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Original Article / *Özgün Makale*

Sublobar resections in early-stage non-small cell lung cancer

Erken evre küçük hücreli dışı akciğer kanserinde sublobar rezeksiyonlar

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ABSTRACT

Background: This study aims to evaluate the outcomes of sublobar resections in patients with early-stage non-small cell lung cancer and to investigate the factors affecting survival.

Methods: Medical files of a total of 63 patients (52 males, 11 females; mean age 64 years; range, 39 to 81 years) who underwent sublobar resection for suspected or known early-stage non-small cell lung cancer between January 2001 and August 2013 were retrospectively reviewed. Data including demographic characteristics of the patients, comorbid conditions, smoking status, surgical margin, visceral pleura invasion, distance from surgical margin to tumor, tumor size, pathological N status, cell type, tumor localization, and recurrences were recorded.

Results: Survival was significantly longer in the patients with negative surgical margin for tumor (R0) than in those with positive margin (R1) (94.1 months vs. 32.2 months, p<0.01). Survival was also significantly longer in the patients without lymphatic invasion (p<0.01).

Conclusion: In early-stage lung tumors, sublobar resection can be performed, if complete resection is performed. Lymphatic invasion is a negative prognostic factor for survival following sublobar resection.

Keywords: Early stage, lung cancer, sublobar resection, survival.

ÖZ

Amaç: Bu çalışmada erken evre küçük hücreli dışı akciğer kanserli hastalarda sublobar rezeksiyonların sonuçları değerlendirildi ve sağkalımı etkileyen faktörler araştırıldı.

Çalışma planı: Ocak 2011 - Ağustos 2013 tarihleri arasında şüpheli veya bilinen erken evre küçük hücreli dışı akciğer kanseri nedeniyle sublobar rezeksiyon yapılan toplam 63 hastanın (52 erkek, 11 kadın; ort. yaş 64 yıl; dağılım 39-81 yıl) tıbbi dosyası retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, eşlik eden hastalıklar, sigara içiciliği, cerrahi sınır, viseral plevra invazyonu, tümörün cerrahi sınıra uzaklığı, tümör boyutu, patolojik N durumu, hücre tipi, tümör yerleşim yeri ve nüksler kaydedildi.

Bulgular: Sağkalım, cerrahi sınırı tümör için negatif olan (R0) hastalarda, pozitif olan (R1) hastalara kıyasla, anlamlı olarak daha uzun (32.2 aya kıyasla 74.1 ay, p<0.01) idi. Lenfatik invazyon olmayan hastalarda da sağkalım anlamlı düzeyde daha uzun idi (p<0.01).

Sonuç: Erken evre akciğer tümörlerinde komplet rezeksiyon yapılacak ise, sublobar rezeksiyon yapılabilir. Lenfatik invazyon, sublobar rezeksiyon sonrası sağkalım için negatif prognostik faktördür.

Anahtar sözcükler: Erken evre, akciğer kanseri, sublobar rezeksiyon, sağkalım.

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Sublobar resection (SR) techniques have been initially used in the treatment of benign diseases.[1] In patients with early-stage non-small cell lung cancer (NSCLC), SRs preserve the lung functions, compared to lobectomy, and they are used to prevent impairment of quality of life in patients with limited pulmonary functions.[1] The main question of debate in SR is the selection of eligible patients who are able to tolerate lobectomy. The reason for this is probably the results reported in the study performed by the Lung Cancer Study Group.[2] The study conducted by the Lung Cancer Study Group reported an increase in local recurrence rate and in cancer-related deaths, if SR is performed instead of lobectomy.[2] In recent years, some authors have advocated that segmentectomy provides equivalent outcomes to lobectomy. However, significant differences have been reported compared to lobectomy, segmentectomy, and wedge resection in selected patient population.

Currently, a treatment algorithm for primary NSCLC is available in the National Comprehensive Cancer Network (NCCN) guideline.[3] In the present study, we aimed to evaluate the outcomes of SRs in patients with early-stage NSCLC and to investigate possible factors affecting survival.

PATIENTS AND METHODS

Medical files of 94 patients who underwent SR with a preliminary or definitive diagnosis of NSCLC between January 2001 and August 2013 at the Department of Thoracic Surgery of Medical Faculty of Ankara University Faculty of Medicine were retrospectively reviewed. Patients with synchronous or second primary lung cancer, those with any other previous malignancy or those who were on preoperative or postoperative adjuvant therapy were excluded. Finally, a total of 63 patients (52 males, 11 females; mean age 64 years; range, 39 to 81 years) having Stage 1A, 1B, and 2A tumor who underwent wedge resection (n=50) or segmentectomy (n=13) and fulfilling the study inclusion criteria were included. A written informed consent was obtained from each patient. The study protocol was approved by the Clinical Research Ethics Committee of Ankara University Faculty of Medicine (Approval number: 07-300-14; Date: April 28, 2014). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were re-staged according to the 7th edition of the Tumor, Node, Metastasis (TNM) staging system of the International Association for the Study of Lung Cancer (IASLC). Data including demographic characteristics of the patients, cigarette smoking, comorbid conditions, pulmonary function tests (PFTs), tumor localization, resection types, complications, tumor size, positive surgical margins, distance from surgical margin to tumor in wedge resections, cell type, differentiation, visceral pleura invasion, lymphatic and vascular invasion, pathological T, pathological N, disease stage, recurrence, and survival were recorded. During surgery, mediastinal lymph node sampling was performed in all patients, regardless of the route of intervention and the type of resection. Decision between wedge resection and segmentectomy was made at the discretion of the surgeon. All patients were preoperatively evaluated via PFTs, electrocardiography, blood biochemistry and complete blood count analyses, posteroanterior and lateral radiographs, and thoracic computed tomography (CT). To screen the patients for distant metastases, abdominal-cranial CT bone scintigraphy or, after the year 2006, cranial CT-positron emission tomography (PET)-CT were used.

None of the patients required mediastinoscopy for preoperative staging. Patients with a clinical suspicion of distant metastasis were excluded. Preoperative histological diagnosis was available only in 12 patients. Considering that the surgical approach would not pose a bias on survival, the patients who underwent video-assisted thoracic surgery (VATS) (n=2) were also included.

In all patients, postoperative monitoring included lung radiography at one and three months, thoracic CT at six months, thoracic, abdominal, and cranial CT at one year, lung radiography at 18 months, and then yearly CT scans. The patients with suspected lesions in these analyses were evaluated by dynamic CT, bone scintigraphy, bronchoscopy, and PET-CT. The patients with local recurrence or metastasis received adjuvant chemoradiotherapy. Survival was defined as the time from the date of surgery to the date of death or to the date of study termination for the patients who survived. Disease-free survival (DFS) was defined as the time to the first local recurrence or distant metastasis.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Numerical variables were expressed in mean ± standard deviation (SD) and median (min-max) values, whereas categorical variables were expressed in number and percentage. The Kaplan-Meier product-limit estimation method was used to estimate overall survival (OS) and DFS. Survival curves of different

Table 1. Evaluation of patients according to survival times

Parameters	n	%	Survival (month)	*p*
Age (year)				0.234
<70	39	61.9	98	
≥70	24	38.1	58.8	
Gender				0.257
Female	11	82.5	107.1	
Male	52	82.5	74.5	
Cigarette smoking				0.486
Yes	50	79.4	93.5	
No	13	20.6	67.9	
Comorbid conditions				0.463
Yes	42	66.7	71.6	
No	21	33.3	108.4	
Resection type				0.368
Segmentectomy	13	20.6	117.5	
Wedge resection	50	79.4	74.7	
Resection margin				<0.01
R0	55	87.3	94.1	
R1	8	12.7	32.2	
Cell type				0.808
Squamous cell carcinoma	17	27	79.8	
Adenocarcinoma	32	50.8	82.8	
Bronchoalveolar carcinoma	9	14.3	50.2	
Other*	5	7.9	82.3	
Tumor size				0.302
≤2 cm	42	66.7	97.5	
2.1-3 cm	16	25.4	69.6	
≥3.1 cm	5	7.9	45	
Tumor to surgical margin distance				0.066
≤1 cm	32	50.8	58.5	
>1 cm	31	49.2	103.6	
Visceral pleura invasion				0.356
Yes	27	42.9	94.7	
No	36	57.1	74.4	
Lymphatic invasion				<0.01
Yes	4	6.3	11.3	
No	59	93.7	85.8	
Vascular invasion				0.565
Yes	6	9.5	22	
No	57	90.5	83.9	
Pathological T stage				0.507
T1a	29	46	94.7	
T1b	4	6.3	55.7	
T2a	300	47.6	68.4	
Pathological N stage				0.110
N0	60	95.2	86.4	
N1	3	4.8	37.3	
Disease stage				0.209
1A	33	52.4	96.4	
1B	27	42.9	80.8	
2A	3	4.8	37.3	
Indication for sublobar resection**				0.855
Group 1	27	42.9	66.9	
Group 2	36	57.1	94	

* Three patients had large cell carcinoma and two patients had non-subtyped non-small cell lung carcinoma (NSCLC); ** Group 1 included the patients undergoing sublobar resection due to comorbid conditions and limited pulmonary functions and Group 2 included the patients undergoing sublobar resection but could tolerate lobectomy.

groups were compared using the log-rank test. A *p* value of <0.05 was considered statistically significant.

RESULTS

The median survival was 86 (range, 1 to 151) months. In the survival analyses, the two-year overall survival rate was 83% and the five-year OS rate was 59.6%. Evaluation of the patients according to survival times are presented in Table 1. No significant difference was found in terms of survival according to gender (p=0.257) and between the patients classified according to their age (those ≥70 years and those <70 years; p=0.234).

The patients were further divided into four groups according to the forced expiratory volume in one second (FEV_1) values as follows: FEV_1 <40%, FEV_1 40-60%, FEV_1 61-79%, and FEV_1 ≥80%. No significant difference in the survival was found among the FEV_1 groups (p=0.72).

Evaluation of the tumors according to their localizations revealed that the tumor was in the right superior lobe in 18, in the middle lobe in six, in the right inferior lobe in 15, in the left superior lobe in 19, and in the left inferior lobe in five patients. The median tumor size 20 (range, 7 to 50) mm. There was no significant difference in survival among the tumor size groups (p=0.302).

The tumors were further histopathologically divided into four groups as squamous cell carcinoma (n=17), adenocarcinoma (n=32), bronchoalveolar carcinoma (according to the old classification) (n=9), and others (n=5; three large cell carcinomas; two NSCLC as subtyping was not available). No significant difference in survival was found among the patient groups according to histopathological cell type (p=0.808).

Evaluation of the tumor size on histopathological examinations revealed that the patients were distributed among T1a (n=29), T1b (n=4), and T2a (n=30) stages. Evaluation of the pathological N stages revealed that there were 60 patients in the N0 group and three patients in the N1 group. No significant difference in survival was observed among the patients grouped according to the pathological T stage and among the patient groups according to the pathological N stage (p=0.507 and p=0.110, respectively).

Visceral pleura invasion was positive in 27 patients, vascular invasion was positive in six patients, and lymphatic invasion was positive in four patients. While no significant difference was observed among the patients with and without visceral pleura invasion or those with and without vascular invasion (p=0.356 and p=0.565, respectively), survival was significantly shorter in the patients with lymphatic invasion than in those without (11.3 months and 85.8 months, respectively; p<0.01).

According to the disease stage, there were 33 patients in Stage 1A, 27 patients in Stage 1B, and three patients in Stage 2A. There was no significant difference in survival among the patients according to the disease stage (p=0.209).

The median distance from the surgical margin to tumor was 4 (range, 0 and 15) mm. While the surgical margin was microscopically negative (R0) for tumor in 55 patients, it was microscopically positive (R1) for tumor in eight patients. Although there was no significant difference in survival between the patients groups according to the distance between the tumor and the surgical margin (those with a distance of ≤1 cm [n=32] and those with a distance of >1 cm [n=31]; p=0.066), survival was significantly longer in the R0 group than in the R1 group (94.1 months and 32.2 months, respectively; p<0.01).

The patients were further divided into two groups according to the indications for SR as those undergoing SR due to comorbid conditions and limited pulmonary functions (Group 1, n=27) and those undergoing SR, but could tolerate lobectomy (Group 2, n=36). No significant difference in survival was found between the two groups (66.9 months in Group 1 and 94 months in Group 2, p=0.85; Table 1).

Of all patients, 50 (79.4%) underwent wedge resection and 13 (20.6%) underwent segmentectomy. While the median survival was 117.5 (range, 1 to 142 months in those undergoing segmentectomy, it was 74.7 (range, 4 to 151) months in those undergoing wedge resection. No significant difference in survival was found between the two groups (p=0.368).

Following surgery, 16 patients received adjuvant chemotherapy, two patients received radiotherapy, and eight patients received chemoradiotherapy. There was no significant difference in survival between the patients receiving adjuvant therapy and those not receiving adjuvant therapy (91.5 months and 83.5 months, respectively; p=0.47).

In the present study, the median DFS was 53.2 (range, 6 to 73) months. In the survival analyses, the two-year and five-year DFS rates were 81.5% and 53.6%, respectively. Although no significant difference was found in the median survival according to smoking status (p=0.486; Table 1), the median

Table 2. Evaluation of patients according to disease-free survival

Parameters	p
Cigarette smoking	0.034
Yes	
No	
Tumor size	0.01
≤2 cm	
2.1-3 cm	
≥3.1 cm	
Stage	0.042
1A	
1B-2A	

DFS was significantly longer in non-smokers than in smokers (54.3 months and 38.6 months, respectively; p=0.034; Table 2).

Furthermore, the median DFS did not significantly differ among the patients according to the cell types (p=0.39), type of SR (38.6 months in those undergoing segmentectomy and 54.5 months in those undergoing wedge resection; p=0.65), and distance from the surgical margin to the tumor (47.9 months in those with a distance of ≤1 cm and 56.3 months in those with a distance of >1 cm, p=0.63).

The median DFS for the three groups divided according to the tumor size as those with a tumor of ≤2 cm, those with a tumor of 2.1-3 cm, and those with a tumor of ≥3.1 cm was 59.1 months, 39.2 months, and 18.5 months, respectively. The median DFS was found to significantly increase with decreasing tumor size (p<0.01).

The analysis for DFS according to the disease stage was performed between the patients with Stage 1A and the others (those with Stage 1B and those with Stage 2A), since the number of patients in Stage 2A was quite limited. The median DFS was found to be significantly longer in the Stage 1A group (60.1 months and 41.3 months, respectively; p=0.04).

DISCUSSION

In the present study, we evaluated the outcomes of SRs in patients with early-stage NSCLC and investigated possible factors affecting survival. Our study results showed that survival was significantly longer in the patients with negative surgical margin for tumor (R0) than in those with positive margin (R1). In addition, patients without lymphatic invasion had a longer survival.

In a study comparing lobectomy and SRs in elderly patients, no significant difference was found between the groups regarding five-year survival rate (60.9% and 63.4%, respectively; p=0.558).[4] Similarly, Mery et al.[5] evaluated the effects of SR on the treatment in elderly patients with early-stage tumors and found no significant difference regarding survival between the SR and lobectomy groups for the patients aged over 75 years. However, they observed that survival was significantly improved in younger patients in the lobectomy group.[5] In the present study, the mean survival time was 98 months in the patient aged <70 years and 68.8 months in those aged ≥70 years; although not statistically significant, a clinical difference could be considered. Age is not a definite criterion in selecting patients for a certain type of resection. Nevertheless, it is important to note that age has an impact on patient selection due to increased comorbidity, impaired pulmonary functions, and prolonged healing period with increasing age.

Tsutani et al.[6] compared lobectomy, segmentectomy, and wedge resection for surgical procedure choice in adenocarcinoma patients with Stage 1A ground-glass opacity nodule. While they observed no significant difference among the surgical groups regarding three-year recurrence-free survival in patients with T1a tumors, segmentectomy was reported to be significantly superior to wedge resection in the patient with T1b tumors.[6] In the present study, 50 patients underwent wedge resection and 13 patients underwent segmentectomy. The mean survival was 117.5 months in the segmentectomy group and 74.7 months in the wedge resection group. No significant difference in survival was observed between the groups (p=0.368). The mean DFS was 38.6 months in the segmentectomy group and 54.5 months in the wedge resection group (p=0.65). Based on survival analyses, we concluded that survival was clinically improved in the segmentectomy group, although it did not reach statistical significance.

Tumor size is one of the prognostic factors in NSCLC. There are studies showing that SR yields similar oncological outcomes to lobectomy in small-size tumors.[7] Fan et al.[8] published a meta-analysis in which they evaluated a total of 24 studies comparing lobectomy and sublobectomy protocols in Stage 1 NSCLC patients during a 20-year period. According to the outcomes, there was no significant difference in OS rates between the lobectomy and sublobectomy groups in Stage 1A NSCLC patients with a tumor size of <2 cm (p=0.970). Survival was reported to be significantly improved in the lobectomy group, when

all Stage 1 patients were included (p=0.0006).[8] In similar studies, no significant difference was reported in terms of local recurrence or survival for SRs in the tumors <1 cm in size.[9] Fernando et al.[10] also reported no significant difference in survival rates between lobectomy and SR groups for the tumor size of <2 cm and concluded that survival was significantly longer in the lobectomy group for the tumor size of 2 to 3 cm. In the present study, the patients were divided into three groups according to the tumor size as ≤2 cm, 2.1-3 cm, and ≥3.1 cm. The mean survival was 97.5 months, 69.6 months, and 45 months, respectively. Although survival analysis revealed no statistically significant difference among these three groups (p=0.302), the difference was considered clinically significant. In addition, the mean DFS was 59.1 months in the first group, 39.2 months in the second group, and 18.5 months in the third group. It was observed that DFS was significantly prolonged with decreasing tumor size (p<0.01).

How to achieve a safe surgical margin in SRs is a common question. In this regard, the point that must be kept in mind is that the largest margin would be the most optimal approach. Some authors have suggested that negative surgical margin needs to be confirmed intraoperatively by cytology.[11] The more common opinion is the necessity of at least a distance of 1 cm from surgical margin to tumor. Sawabata et al.[12] proposed that a surgical margin distance greater than the maximum tumor size was required to minimize the risk of local recurrence.[12] In the studies accepting 1 cm as the distance from surgical margin to tumor, a distance of ≥1 cm was found to be associated with a decreased local recurrence rate, whereas a distance of <1 cm was associated with an increased local recurrence rate.[13,14] In the present study, while surgical margin was microscopically negative (R0) in 55 of 63 patients, there was a microscopic tumor in the surgical margin in eight patients (R1). The mean survival was found to be significantly longer in the R0 group than in the R1 group (74.1 months and 32.2 months, respectively p<0.01). The mean distance from the surgical margin to tumor was 5 mm (range, 0 to 15 mm). The patients were divided into two groups as those with a surgical margin distance of ≤1 cm (n=32) and those with a surgical margin distance of >1 cm (n=31) and no significant difference in survival (p=0.066) and DFS (p=0.63) was found between these two groups.

In their study, Koike et al.[15] evaluated the risk factors for locoregional recurrence following SR and multivariable analysis showed that wedge resection, microscopically positive surgical margin, visceral pleura invasion, and lymphatic invasion were independent risk factors for locoregional recurrence. Also, Higgins et al.[16] examined the effects of lymphovascular invasion on staging and adjuvant therapy in NSCLC patients and found no significant relationship between visceral pleura invasion and lymph node involvement (p=0.08). In a multicenter study, Tsutani et al.[17] evaluated oncological outcomes of lobectomy and SRs in Stage 1A NSCLC patients and found no significant difference between the groups in terms of DFS and OS (p=0.14), as well as pleural invasion (p=0.45). Lymphovascular invasion is both a negative prognostic factor and a determinant of indication for adjuvant therapy in some malignancies. In their study, Higgins et al.[16] found a significant relationship between lymphovascular invasion and regional lymph node invasion using univariate analysis. In the present study, lymphatic and vascular invasions were evaluated separately. No significant difference was found in survival between the patients with vascular invasion (n=6) and in those without (n=57) (p=0.565). However, the mean survival was significantly longer in the group without lymphatic invasion (n=59) than in the group with lymphatic invasion (n=4) (85.8 months and 11.3 months, respectively; p<0.01).

In a systematic literature review including 16 studies on SR, De Zoysa et al.[18] reported shortened survival in the SR group in three studies. However, further analyses revealed that the patients were older and lymph node sampling was limited in the SR groups; accordingly, after adjusting these variables, they found no significant difference in survival rates. Tumor size was claimed to be a significant prognostic factor in six studies and only two of them reported a survival equivalent to lobectomy. Three studies demonstrated increased locoregional recurrence rate in SR. Also, in three studies, SR was associated with significantly lower surgical morbidity, shorter hospital stay, and better preserved pulmonary functions.[18] In the present study, the patients were distributed among Stage 1A, Stage 1B, and Stage 2A. The mean survival was 96.4 months in those with Stage 1A disease, 80.8 months in those with Stage 1B disease, and 37.3 months in those with Stage 2A disease. No statistically significant difference in survival was found between the groups (p=0.209); however, survival gradually decreased with increasing stage. Due to the limited number of patients with Stage 2A disease, the patients were classified as those with Stage 1A disease and others for DFS analyses. Accordingly, DFS was found to be significantly longer in those with Stage 1A disease (p=0.042).

Due to the fact that it was a single center study, the number of patients was limited. In the past, lobectomy was considered as the first treatment option.

In the present study, the five-year survival rate was 59.6%, despite higher number of wedge resections and no significant difference was observed between the resection type groups in terms of survival. In addition, survival was significantly longer in the group without lymphatic invasion. The disease-free survival analyses revealed that cigarette smoking, a tumor size of >2 cm, and a disease stage higher than 1A significantly shortened the disease-free survival following sublobar resection, although it did not significantly differ according to the resection type.

In conclusion, for early-stage tumors, sublobar resection with segmentectomy or wedge resection can be safely used in selected patients, if complete resection and lymph node staging are performed. Sublobar resection can be particularly preferred in patients who are unable to tolerate lobectomy due to pulmonary reasons or other comorbidities, or if possible, in early-stage NSCLC <2 cm in size with peripheral localization and without endobronchial involvement. However, further long-term studies in larger series are needed to draw a firm conclusion.

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