

## Factors Affecting Long-Term Survival Following Pulmonary Metastasectomy of Renal Cell Carcinoma

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**Purpose:** Role of pulmonary metastasectomy of renal cell carcinoma (RCC) is significant considering its contribution to survival rates. The aim of this study is to present the prognostic factors affecting the surgical outcomes and long-term survival.

**Materials and Methods:** Forty-eight patients who had undergone pulmonary metastasectomy of RCC between 2000 and 2018 were analyzed in terms of gender, age, subtypes and pathological T stages of RCC, side and size of pulmonary metastases, disease-free interval (DFI) and type of lung resections in order to reveal the prognostic factors from the stand point of selecting suitable patients for lung metastasectomy.

**Results:** Overall survival was  $56.2 \pm 21.7$  months. Survival time was less than 3 years for 7 (14.6%), between 3 and 5 years for 11 (22.9%) and more than 5 years for 30 (62.5%) patients. Young age, female gender, unilateral pulmonary lesions, longer DFI, lung metastases limited in number and volume were statistically significant for better survival rates ( $P < .05$ ) whereas subtypes and pathological stage of the primary tumor or the type of pulmonary metastasectomy did not act on the outcomes ( $P > .05$ ).

**Conclusion:** The most distinctive factor affecting the surgical outcomes is the complete resection of lung metastases rather than the extent of the surgery. This study clearly states that patients aged under 50 years with unilateral lung metastases counting less than 3 and measuring smaller than 4 cm<sup>3</sup>, and also DFI lasting longer than 32 months benefit from pulmonary metastasectomy of RCC.

**Keywords:** lung metastases; metastasectomy; renal cell carcinoma; surgery; survival

## INTRODUCTION

Renal cell carcinoma (RCC) counts for 2% of all malignancies. Almost 30% of the patients have distant metastases at the initial presentation while the other one-third will develop metastases during the follow-up<sup>(1)</sup>.

The most common metastatic sites of RCC are lungs, accompanied by bones and lymph nodes at a rate of 45.2%, 29.5% and 21.8%, respectively. The 5-year survival of patients with untreated metastatic RCC ranges from 0% to 18% whereas pulmonary metastasectomy of RCC increases the survival rate up to 54%<sup>(2)</sup>.

In the past decade many researches have focused on solitary metastasis and long disease-free interval (DFI) as good prognostic factors for pulmonary metastases of RCC. Barely has it remained unclear whether the survival rates are affected by the clinical features of the patients or the applied therapeutic approaches.

The purpose of this study was to analyze the prognosis of pulmonary RCC metastases in deference to demographic variables, tumor relevant characteristics and surgical contents of pulmonary metastasectomy by including a vast of number of factors which had been already associated with prognosis in recent researches in addition to unprecedented entities such as the volume of lung metastases and the type of pulmonary resections.

## PATIENTS AND METHODS

*Study population*

Following the approval of Faculty's Ethic Committee (code: NK.GOK.2019.118.07), the data of 48 cases who had undergone pulmonary metastasectomy of RCC between 2000 and 2018 were retrospectively analyzed. The patients who had presented uncomplete lung metastasectomy which was confirmed by reports of pathological or radiological examinations, who had not participated in the follow-up audit and who had died because of any causes other than malignancies were excluded from the study. The deaths related to RCC metastasis were confirmed by both radiological studies and biopsies. Main criteria for lung resection were completely resectable pulmonary metastases, adequate respiratory reserve confirmed via pre-operative pulmonary function tests and absence of residuary or recurrent tumor of primary RCC and also any extrapulmonary metastases.

*Study design*

Whole group of patients were evaluated in terms of gender, age, subtypes and pathological T stages of RCC, side and size of pulmonary metastases, DFI and type of metastasectomy regarding the 5-year survival. Age was

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**Table 1.** Descriptive statistics of the patient group.

Parameters	Patients (N = 48)
Age, year; mean $\pm$ SD (range)	52.71 $\pm$ 10.80 (30 – 77)
Disease free interval, month; mean $\pm$ SD (range)	32.13 $\pm$ 13.60 (8 - 63)
Number of pulmonary metastases; mean $\pm$ SD (range)	3.31 $\pm$ 2.32 (1 – 9)
Volume of pulmonary metastases, cm <sup>3</sup> ; mean $\pm$ SD (range)	4.02 $\pm$ 1.74 (1.6 – 7.6)
Survival time, month; mean $\pm$ SD (range)	56.21 $\pm$ 21.77 (11 – 82)

noted for two cohorts, younger and older than 50 years while DFI was reported as the time between the diagnosis of RCC and the pulmonary metastasectomy and also was divided into two intervals lasting longer or shorter than 32 months. Both T1 and T2 staged RCCs were only in the kidney while a T1 tumor was 7 cm or smaller and T2 was larger than 7 cm. A T3 staged RCC was invading the tissue around the kidney or a major vein like the renal vein or vena cava but was not growing into the adrenal gland or beyond Gerota's fascia whereas a T4 staged RCC was recognized to be growing beyond Gerota's fascia and into the adrenal gland. Subtypes of RCCs were noted as clear cell, papillary, chromophobe, cystic-solid and medullary depending on the analyzed pathological reports. Side of the pulmonary metastases was right, left or bilateral. Size of the lung metastases was calculated by soft-ware derived volumetry as volume whereas the overall volume was the sum of all metastases in the presence of two or more resected pulmonary lesions. Regarding the number of lungs metastases, cases were grouped as solitary, two and 3 or more resected lesions. All the limiting values to organize the patients into statistical groups for age, DFI, number and volume of lung lesions were accepted as mean values for each variable. Regarding the extended interval of the study and altering modalities of systematic treatments within this period, the status of pre-operative and post-operative administration of cytokines and targeted therapies was not included in the research.

### Surgical technique

Primary RCC had been treated by radical nephrectomy while none of the patients had lung metastases at the time of RCC diagnosis. Pulmonary metastasectomy all applied via thoracotomy were anatomical resections as segmentectomy or lobectomy and also nonanatomical resections including wedge resections or precision excisions.

### Outcome assessment

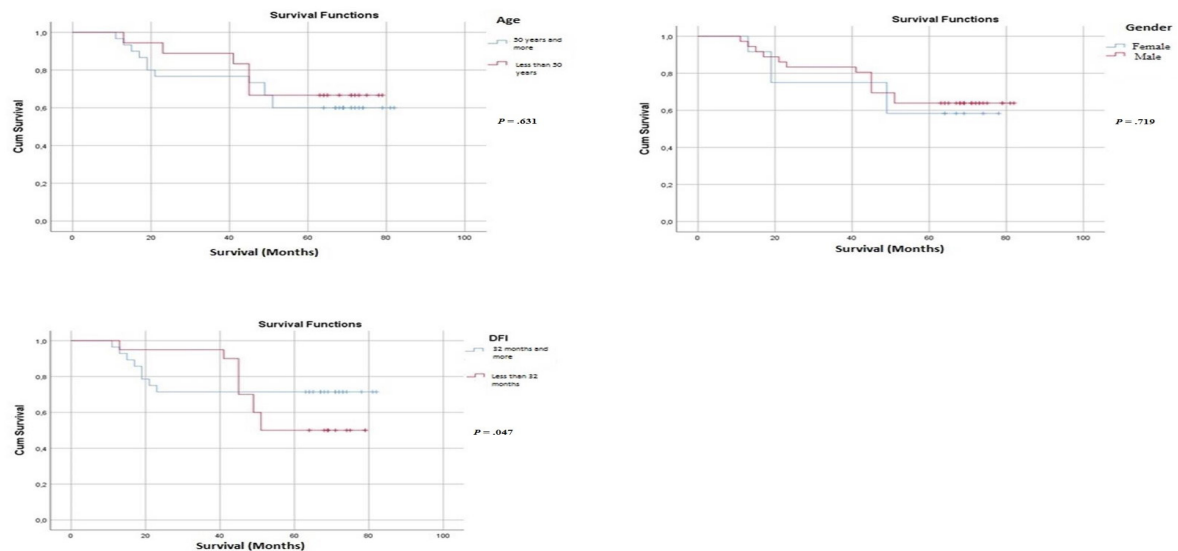
The primary outcome of interest was the type of surgery applied for pulmonary metastasectomy. The secondary outcomes were the number and volume of RCC metastasis. This study hypothesized that the patients with lung metastasis limited in size will develop better prognosis regardless of the content of lung metastasectomy.

### Statistical Analysis

SPSS (IBM SPSS for Windows, ver.24) statistical package program was used for calculations. In calculating the sample width of this study, Power (the test of power) was determined by taking at least 0.80 and Type 1 Error 0.05. Descriptive statistics for continuous variables in the study were expressed as mean, standard deviation, minimum and maximum; categorical variables were expressed as number (n) and percentage (%). Cox Regression was applied to analyze the influence and risk ratios of all variables over survival times. Pearson's Chi-square test was used to determine the relationship between categorical variables. Kaplan-Meier analysis

**Table 2.** Relation between general features of the patients and long-term survival.

Parameters		N (%)	P-value
Age (years)	$\geq 50$	30 (62.5)	0.294
	$< 50$	18 (37.5)	
Gender	Female	12 (25)	0.522
	Male	36 (75)	
Subtype of RCC	Clear cell	37 (77.1)	0.724
	Papillary	7 (14.5)	
	Chromophobe	2 (4.2)	
	Cystic-solid	1 (2.1)	
	Medullary	1 (2.1)	
T Stage of RCC	T1	1 (2.1)	0.368
	T2	12 (25)	
	T3	35 (72.9)	
Side of pulmonary metastases	Right	19 (39.6)	0.081
	Left	20 (41.7)	
	Bilateral	9 (18.8)	
Number of pulmonary metastases	Solitary	11 (22.9)	0.033
	2	22 (45.8)	
	$\geq 3$	15 (31.3)	
Disease free interval (months)	$\geq 32$	28 (58.3)	0.039
	$< 32$	20 (41.7)	
Volume of pulmonary metastases (cm <sup>3</sup> )	$\geq 4$	22 (45.8)	0.001
	$< 4$	26 (54.2)	
Pulmonary resection	Nonanatomical	35 (72.9)	0.194
	Anatomical	13 (27.1)	
Survival time (years)	$\leq 3$	7 (14.6)	-----
	Between 3 and 5	11 (22.9)	
	$\geq 5$	30 (62.5)	



**Figure 1.** Effect of demographical factors on survival.

and Long- rank test was applied to compare the variables in terms of survival. The statistical significance level was taken as 5% in the calculations.

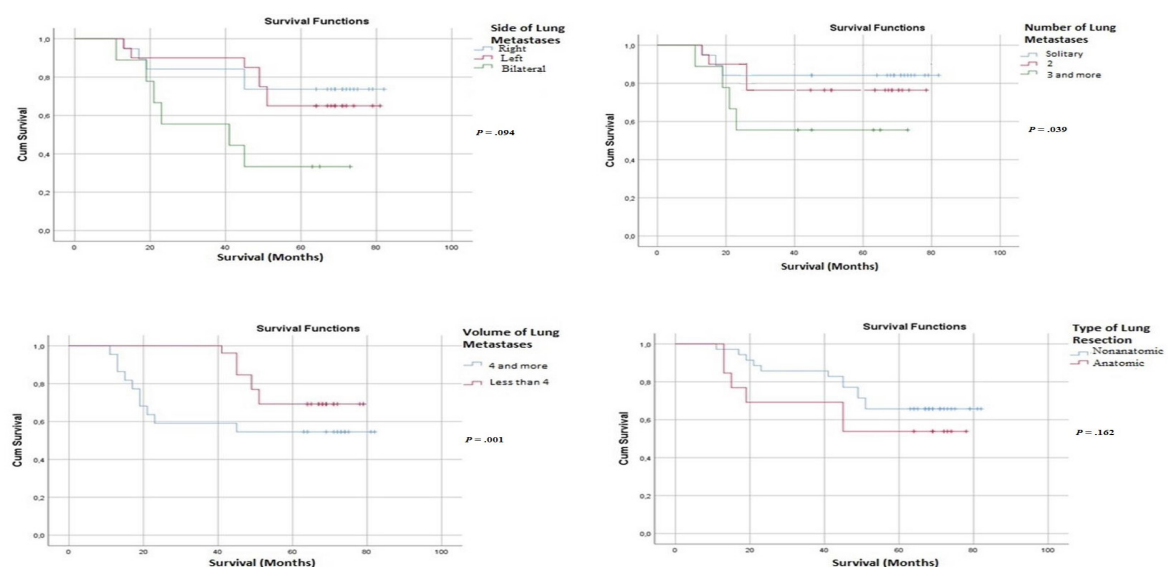
## RESULTS

Among a total of 48 patients, 12 (25%) were female and 36 (75%) were male. The mean age of the patients was  $52.7 \pm 10.8$  years while 30 of the cases (62.5%) were 50 years or older. Subtypes of RCC were clear cell in 37 (77.1%), papillary in 7 (14.5%), chromophobe in 2 (4.2%), cystic-solid in 1 (2.1%) and medullary in 1 patients (2.1%). Majority of RCC pathological T-stage was T3 which counts for 72.9% of all cases. Pulmonary metastases were right-sided at 19 (39.6%), left-sided at 20 (41.7%) and bilateral at 9 (18.8%) cases. Average of DFI was  $32.1 \pm 13.6$  months whereas 28 (58.3%) patients had a DFI outlasting 32 months. The average number of pulmonary metastases was  $3.3 \pm 2.3$  and 22

(45.8%) patients had three or more metastatic lesions. Metastases had an average volume of 4.02 (range: 1.6-7.6) cm<sup>3</sup>. Nonanatomical pulmonary resections were performed for 35 (72.9%) cases and anatomical resections for 13 (27.1%) patients. All the lung resections were complete (R0).

Follow-up of the patients ranged from 11 to 82 months. Average of overall survival was  $56.2 \pm 21.7$  months. Survival time was less than 3 years for 7 (14.6%), between 3 and 5 years for 11 (22.9%) and more than 5 years for 30 (62.5%) patients.

Following R0 pulmonary metastasectomy, local recurrence was detected in the lung in two patients whereas distant metastases in one organ occurred in 4 patients (brain n=2, bone n=1, liver n=1) and 2 patients suffered from multiple metastases. All of these six patients died failing to survive for 3 years. Data relating the clinical and demographic features of the patients are given in



**Figure 2.** Clinical features related to long-term survival.

**Table 1.**

Considering the relevance between categorical variables and long term survival, it is obvious that 5-year survival is significantly related with longer DFI and pulmonary metastases appearing less both in size and number ( $P < .05$ ). (Table 2).

On the other hand, series of analysis performed by Cox Regression test clearly prove that young age, female gender and unilateral pulmonary lesions also result in 3.2, 2.1 and 1.7-fold longer survivals following pulmonary metastasectomy ( $P < .05$ ).

Demographical and clinical factors contributing to survival after lung metastasectomy are also illustrated as curves in Figure 1 and Figure 2.

No per-operative or post-operative deaths occurred. In the post-operative period, none of the patients encountered mortality or major morbidity except two developing pneumonia and 3 prolonged air leakage but all were managed without any persistent complications.

## DISCUSSION

The findings of this study clearly show that female RCC patients in younger ages developing unilateral lung metastases which are limited in size and volume and also presenting longer DFI benefit from pulmonary metastasectomy.

RCC presents with metastatic disease in approximately one-third of the patients. The most common sites of metastases are lung, bone and lymph nodes. Regarding the overall outcomes of the metastatic process, disparate consequences develop from different sites of metastases. Bone, liver and brain metastases of RCC are associated with poor outcomes whereas lung and pancreatic metastases are related to more favorable prognoses. Moreover, metastases only to the lung are credited with better survival rates than RCC metastases in any other locations<sup>(2-4)</sup>.

Since Barney and Churchill performed the first resection of a pulmonary metastases of RCC in 1939, metastasectomy of lung metastases from RCC constitutes the best choice of treatment in patients with completely resectable pulmonary lesions<sup>(5)</sup>. Since then, precepts of a pulmonary metastasectomy including a primary tumor kept under control, possibility of a complete resection, no other extrapulmonary metastases and a good performance status of the patient applies to RCC metastasizing to lungs.

Median survival with untreated metastatic RCC is approximately 10 months<sup>(3,4)</sup>. Recent studies report response rate of cytokine-based immunochemotherapy and targeted therapy such as VEGF inhibitors or mTOR inhibitors up to 20% while 5-year survival rate ranges from %36 to %54 following complete resection of lung metastases from RCC<sup>(5,6)</sup>. Considering the long-term survival rates, incomplete resection of metastatic lesions leads to almost 10-fold evaluated risk in correlation to patients with complete resection<sup>(7)</sup>. Our study presents 62.5% as a 5-year survival rate which considerably exceeds the results of surgery announced in the recent studies<sup>(8-10)</sup>. This circumstance may result from applying the general principles of a pulmonary metastasectomy strictly and excluding the patients who did not meet the criteria from surgery.

This study states young age (<50 years) and female gender as good prognostic factors for patients who had pulmonary metastasectomy from RCC. Nevertheless,

this finding was not investigated or included in other recent studies.

The other significant risk factors are localization and quantity of lung metastases. The patients who developed unilateral lung lesions that appear less both in size and number benefit more from pulmonary metastasectomy. Although right or left side of a lung metastases does not constitute an evident risk factor, unilateral lesions contribute to longer survival times. The best prognosis have been reported with solitary metastasis, therefore many recent studies limit their comparison to cases with solitary versus multiple metastases while Hofmann et al. announced that worse prognosis was combined with more than 6 metastases<sup>(1)</sup>. Unfortunately, we could not find any study that investigate the correlation of the size or volume of lung metastases from RCC and survival. In our experience, more than three resected lung metastases or lesions measuring larger than 4 cm<sup>3</sup> clearly indicate a poor prognosis.

DFI is the period between treatment of a primary RCC and development of lung metastases and also accepted to be associated with better survival<sup>(11,12)</sup>. In our metastasectomy series, DFI longer than 32 months was a good prognostic factor.

Although the histological type in addition to the tumor size have been accepted to present a potential metastatic risk for RCC, our findings failed to determine any relationship between pathological stage and long-term survival<sup>(12,13)</sup>.

Reviewing the current findings, type or extent of pulmonary metastasectomy from RCC do not appear to be a prognostic factor. Moreover, current literature also lack studies focusing on surgical results. This study clearly reveals that better prognosis is associated with a complete metastasectomy rather than content or method of the applied surgery.

The principal limitation of this workup was its retrospective design. Additionally, results shall be corroborated by larger cohorts of cases from multicenter practices.

## CONCLUSIONS

Role of pulmonary metastasectomy from RCC is significant because of its contribution to long-term survival. The most determinant factor affecting the surgical outcomes is the complete resection of lung metastases while the type or extent of the surgery is not associated with a better survival. Findings of this study strongly suggest lung metastasectomy to patients with unilateral lung metastases counting less than three and measuring smaller than four cm<sup>3</sup> and also DFI lasting longer than thirty-two months.

## ACKNOWLEDGEMENT

This study was approved in Ethic Committee of Tekirdag Namik Kemal Faculty of Medicine, as a research project.

## CONFLICT OF INTEREST

The author reports no conflict of interest.

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