

## Surgical Resection of Pulmonary Metastasis from Renal Cell Carcinoma

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**Background:** Renal cell carcinoma has shown less response to systemic therapies including chemotherapy, radiation, and immunotherapy than other cancers. Surgery has therefore become an important treatment tool. The protocol for treatment is the same for pulmonary metastasis of renal cell carcinoma. We performed surgery for pulmonary metastatic renal cell carcinomas and analyzed the results. **Materials and Methods:** We retrospectively analyzed 15 patients who had undergone pulmonary metastasectomy from renal cell carcinoma at our hospital from January 2005 to December 2009. **Results:** No patients had extrathoracic metastasis. The mean age was 60.2 years (range 35~73). There were 12 male and 3 female patients. The number of synchronous and metachronous patients were 8 and 7, respectively. The mean survival times of synchronous and metachronous patients were 32.6 and 42.9 months, respectively. 6 patients had single lesions and 9 patients had multiple (more than 3) lesions. The surgical procedures included wedge resection (10), lobectomy (2), wedge resection with segmentectomy (2), and segmentectomy (1). Median observation and survival time were 54.1 and 34.9 months. The 1-year and 3-year survival rates were 80% and 50%, respectively. **Conclusion:** Pulmonary resection for pulmonary metastatic renal cell carcinoma was found to be a safe and effective treatment modality when complete resection was performed.

Key words: 1. Metastasectomy  
2. Renal cell carcinoma  
3. Prognosis

### INTRODUCTION

Many studies have been published on the effects of pulmonary metastasectomy [1,2]. Because effective chemotherapy, radiation, and biologic therapies have not been introduced to date, surgical treatments seem to represent the most effective treatment. Renal cell carcinoma accounts for about 2% of all cancers [3,4]. The lungs are the most frequent site for metastases, and nearly 20% of all patients with renal cell carcinoma have pulmonary metastases when they are first diagnosed [3,5-8]. The prognosis for patients with unresected metastatic

renal cell cancer is very poor. The mean survival time is from 6 to 10 months and the 5-year survival rates reported range from 5% to 10% [3,4,8,9]. The complete resection of metastatic lesions offers markedly improved survival rates [4, 5]. The role of pulmonary metastasectomy still represents a widely debated issue due to the introduction of new immunotherapies and biologic therapies [10]. A retrospective analysis of patients with pulmonary metastases from renal cell carcinomas was performed to show the effects of pulmonary metastectomy.

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## MATERIALS AND METHODS

From January 2005 to December 2009, 15 patients underwent pulmonary resection of renal cell carcinoma metastasized to the lung at our cancer center. Medical records were retrospectively reviewed.

All patients who underwent resection of their pulmonary metastases met the following criteria: (1) pulmonary lesions were deemed resectable by not only the radiological examinations but also by the patients' general conditions, (2) metastatic disease was limited to the thorax, (3) locoregional control of their primary renal lesions was obtained or obtainable, and (4) metastasectomy was performed for complete resection or for pathologic diagnosis for further treatment plans.

All patients were retrospectively analyzed for gender, age, systemic therapy, disease-free interval, type of pulmonary resections, number of pulmonary metastases, stage of renal cell carcinoma, and completeness of resection. Disease-free interval was defined as the time between nephrectomy and metastasectomy in metachronous patients. Actuarial survival curves were estimated using the Kaplan-Meier method. Statistical comparisons among prognostic factors were made using the log-rank test. Because of the small number of cases, a p-value less than 0.1 was considered statistically significant.

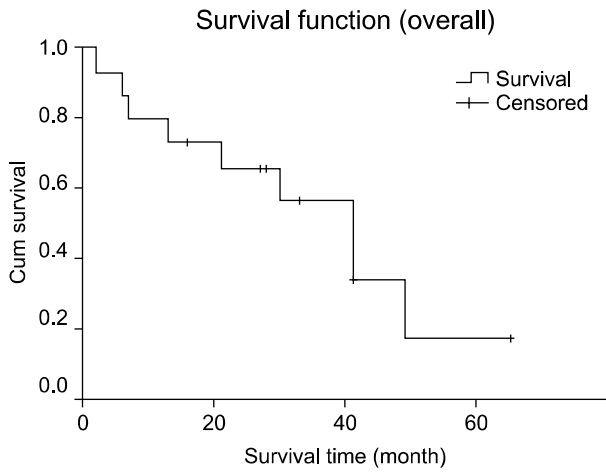
## RESULTS

15 patients with pulmonary metastases from renal cell carcinoma underwent pulmonary resections (Table 1). The median age was 60.2 years, with a range of 35~73 years. 12 patients were male and 3 patients were female, and the sex ratio was 4 : 1. There were 3 cases of stage I renal cell carcinoma, 3 cases of stage II, 1 case of stage III, and 8 cases of stage IV. 10 patients underwent wedge resections (including both sided), 2 patients underwent lobectomy, 2 patients underwent segmentectomy with wedge resection, and 1 patient underwent segmentectomy. Median observation time was 54.1 months. 9 patients died during observation and 6 patients died of progressive renal cell carcinoma. Median survival time was 34.9 months. The 1-year and 3-year survival rates were 80% and 50%, respectively (Fig. 1). The median survival time of male and female patients was 35.0 and 37.0

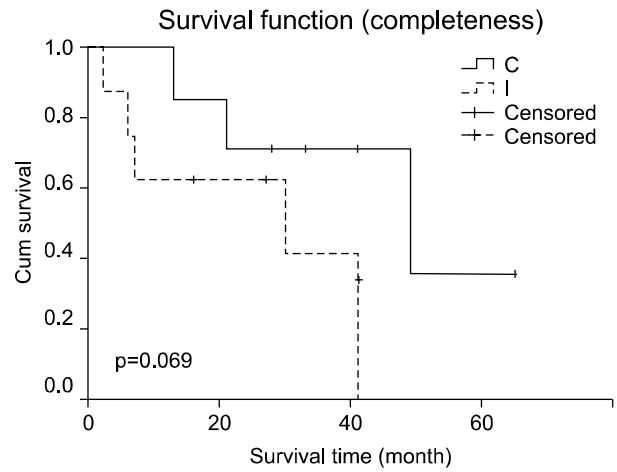
**Table 1.** Patients' characteristics

Gender	
Male	12 patients
Female	3 patients
Nephrectomy	
Right	6 patients
Left	9 patients
Stage of renal cell carcinoma	
I	3 patients
II	3 patients
III	1 patient
IV	8 patients
Disease-free interval	
Metachronous 7 patients	58.4 months (24~144 months)
Laterality	
Unilateral lesions	8 patients
Bilateral lesions	7 patients
Number of tumors	
Single lesion	6 patients
Multiple lesions (more than 3)	9 patients
Size of tumor	
Single lesion	15.8 mm (7.3~34.1 mm)
Multiple lesions( largest one)	14.8 mm (7.2~33.9 mm)
Performance (ECOG)	
Single lesion	0.83 (0~2)
Multiple lesions	0.77 (0~1)
Surgical procedure	
Wedge resection	10 patients
Segmentectomy	1 patient
Lobectomy	2 patients
Segmentectomy and lobectomy	2 patients
Survival time	
Complete resection	45.6 months (24~60 months)
Incomplete resection	25.2 months (13~42 months)
Systemic therapy	
Before metastasectomy	3 patients
After metastasectomy	7 patients
Completeness of resection	
Complete resection	7 patients
Incomplete resection	8 patients

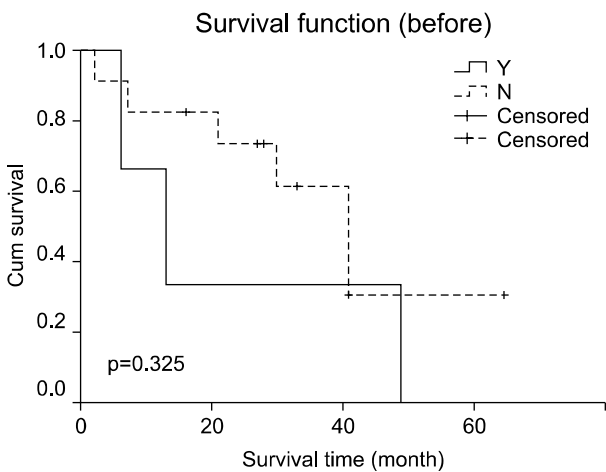
months, and there were no significant differences between genders (p-value 0.821). 7 patients underwent complete resection of the pulmonary metastases and 8 patients underwent incomplete resection, due to more lesions being found than were known during preoperative evaluation and the need for pathological confirmation to further plan treatment. The median survival time in patients with incomplete resections was 25.2 months compared with 45.6 months in patients with



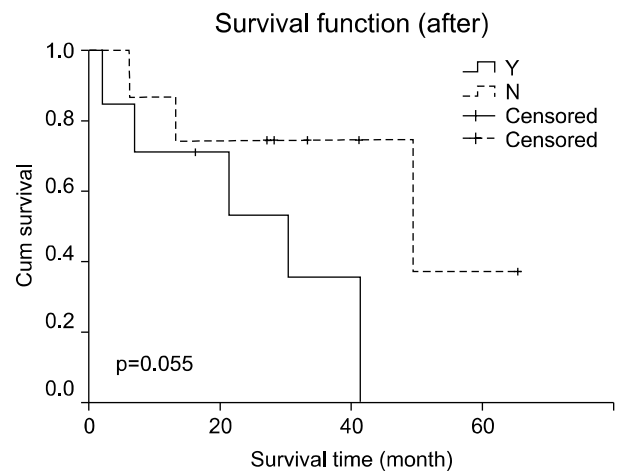
**Fig. 1.** Overall survival time was 34.9 months. The 1-year and 3-year survival rates were 80% and 50%, respectively.



**Fig. 2.** Completeness of resection (C=Complete resection; I=Incomplete resection). Complete resections provided longer-term survival than incomplete ones (45.6 vs 25.2 months).



**Fig. 3.** Systemic therapy (Before=Systemic therapy before pulmonary resection; After=Systemic therapy after pulmonary resection; Y=With systemic therapy; N=Without systemic therapy). Systemic therapy after pulmonary resection provided a statistically different survival but, paradoxically, receiving systemic therapy provided shorter survival than not doing so.



complete resections, which constituted a significant difference (p-value 0.069)(Fig. 2). Pulmonary metastases were diagnosed synchronously in 8 patients and metachronously in 7 patients. The median survival time was 42.9 months for metachronous patients versus 32.6 months for synchronous patients. There was no significant difference between the two groups (p-value 0.660). 6 patients had a single lung metastasis and 9 had more than three metastases, the median survival was 43.7 and 26.6 months respectively and there was no significant difference between the two groups (p-value 0.128). Only 3 patients

received systemic therapy (IL-2, INF-a) after the nephrectomy and before the pulmonary metastasectomy, and 7 patients received systemic therapy (IL-2, INF-a, 5-FU) after pulmonary metastasectomy. Systemic therapy before pulmonary resection provided no statistically significant survival improvement, systemic therapy after pulmonary resection resulted in a statistically significant difference in survival, but, paradoxically, receiving systemic therapy resulted in shorter survival than no therapy (p-value 0.055)(Fig. 3). There was no significant difference for the stage of primary renal cell carcinoma (p-value

0.482). There were 2 complete resection patients and 2 incomplete resection patients who were suspected of having metastatic mediastinal lymph nodes before pulmonary metastectomy, but dissections of the nodes were not performed. After pulmonary metastectomy, recurrence in the lung developed in 2 of 7 complete resection patients. Metastases to other organs were found in 10 patients, including the mediastinal lymph nodes for 6 patients, bones for 5, liver for 3, and the brain for 2. A single metastasis occurred in 4 of the patients and multiple organ metastases occurred in 6 patients.

## DISCUSSION

Many studies have been conducted on pulmonary metastectomy, and it has become the standard therapy for various metastatic solid malignancies to the lungs [2,4,5,11-14]. Metastases of primary tumors that do not respond well to chemotherapy, radiotherapy, or a combination of both therapies are especially well suited for surgical resection. One third of patients with renal cell carcinoma present with synchronous pulmonary metastases, and of the remainder, 50% ultimately develop pulmonary metastases [2]. The lung is the most frequently affected metastatic site in patients with renal cell carcinoma [4-6,10,11]. The prognosis of patients with unresected metastatic renal cell cancer is very poor, the mean survival time is from 6 to 10 months and the 5-year survival rates reported range from 5 to 10% [5,9,13]. The patients with renal cell carcinoma can benefit from systemic therapies including cytokines and immunotherapy, but the effects of systemic therapies on pulmonary metastasis are small, achieving responses in 15% to 35% of these patients [1,3,9,11,13]. The first resection of a pulmonary metastasis in a patient with renal cell carcinoma was performed by Barney and Churchill in 1939. Since then, surgery remains the safe and effective treatment for patients with pulmonary metastases [1-3,5,11,15]. Most pulmonary metastases are located peripherally and are frequently immediately subpleural, amenable to a wedge resection. It appears that wedge resection, if feasible, is as effective as anatomic resection [14]. If there is no other metastatic lesion and complete resection is possible, metastectomy should be considered for longer survival [11].

According to the studies, the most important determinant of

survival was resectability. The overall 5-year survival for patients who underwent complete resection was 36%, with a median survival of 35 months. In those patients who had undergone incomplete resection, the 5-year survival rate was only 13%, and the median survival was 15 months [6,11]. In our study, the median survival time in patients with incomplete resections was 25.2 months, compared with 45.6 months for patients with complete resections. There was a significant difference between the two groups. Future studies could investigate preoperative assessments and the possibility of complete resection with an adequate pulmonary reserve, including an appraisal of the number of nodules, consideration of the location of nodules, and an evaluation of postoperative pulmonary function [2,11]. The computed tomographic (CT) scan and PET-CT of the chest are regarded as the most important preoperative examinations, and we also referred to the chest CT and PET-CT for complete resection. Functional loss after three or more non-anatomical resections is comparable with that observed for lobectomy [16].

According to multiple studies, a long disease-free interval (DFI) is considered a favorable prognostic factor in cases of pulmonary metastasis. One study reported that patients with a DFI of 48 months or more achieved a 5-year survival of 46%, compared to 26% for those with a DFI of less than 48 months [5], and another study reported the 5-year survival rate in patients with a DFI of more than 23 months was 47%, compared to 24.7% in patients with a DFI of 23 months or less [2-5,13,17]. Longer DFI does not always imply slow tumor growth or the absence of other metastases. One study reported that late renal cell carcinoma metastases are often combined with rapid disease progression [13], and there was no survival difference between synchronous and metachronous patients in our study. The median DFI of metachronous patients was 58.4 months. The survival of the metachronous patients by DFI could not be estimated due to the small number of cases.

The number of metastatic lesions discovered before or during operation has been studied. Some studies have reported that the number of metastases was highly significant and that patients with single metastases had a survival of 43% at 5 years, compared with 34% for those with two or three metastases, and 27% for those with four or more metastases, but

other studies reported that the number of metastases was not an important factor [5,10,14,18]. Univariate analysis of our data shows that the number of metastases is not a relevant prognostic factor. The indication for operation cannot be based only on the number of metastatic lesions, since some patients with multiple metastatic lesions show longer than 5-year survival. The greater the number of pulmonary nodules identified by preoperative chest CT in combination with renal disease, the higher the probability of incomplete resection [15]. Pulmonary metastasis with incomplete resection has a longer survival than unresected pulmonary metastasis. This shows that incomplete resection can attenuate the tumor burden and can potentiate the immune system and the effects of systemic therapy [11].

The role of metastasectomy for renal cell carcinoma in the era of emerging effective systemic therapy (usually immunotherapy) has not yet been defined, except for solitary metastasis. In order to achieve complete eradication of metastatic disease, we propose these guidelines [11]. First, we would encourage aggressive surgical resection of the clinically solitary metastasis, whether synchronous or metachronous. Continued follow-up of those patients may be necessary indefinitely, because relapse is quite likely, but adjuvant systemic therapy should not be initiated unless it is within protocol. Second, limited metastases in only one organ may behave similarly to a solitary metastasis, and if the metastases are in a site amenable to surgical resection, e.g., lung, initial surgery might be reasonable. Systemic therapy for these patients is highly recommended and need not necessarily wait for recurrence. Third, for patients with multiple metastases, initial systemic therapy followed then by resection of any residual disease in selected patients seems to be supported by the experience at several medical centers.

There are several limitations to our analysis. The biggest limitation is the number of cases. Since the number of patients for pulmonary metastasectomy of renal cell carcinoma was so small in our institution, it would be difficult to determine a certain decision. A large-scale prospective study involving multiple institutions is necessary.

Because pulmonary metastasectomy for renal cell carcinoma is safe, survival depends on a complete resection of pulmonary disease and an adequate pulmonary reserve.

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Jae Jun Kim, et al

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