarından diseke edilen lenf nodlarının toplam sayısı ile hastaların sağkalımları arasında ilişkinin anlamlı olup olmadığı değerlendirildi. Hastalar iki gruba ayrıldı: Grup A diseke edilen lenf nodu sayısı dokuzdan az olan hastaları içerir iken grup B diseke edilen lenf nodu sayısı dokuz ve dokuzdan fazla olan hastaları içeriyor idi. Her iki grubun sağkalım oranları karşılaştırıldı.

Bulgular: Sağkalım oranı grup B ile kıyaslandığında grup A'da daha düşük idi ve bu fark istatistiksel olarak anlamlı idi. Çok değişkenli Cox regresyon analizi, diseke edilen lenf nodu sayısının bağımsız bir prognostik faktör olduğunu (yaş, cinsiyet, T evresi, rezeksiyon tipi ve histopatolojik alt tipe ek olarak) ortaya koydu.

Sonuç: Küçük hücreli dışı akciğer kanserinde evresi T_{1a}-T_{2a} N_0 olan hastalarda diseke edilen lenf nodu sayısı sağkalımı etkiler. Cerrahlar akciğer kanseri cerrahisinde mümkün olduğunca çok sayıda lenf nodunu diseke etmeye çalışmalıdılar.

Anahtar sözcükler: Akciğer kanseri; lenf nodu; cerrahi; sağkalım.

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Cancer is one of the leading causes of death worldwide, accounting for 7.6 million deaths, and lung cancer is responsible for more cancer-related deaths than any other cancer type.[1] Currently, it is agreed that the best treatment for non-small cell lung cancer (NSCLC) without distant metastasis is complete tumor removal. However, several prognostic factors are associated with the outcome following lung resection for bronchial carcinoma. Mediastinal lymph node (LN) involvement is one of the most important and significant factors predicting survival in patients with NSCLC.

There is currently no consensus or generally accepted standard concerning the amount of LN tissue that needs to be excised and evaluated for proper N staging of NSCLC.[2] Thus, even if excised LN tissue is considered necessary for accurate staging in most cases; the number of LNs that is needed for histopathological analysis and the procedures to be used during their excision is still subject to debate. The lack of a standardized approach in this regard has lead to a multitude of different clinical practices for N staging in NSCLC, ranging from relatively less invasive methods involving only the examination of the mediastinum with little or no dissection, to more invasive methods involving the dissection and removal of a considerable amount of LN tissue.

Although some authors suggest that systematic LN excision is not necessary for NSCLC patients in certain circumstances,[3-5] recent studies state that the number of resected LNs is one of the most important prognostic factors in stage I disease.[6-8] The researchers of this study present data supporting the hypothesis that the number of LNs dissected might increase survival rates treated surgically for N_0 NSCLC. Thus, in this study, we aimed to investigate the effect of the number of dissected LNs on survival in patients operated on for T_{1a}-T_{2a} N_0 NSCLC.

PATIENTS AND METHODS

Between January 2005 and December 2009, 562 anatomic resections were performed for patients with NSCLC in Department of Thoracic Surgery of Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital. Of these, 150 T_{1a}-T_{2a} N_0 NSCLC patients (stage I, according to seventh edition of TNM Classification of Malignant Tumors) with complete resection (also known as a R_0 resection) were staged after final histopathological examination. T_1 has been subclassified into T_{1a} (≤2 cm in size) and T_{1b} (>2-3 cm in size), and T_2 has been subclassified into T_{2a} (>3-5 cm in size). Pathological staging was used in the study.

Although there were 150 patients eligible for the study, nine patients were lost to follow-up and not included in the study. Ultimately, a total of 141 patients, (128 males, 13 females; mean age 63±8.7 years; range 37 to 82 years) were included.

The patients were divided into two groups: group A included patients having less than nine dissected LNs whereas group B included patients with nine or more dissected nodes. The survival rate of the two groups was also compared. In our study group, the mean number of LNs resected was 9.9; so, the two groups mentioned above were formed according to this data by choosing the cut-off point at nine resected LNs. Patients who underwent neoadjuvant or adjuvant chemo/radiation therapy, incomplete resections, and wedge resections were excluded.

Chest X-ray, computed tomography (CT) scan, and fiber optic bronchoscopy were used for locoregional assessment of lung cancer. Positron emission tomography/CT scan was used after 2006 for detecting distant organ metastasis and invasive mediastinal staging was performed for possible mediastinal LN metastases according to the scanning results. Based on the imaging results, mediastinal nodes with fluorodeoxyglucose uptake more than 2.5 or enlarged LNs (short axis diameter over 1.0 cm) in the mediastinum on CT scan were evaluated by utilizing invasive methods to ascertain the presence or absence of metastases. The physiological criteria for selection of the patients were performed according to American College of Chest Physicians guidelines.[9]

The standard surgical approach was posterolateral thoracotomy. Two chest drains were placed routinely. The patients stayed in the intensive care unit for the first 24 hours and then taken to thoracic surgery ward unless there was a major early postoperative problem. All patients underwent complete anatomic resection with either mediastinal node dissection or sampling. Samples were always obtained from a minimum of three mediastinal LN sites, which included mostly the subcarinal sites on both sides of the body. The significance between the total number of dissected LNs from both N_1 and N_2 stations and the survival of the patients were evaluated.

The evaluated clinicopathological parameters were age, sex, cancer site (right and left lung), tumor-node-metastasis stage, histopathologic subtype, tumor size, number of resected nodes, and survival rates.

The follow-up data were collected based on outpatient clinical calls and telephone surveys. All patients were followed-up in terms of history, physical

examination, and chest and upper abdominal CT scan every three months for the first year, every six months for the first second and third years, then annually every year thereafter. In cases with suspicious recurrence or metastasis, patients were subjected to further diagnostic methods.

Statistical analysis

Data were entered and analyzed with IBM SPSS Statistics for Windows, Version 20.0 software program (IBM Corporation, Armonk, N.Y., USA). Survival was analyzed with the Kaplan-Meier method and the curves were compared by using a log-rank test. The multivariate analysis was performed by using the Cox proportional hazard model. Frequency comparisons were carried out by the chi-square test between two groups. Results were considered significant if $p<0.05$.

RESULTS

There were 33 $T_{1a}N_0M_0$ (23%), 35 $T_{1b}N_0M_0$ (25%), and 73 $T_{2a}N_0M_0$ patients (52%) in the whole study population of 56 patients (40%) with left-sided tumors and 85 patients (60%) with right-sided tumors.

The surgical procedures included 106 lobectomies (75%), 12 bilobectomies (9%), seven sleeve lobectomies (5%) and 16 (11%) pneumonectomies. Pathologic examination of the resected specimens revealed squamous cell carcinoma in 74 patients (52.5%), adenocarcinoma in 57 patients (47.5%), and large cell carcinoma in 10 patients (7%). The clinicopathological characteristics of the patients are summarized in Table 1.

Overall morbidity was 31.2%; 45 of the 141 patients had postoperative complications. The most common postoperative complication was prolonged air leak (n=25, 17.7%). Other postoperative complications were arrhythmia (n=23, 16.3%), pneumonia (n=20, 14.2%), wound infection (n=19, 13.5%), atelectasis (n=13, 9.2%), mechanical ventilation >24/h (n=12, 8.5%), and pleural empyema (n=10, 7%). The mortality was 2.8%; four deaths among 141 patients. Mean postoperative hospital stay was 9.2±3.8 days.

In total, 1,377 LNs were resected (T_{1a}=320, T_{1b}=325, and T_{2a}=732). The mean number of excised LNs was 9.9±4.4, with 10.8±5.2 LNs on the right side and 8.6±3.3 LNs on the left side. At least five LNs were resected in the majority of patients (80%). The percentage of patients with subcarinal LN dissection was 83.7% (118/141). The mean number of resected LNs in group A was 5.7±2.5 compared to 13 LNs in group B.

Table 1. Patients' baseline characteristics

Variables	n	%	Mean±SD	Median survival (months)	5 years survival (%)	*p*
Age (years)			63±8.7	–	–	
<60	44	31		80.4	67	0.039
≥60	97	69		62.5	51	
Gender	–	–	–	–	–	
Male	13	9		54.1	63	0.98
Female	128	91		62.8	80	
Type of resection	–	–	–	–	–	
Pneumonectomy	16	11		55.5	50	0.562
Lobectomy	125	89		69.5	60	
Histopathologic subtype	–	–	–	–	–	
Squamous cell carcinoma	74	52.5		71	57	0.71
Adenocarcinoma	57	40.5		67.2	59	
Large cell carcinoma	10	7		59.4	52	
Pathologic stage	–	–	–	–	–	
1a	33	23		79.6	68	0.078
1b	35	25		52.9	45	
2a	73	52		67.9	56	
Number of harvested lymph nodes	–	–	–	–	–	
<9	75	53		52.3	38	<0.001
≥9	66	47		84.8	77	
Total	141	100		68.7	55.6	–

SD: Standard deviation; *p* value: Kaplan-Meier analysis with log-rank test.

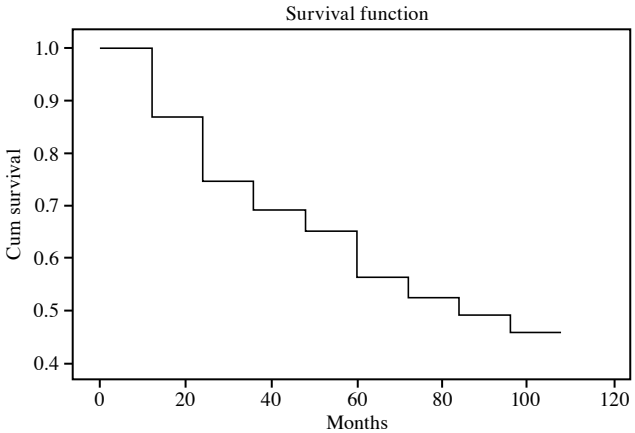

Figure 1. Overall Kaplan-Meier survival in patients with pathological stage I non-small cell lung cancer.

Complete follow-up data were obtained for 141 patients as of January 1, 2005. Seventy-three (51.7%) patients were alive at the end of the study. All surviving patients were followed-up at least three months postoperatively and the mean follow-up time was 48±11.6 months.

The five-year survival rate of all 141 patients was 55% (median survival 68.7 of months) (Figure 1). The five-year survival rate was 68% (n=33) for T_{1a}, 45% (n=35) for T_{1b}, and 56% (n=73) for T_{2a}. The overall survival estimates were stratified by older age, sex, type of resection, histopathologic subtype, and pathologic stage. The numbers of resected LNs are shown in Figure 2. The five-year survival rate was significantly higher in patients who underwent lobectomy and in group B patients from whom nine or more LNs were removed. As shown in Figure 3, increased survival was associated with more than nine to 10 LNs resected.

The univariate analysis identified older age (60≥ vs. <60, p=0.039) and number of resected LNs (1-8 vs. ≥9, p<0.001) as poor prognostic factors. There were no statistically significant differences between survival rates in terms of sex, type of resection, and histopathologic subtype (Table 1). The multivariate analysis revealed the number of resected LNs and age as independent prognostic factors (Table 2).

DISCUSSION

We demonstrated that a high number of resected LNs and older age were associated with better overall survival in stage I non-small cell lung cancer after complete resection in univariate analysis. However, other variables were not found to predict survival in these patients. In addition, the multivariate analysis

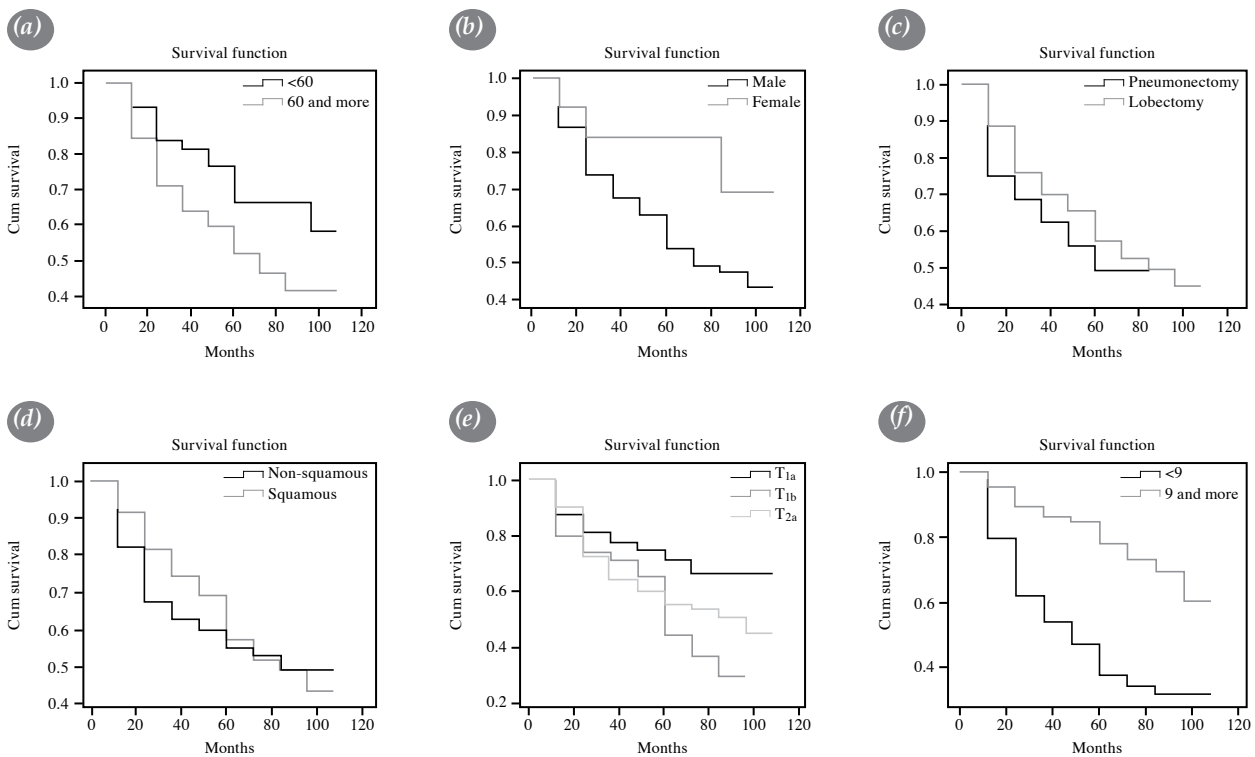

Figure 2. (a) Kaplan-Meier survival estimates stratified by older age, **(b)** gender, **(c)** type of resection, **(d)** histopathologic subtype, **(e)** pathologic tumor stage, and **(f)** number of resected lymph nodes.

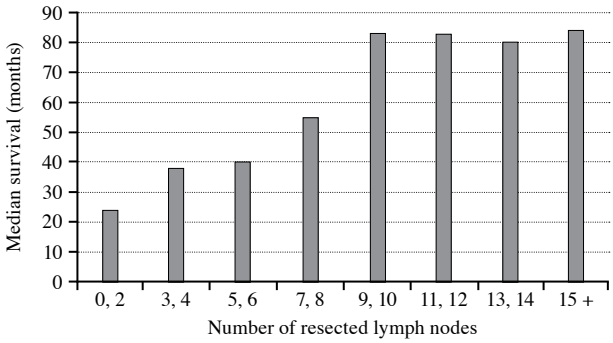

Figure 3. Median survival by number of resected lymph nodes.

showed that the number of resected LNs and older age were correlated with the prognosis of lung cancer patients. None of the other variables were statistically significantly determined survival. The survival was lower in the group with less than nine total dissected LNs and both results were statistically significant.

The N category and adequate LN dissection influence the prognosis in non-small cell carcinoma. Survival rates were higher if the LNs are negative for lung cancer at the time of diagnosis. Therefore, the detection of LN metastasis is critical in lung cancer patients, although the extent of lymphadenectomy in early stage non-small cell lung cancer has been controversial. Recent studies have indicated that mediastinal LN dissection vs. sampling and the higher number of resected LNs are associated with better survival rates.[8,10,11]

The surgeon's inability to intraoperatively determine the presence or absence of the tumor within the mediastinal LNs without biopsy was demonstrated by Gaer and Goldstraw.[12] The intraoperative visual and tactile evaluation of resected mediastinal LNs was compared with the histopathologic diagnosis. The nodal status evaluation through an unopened mediastinal pleura would cause inadequate staging with less accurate results. This situation could be explained by stage migration, the so-called "Will Rogers" phenomenon.[13] This means that the proportion of patients staged as N_0 may, in fact, have had cancer metastasis in the regional LNs. Failure to resect all mediastinal and hilar LNs and to examine them pathologically may result in an inaccurate staging of such patients. This means that a high rate of node negative patients, in fact, have nodal metastases that were missed during the histopathologic examination. In this series, the researchers demonstrated a typical Will Rogers phenomenon between T_{2a} and T_{1b} status. The five-year survival rate of T_{2a} patients was higher than T_{1b} patients (56% vs. 45%). The mean number of LN resected in T_{1b} patients was 9.2±4.3 (range, 2-18) compared to 10±4.9 (range, 3-26) in T_{2a} patients, but the difference was not statistically significant (p=0.517). This indicates that accurate LN staging may not have been performed properly in T_{1b} patients.

Goldstraw[14] recommended that the minimum requirement for accurate nodal staging include the removal of at least six LNs from hilar and mediastinal

Table 2. Multivariate analyses of prognostic factors in surgically resected pathological stage I non-small cell lung cancer

Variables	Multivariate analysis		95% CI	
	p	Hazard ratio	Lower	Upper
Age (years)				
Age ≥60/<60	0.029	0.524	0.293	0.935
Gender				
Female/Male	0.583	1.413	0.411	4.852
Type of resection				
Pneumonectomy/lobectomy or bilobectomy	0.571	1.242	0.587	2.629
Histopathologic subtype				
Squamous cell carcinoma/ non-squamous cell carcinoma (adenocarcinoma and large cell carcinoma)	0.329	1.277	0.782	2.087
Pathologic stage				
T_{1a}/T_{1b}	0.104	0.552	0.270	1.129
T_{1b}/T_{2a}	0.197	1421	0.834	2.420
Number of harvested lymph nodes				
<9/≥9	<0.001	3.594	2.153	6.000

CI: Confidence interval.

stations, one of which at least had to be subcarinal. Similar results were reported by Gajra et al.[15] Several others suggested the examination of at least 10 LNs and three mediastinal stations.[10,16,17] In one recent study, an American College of Surgeons Oncology Group (ACOSOG) Z0030 trial, a randomized, multi-institutional, prospective trial has been designed to determine whether long-term survival is affected by node dissection vs. sampling.[8] This study also indicates that the number of LNs resected during mediastinal LN dissection should be 12 or more, with nodes removed from stations 2R, 4R, 7, 8, 9, and 10R on the right, and stations 4L, 5, 6, 7, 8, 9, and 10L on the left. Ou and Zell[6] found similar results in their studies.

In ACOSOG Z0030 trial, it was revealed that there were at least six nodes removed in 99% of the cases, and the median number of mediastinal LNs resected was 18. In the current study, five or more mediastinal LNs were resected in 95% of the patients, and the median number of resected LNs was 9.9.

There are several studies showing significant associations between a higher number of resected negative LNs and better survival rate in patients with node-negative lung cancer in the literature.[8,18-20] Padilla et al.[21] reported that the number of excised nodes had no influence on survival in stage IA patients. Recently, Riquet et al.[22] and Wu et al.[23] demonstrated that extent of mediastinal lymphadenectomy is not associated with overall survival. Instead, they recommend performing a complete hilar and mediastinal lymphadenectomy following established anatomical boundaries. Izbicki et al.[24] demonstrated that lymphadenectomy did not have an effect on survival for patients with pN_0 disease in a prospective randomized trial. The researchers of current study demonstrated that a higher number of dissected LNs was associated with better overall survival in non-small cell lung cancer. In this study, the mean number of LNs excised was 9.9 and for that reason the researchers proposed a cut-off point at nine resected LNs. Thus, the statistical analysis demonstrated that the five-year survival rate was significantly higher for patients with nine or more LNs dissected, compared to those with fewer than nine dissected LNs.

The current study has several limitations. First, the study had a retrospective design and included single institution analysis with a moderate population. In addition, possible fragmentation of LNs during dissection may lead to an indefinite conclusion regarding the number of LNs dissected. Ludwig et al.[25] reported that if such situation is random, this would bias the results toward the null, so the association may be stronger than we mentioned.

In conclusion, a patient with higher number of resected lymph nodes was more likely to survive longer. This was considered as an independent risk factor for the prognosis of stage I lung cancer patients. Possible hypothesis for higher survival may be based on more accurate staging with increased number of dissected lymph nodes and resected lymphatic pathways for preventing lymphatic spread of the tumor.

Declaration of conflicting interests

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