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Original Article / *Özgün Makale*

The prognostic effect of lymph node dissection in secondary lung tumor metastasectomies

Sekonder akciğer metastazektomilerinde lenf nodu diseksiyonunun prognoza etkisi

Salih Duman[1], Berk Çimenoğlu[2], Melike Ülker[1], Melek Ağkoç[1], Suat Erus[3], Berker Özkan[1], Murat Kara[1], Alper Toker[4]

Institution where the research was done:
Istanbul University Istanbul Faculty of Medicine, Istanbul, Türkiye

Author Affiliations:
[1]Department of Thoracic Surgery, Istanbul University Istanbul Faculty of Medicine, Istanbul, Türkiye
[2]Department of Thoracic Surgery, Health Sciences University, Kartal Dr. Lütfi Kırdar Training and Research Hospital, Istanbul, Türkiye
[3]Department of Thoracic Surgery, Koç University, Istanbul, Türkiye
[4]Department of Cardiovascular and Thoracic Surgery, West Virginia University Heart and Vascular Institute, West Virginia, USA

ABSTRACT

Background: In this study, we aimed to investigate the prognostic effect of lymph node dissection in secondary lung tumor metastasectomies.

Methods: Between January 2001 and December 2015, a total of 201 patients (122 males, 79 females; mean age: of 41.4±19.2 years; range, 3 to 79 years) who had pulmonary metastasectomy due to colorectal carcinoma, renal cell carcinoma, and soft tissue - skeletal sarcomas were retrospectively analyzed. The clinicopathological features of the patients, overall survival, and complication rates according to the presence of lymph node dissection were evaluated.

Results: The most common histopathological subtype was a sarcoma in 118 (58.7%) patients, followed by colorectal carcinoma in 63 (31.3%) patients, and renal cell carcinoma in 20 (10%) patients. A total of 88 (43.7%) patients underwent systematic lymph node dissection with pulmonary metastasectomy. The mean overall survival of patients with and without lymph node dissection were 49±5.9 (95% confidence interval 37.3-60.6) and 26±4.4 (95% confidence interval 17.2-34.7) months, respectively (p=0.003). The five-year survival rates in colorectal carcinoma, renal cell carcinoma, and sarcoma were 52%, 30%, and 23%, respectively (p=0.002). Locoregional recurrences occurred in 15 (35.7%) patients in the lymph node dissection group and in 23 (60.5%) patients in the non-lymph node dissection group (p=0.026). Lymph node dissection did not show a significant relationship regarding to postoperative complications (p=0.09).

Conclusion: Lymph node dissection following pulmonary metastasectomy may improve the overall survival and reduce locoregional recurrence, without any increase in morbidity and mortality.

Keywords: Colorectal carcinoma, lymph node dissection, pulmonary metastasectomy, renal cell carcinoma, sarcoma.

ÖZ

Amaç: Bu çalışmada sekonder akciğer tümör metastazektomilerinde lenf nodu diseksiyonunun prognoz üzerine etkisi araştırıldı.

Çalışma planı: Ocak 2001 - Aralık 2015 tarihleri arasında kolorektal karsinom, renal hücreli karsinom ve yumuşak doku-iskelet sarkomları nedeniyle pulmoner metastazektomi yapılan toplam 201 hasta (122 erkek, 79 kadın; ort. yaş: 41.4±19.2 yıl; dağılım 3-79 yıl) retrospektif olarak incelendi. Hastaların lenf nodu diseksiyonu varlığına göre klinikopatolojik özellikleri, genel sağkalım ve komplikasyon oranları değerlendirildi.

Bulgular: En sık histopatolojik tanı 118 (%58.7) hastada sarkom, 63 (%31.3) hastada kolorektal karsinom ve 20 (%10) hastada renal hücreli karsinom idi. Toplam 88 (%43.7) hastaya pulmoner metastazektomi ile birlikte sistematik lenf nodu diseksiyonu uygulandı. Lenf nodu diseksiyonu yapılan ve yapılmayan hastalarda ortalama genel sağkalım sırasıyla 49±5.9 (%95 güven aralığı 37.3-60.6) ve 26±4.4 (%95 güven aralığı 17.2-34.7) ay idi (p=0.003). Beş yıllık sağkalım kolorektal karsinomlu hastalarda %52, renal hücreli karsinomlu hastalarda %30 ve sarkomlu hastalarda %23 idi (p=0.002). Lokorejyonel nüks, lenf nodu diseksiyonu uygulanan toplam 15 (%35.7) hastada ve lenf nodu diseksiyonu uygulanmayan grupta 23 (%60.5) hastada görüldü (p=0.026). Lenf nodu diseksiyonu ile ameliyat sonrası komplikasyon oranları arasında anlamlı bir ilişki saptanmadı (p=0.09).

Sonuç: Pulmoner metastazektomiyi takiben yapılan lenf nodu diseksiyonu genel sağkalımı uzatmakla birlikte, morbidite ve mortaliteyi artırmadan lokorejyonel nüks oranını azaltabilir.

Anahtar sözcükler: Kolorektal karsinom, lenf nodu diseksiyonu, pulmoner metastazektomi, renal hücreli karsinom, sarkom.

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Correspondence: Salih Duman, MD. İstanbul Üniversitesi İstanbul Tıp Fakültesi Göğüs Cerrahisi Anabilim Dalı, 34093 Fatih, İstanbul, Türkiye.
Tel: +90 506 - 600 78 42 e-mail: dr.salihduman@hotmail.com

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Secondary lung carcinomas account for 20 to 30% of cancer-related deaths, and metastases were limited only in the lung in approximately 25% of these patients.[1] The American pathologist James Ewing,[2] who described Ewing's sarcoma, reported that mechanical factors such as vascular connections of the primary tumor were also effective in the development of metastatic disease in 1928. The lung is an ideal target organ for the development of metastatic disease, since it is an end-organ which have all the blood circulation and common small capillary. The first surgical intervention for metastatic disease in the lung is the nodule excision performed by Weinlechner[3] and Kronnlein[4] who detected nodular lesions in the lung during a chest wall resection in 1882. Later on, pulmonary metastasectomies were found to prolong survival in case of *(i)* the primary tumor was under control; *(ii)* all the pulmonary lesions were resectable; *(iii)* the patient had sufficient pulmonary functions; and *(iv)* no extra thoracic metastasis was present.[5]

The benefit of lymph node dissection (LND) during pulmonary metastasectomy is controversial.[6,7] Several studies have shown that LND in patients with colorectal carcinoma (CRC) undergoing pulmonary metastasectomy has a positive impact on survival.[8,9] In these studies, while the five-year survival rates in patients with mediastinal or intraparenchymal nodal metastases were between 0 and 33.5%, more than 70% of the patients without nodal metastases was expected to live beyond five years. Therefore, some authors have concluded that mediastinal lymphadenectomy is needed for the correct prediction of survival outcome and the determination of the optimal adjuvant therapy.[10] However, the prognostic effect of the LND in different histopathological subgroups of secondary lung tumor metastasectomies is unclear.

In the present study, we aimed to investigate the prognostic effect of LND in secondary lung tumor metastasectomies.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Istanbul University Istanbul Faculty of Medicine, Department of Thoracic Surgery between January 2001 and December 2015. All medical records of a total of 201 patients (122 males, 79 females; mean age: of 41.4±19.2 years; range, 3 to 79 years) who underwent pulmonary metastasectomy for three histopathological subgroups including CRC, renal cell carcinoma (RCC) and soft tissue - skeletal sarcomas were included. Data were extracted from both clinical cancer and pathological databases. Indication for a pulmonary metastasectomy was provided that if the primary disease was under control, no extrathoracic metastases were present, the patient's cardiopulmonary function reserve was adequate, and all pulmonary nodules were resectable. Age, sex, histopathological diagnosis of the primary tumor, number of pulmonary metastases, the type of resection, presence of LND, dissected lymph node stations, and postoperative complications were recorded.

All patients underwent a preoperative work-up including physical examination, complete blood count and blood chemistry, computed tomography (CT) of the chest, positron emission tomography (PET) and magnetic resonance imaging (MRI) of the brain. The type of surgery was grouped as wedge resection, segmentectomy, lobectomy, and pneumonectomy. Precision excision for a small nodule was included in the wedge resection group. In different types of resections applied to the same patient, the larger resection was selected as the resection type. The patients who underwent LND including subcarinal lymph nodes with an additional mediastinal station were assigned in the LND group (n=87), while corresponding patients were determined as the non-LND group (n=114). Of note, LND was decided according to the surgeon's preference.

Postoperative complications were categorized according to Clavien-Dindo classification of surgical complications.[11] Grade 1 complications were classified as minor complications, while Grade 2 and 3 complications were classified as major complications.

Locoregional recurrence was defined as the ipsilateral parenchymal metastases occurred after pulmonary metastasectomy. Overall survival (OS) was determined as the time from the pulmonary metastasectomy to the death or last contact.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Pearson chi-square test, Fisher exact test, independent sample t-test, and Mann-Whitney U test were used for categorical and continuous variables as appropriate. Kaplan-Meier (log-rank test) was used to estimate the survival rates. A p value of <0.05 was considered statistically significant.

Table 1. Demographic characteristics

	n	%	Mean±SD
Age			41.4±19.2
Sex			
Male	122	60.7	
Female	79	39.3	
Type of surgery			
Thoracotomy	166	82.6	
VATS	35	17.4	
Type of resection			
Wedge resection	135	67.2	
Segmentectomy	32	15.9	
Lobectomy	30	14.9	
Pneumonectomy	4	2	
Histopathological subgroups			
Sarcoma	118	58.7	
Colorectal carcinoma	63	31.3	
Renal cell carcinoma	20	10	

SD: Standard deviation; VATS: Video-assisted thoracic surgery.

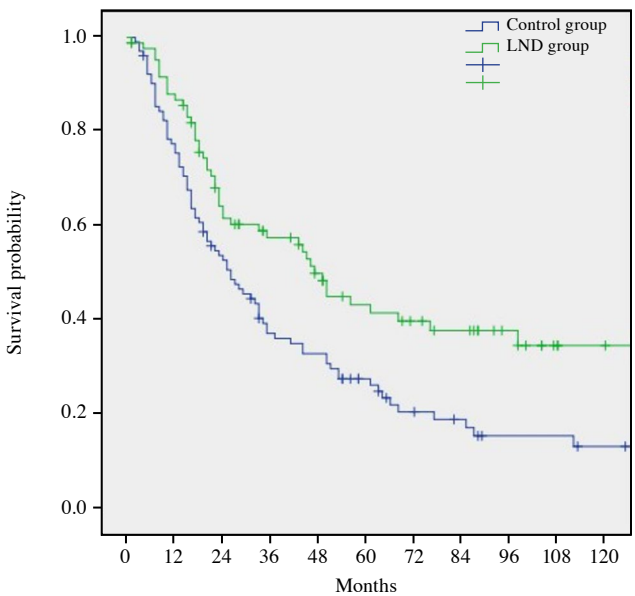
RESULTS

The most common histopathological subtype was soft tissue - skeletal sarcomas in 118 (58.7%) patients. Demographic characteristics of the patients are summarized in Table 1.

The mean OS time of the patients with CRC, RCC, and sarcoma were 68±15.7 (95% confidence interval [CI]: 37.0-98.9), 24±5.8 (95% CI: 12.6-35.3), and 24±2.8 (95% CI: 18.3-29.6) months, respectively (p<0.001) (Figure 1). Also, LND group had a higher mean OS time than the non-LND group (49±5.9 [95% CI: 37.3-60.6] months *vs*. 26 ±4.4 [95% CI: 17.2-34.7] months, p=0.003) (Figure 2). However, the difference between the mean survival times of LND and non-LND groups for each histopathological subtype was not statistically significant (Table 2). Lymph node dissection was applied significantly more in patients with CRC (p<0.001) (Table 2). Locoregional recurrence occurred in 15 (35.7%) and 23 (60.5%) patients in the LND group and in the non-LND groups, respectively (p=0.026).

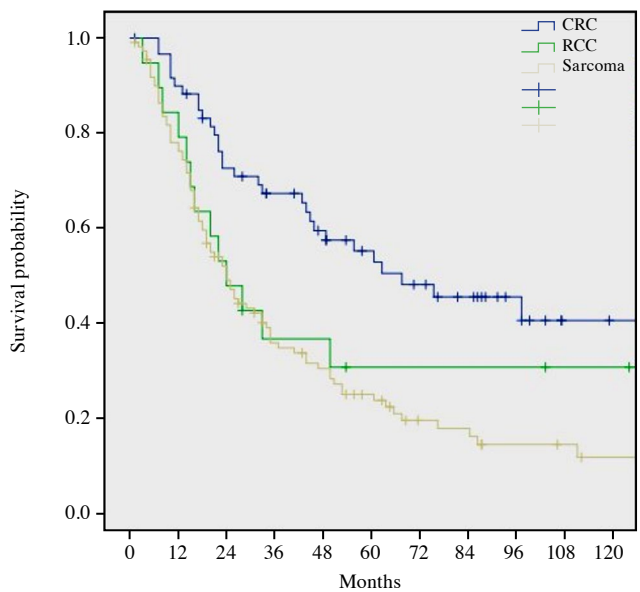
Lymph node metastasis was found in a total of 17 (19.3%) patients in the LND group, and staged as N1 in five patients, skip-N2 in eight patients, and N1+N2 in four patients. The median survival time of the patients with N1, skip-N2 and N1+N2 disease were 94, 15, and 14 months, respectively (p=0.510). In addition, the mean survival time of patients with and without any nodal metastasis were 24±2.6 (95% CI: 18.7-29.2) and 33±6.2 (95% CI: 20.7-45.2) months, respectively (p=0.875).

We observed complications in a total of 36 (17.9%) patients. The most common complications were



LND	85	75	65	55	50	42	39	38	38	38	38
Control	103	92	80	68	58	47	36	29	23	22	22

Figure 1. The survival of with and without lymph node dissection groups.
LND: Lymph node dissection.



CRC	60	50	41	35	31	30	30	30	30	30	30
RCC	19	8	6	6	6	6	6	6	6	6	6
Sarcoma	110	100	88	76	65	56	46	36	29	24	24

Figure 2. The survival of histopathologic subtypes.
CRC: Colorectal carcinoma; RCC: Cenal cell carcinoma.

Table 2. Median survival times and complication rates of LND and non-LND groups

	LND group (n=87)			Non-LND group (n=114)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Number of patients							<0.001*
CRC	49	77		14	23		
RCC	10	50		10	50		
Sarcoma	28	23		90	77		
Median survival time (month)							
CRC			76.0±25.6			33.0±10.3	0.15
RCC			20.0±6.3			28.0±8.9	0.89
Sarcoma			24.0±9.3			25.0±3.8	0.64
All cohort			49.0±5.9			26.0±4.4	0.003*
Complications							
Major complications	7	8.0		12	10.8		
Minor complications	11	12.6		6	5.4		

SD: Standard deviation; CRC: Colorectal carcinoma; RCC: Renal cell carcinoma.

prolonged air leak and pneumonia in 12 (5.9%) and six (2.9%) patients, respectively. The major complication rate in the LND group was 8%, whereas it was 9.9% in the non-LND group (p=0.09). Complications occurred in three (8.6%) and 33 (19.9%) patients in video-assisted thoracic surgery and thoracotomy groups, respectively (p=0.084). There was no 30-day mortality.

DISCUSSION

Pulmonary metastasectomy for secondary lung malignancies has been found to have a positive effect on survival, if the primary disease is under control without any extrathoracic metastasis and the patient is physically fit for a surgical pulmonary resection.[5] Although LND during pulmonary metastasectomy has favorable survival outcomes for these patients, the role of LND in patients with different histopathological subtypes, who undergo pulmonary metastasectomy is unclear. In a survey published by the European Society of Thoracic Surgeons-Pulmonary Metastasectomy Working Group, nearly one-third of the surgeons do not perform any nodal sampling or dissection during pulmonary metastasectomy.[6] In this study, we investigated the role of LND in patients with CRC, RCC and soft tissue - skeletal sarcomas who underwent pulmonary metastasectomy. Our study findings showed that the LND group had significantly longer OS with lesser locoregional recurrences compared to the non-LND group.

Although the survival rates among different cancer types differ, pulmonary metastasectomy for isolated lung metastases of solid tumors have been reported to provide better survival than systemic therapy alone, by the International Registry of Lung Metastases.[12] The number of metastases, completeness of resection and the disease-free interval before pulmonary metastasis were found as prognostic factors in patients undergoing pulmonary metastasectomy. Also, the presence of intrathoracic nodal metastases was found to be associated with poor survival in patients with CRC, RCC, and sarcoma.[13-15] Winter et al.[16] showed that the nodal metastasis was an independent prognostic factor in metastatic RCC. They also showed a slightly increased survival in patients who underwent mediastinal nodal dissection, which could be explained with overlooked lymph node metastases in the control group. Additionally, a trend toward improved survival was identified in another study, in support of LND instead of lymph node sampling during pulmonary metastasectomy for various primary tumor histology.[17] In our study, the LND group had significantly favorable OS and lesser locoregional recurrences than the non-LND group. However, in the histopathological subgroup analysis, there was no significant difference between the groups. This discrepancy in the findings may be due to relatively small number of patients in each subgroup, but higher percentage of CRC patients may have led to a significant difference in the whole cohort, as expected due to better survival rates of CRC.[12,18,19]

In addition to the adverse effect of intrathoracic lymph node involvement on survival, the pattern of positive lymph nodes may have a role on prognosis of secondary lung malignancies. In two studies in which the prognosis of thoracic lymph node involvement

in patients with RCC was evaluated, N1 versus N2 positivity did not appear to create any difference in survival.[14,20] Similarly, Hamaji et al.[21] found no significant difference in survival according to N status or single- versus multi-station metastasis in patients with CRC. However, in the study by Pfannschmidt et al.[22] in which the pulmonary metastasectomies of CRC, RCC and sarcomas were evaluated all together, while median survival was highest in N0 patients, it decreased gradually from N1 to N2 disease. They also showed an increased risk of N2 disease in patients with N1 lymph node involvement compared to N0 disease. In our study, the difference in the median survival time between the different localization of positive lymph nodes had a clinical relevance (78,33, and 18 months for N1, N2 and N1+N2 disease, respectively), although it did not reach statistical significance.

Complication rates of pulmonary metastasectomies were presented around 5.2 to 15.6% with a very low mortality rate.[23,24] It was shown in a randomized-controlled trial that LND was not associated with an increased morbidity rate in comparison to lymph node sampling, in patients who underwent pulmonary resections due to primary lung cancer.[25] Similarly, we did not observe any 30-day mortality, and the complication rate was 18% for all patients. There was no significant difference between the LND and the non-LND groups, in accordance with morbidity.

This study, however, is subject to some limitations. First, its retrospective nature and relatively small number of patients necessitate to interpret the results cautiously. Second, there are different histopathological subtypes and the data of adjuvant treatment including non-uniform treatment modalities are missing.

In conclusion, lymph node dissection following pulmonary metastasectomy appears to prolong the overall survival and reduce locoregional recurrence, without any increase in morbidity and mortality. However, its effect on different histopathological subtypes needs further investigation in prospective, randomized trials.

Ethics Committee Approval: The study protocol was approved by the Istanbul University Istanbul Faculty of Medicine Ethics Committee (Date/no: 2017/116). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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