*Original Article*

# Surgery Outcomes for Pulmonary Metastases from Renal Cell Carcinoma

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Pulmonary metastatic resection is a standard therapy for renal cell carcinoma (RCC). Although patients with pulmonary metastases who do not undergo any treatment have poor prognoses, it has been reported that resection for pulmonary metastases yields good clinical outcomes. We investigated the prognoses of the 10 Japanese patients (eight males, two females) who underwent a surgical resection of pulmonary metastasectomy from RCC at our institution between April 1, 2012 and March 31, 2020 and analyzed the prognostic factors. We determined the prognoses and calculated the 5-year overall survival (OS) and disease-free survival (DFS) rates. To identify prognostic factors, we compared the median DFS duration for each factor. Elderly patients (median age, 75.5 years) were more predominant compared to previous studies, and all 10 patients underwent a complete resection. The 5-year DFS rate was 30.5% (95%CI: 0.045-0.63) and the 5-year OS rate was 80% (95%CI: 0.20-0.97). The following factors were associated with better prognosis: female, disease-free interval $\geq 36$ months, and metastases size $< 12$ mm. These results indicate that complete resection for pulmonary metastases from RCC resulted in good clinical outcomes, particularly for patients with better prognostic factors.

Key words: renal cell carcinoma, pulmonary metastasis, complete resection

Renal cell carcinoma (RCC) may be accompanied by hematogenous metastasis, and distant metastases are noted at the first visit in 25-35% of patients diagnosed with RCC [1-3]. The lung is the most frequent site of metastasis from RCC. Several research groups reported that the 5-year survival rate after a pulmonary metastasectomy was 35-91.3%, suggesting that surgery for pulmonary metastases can result in a good clinical outcome] [1-7]. It was also recently suggested that treatment with immune checkpoint inhibitors can provide good clinical outcomes; however, grade 3 or higher adverse events were observed in 46% of patients in a nivolumab-ipilimumab group and 75.8% of patients in a pembrolizumab-axitinib group [8,9]. For patients who are diagnosed with pulmonary metastases from RCC, the reliable identification of patients who are suitable for surgical treatment and the performance of safe surgery are considered beneficial; however, prognostic factors after a pulmonary metastasectomy, which have been discussed in many reports, have not yet been established [1-7]. We conducted the present study to (*i*) investigate patients' prognoses after pulmonary metastasectomy and (*ii*) identify prognostic factors that are related to survival benefits.

## Patients and Methods

This was a retrospective, single-center observational study. The study protocol was approved by the Institutional Review Board of the Iwakuni Clinical Center (approval no. 0194). At our institution, surgery

for pulmonary metastases from RCC is conducted based on Thomford's criteria and Kondo's criteria [10, 11]. Our criteria are as follows: safe surgery for the patient is possible; the primary malignancy and extrapulmonary metastasis are controlled; and it is considered that complete resection for pulmonary lesions is possible. The 10 patients who underwent surgery for pulmonary metastases from RCC at Iwakuni Clinical Center between April 1, 2012, and March 31, 2020 were eligible for the study. The patients were referred to our department from the urology department of our hospital or local clinics. One patient was referred to our department for a third pulmonary metastasectomy; we analyzed the data of the patient's first pulmonary metastasectomy. We usually perform a partial resection for pulmonary metastases, but in some cases with central lesions we perform a segmentectomy. After their pulmonary metastasectomies, the patients were examined every 3 months by computed tomography (CT) for the first 2 years, and the follow-up period was gradually extended.

We determined the patient characteristics and outcome data (including recurrence and survival) after the pulmonary metastasectomies. The following factors were collected for the statistical analyses: patient age, sex, histology of RCC, pT staging of RCC, initial nodal status of the primary tumor, the disease-free interval (DFI), the number of metastases, the size of the metastases, and the surgical procedure performed for pulmonary metastases. We defined the patient's age as the age at the patient's first surgical treatment for pulmonary metastasis. The pT staging of RCC was classified into pT1 ($\leq 7$ cm) and $> $pT1 ($> 7$ cm or tumor extension into other tissues) based on The General Rule for Clinical and Pathological Studies on RCC (4th edition). The DFI was calculated from the date of the patient's surgery for RCC to the date of the patient's pulmonary metastasis diagnosis. When there were multiple metastases, the largest size of metastasis was considered.

All statistical analyses were performed using EZR ver. 1.41 (October 1, 2019). Recurrence and survival probabilities were analyzed using the Kaplan-Meier method, and recurrence was calculated using the log-rank test. A $p$-value $< 0.05$ was considered significant. Data were censored on December 31, 2020. Patients who were lost to follow-up were censored at the date of last contact. Disease-free survival (DFS) was calculated from the date of surgery to the date of disease recur-

rence or death from any cause. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause. The median duration of DFS was compared for each factor. The cut-off values for age, DFI, and size of metastases were set based on the population medians.

## Results

*Patient characteristics.*　　The median age of the patients was 75.5 (range, 60-83) years. Two patients were women. All patients underwent a nephrectomy for clear cell carcinoma with no lymph node metastasis. Complete resection was performed for pulmonary metastases in all 10 patients. The median DFI was 40.5 (range 0-149) months, and pulmonary metastases with RCC were noted in two patients. We performed a partial resection in seven patients and segmentectomy in three patients with central lesions (Table 1).

*Perioperative complications and prognosis after pulmonary metastasectomy.*　　One patient experienced a complication associated with the surgery; the patient underwent a left lingular segmentectomy and developed arrhythmia, necessitating medication on the second postoperative day. Because the arrhythmia did not persist, we checked the patient's Holter electrocardiography and stopped administering the drug on the 23rd postoperative day.

Five patients experienced recurrence after pulmonary metastasectomy, and only one patient died. The 5-year DFS rate was 30.5% (95% confidence interval [CI]: 0.045-0.63), and the 5-year OS rate was 80% (95%CI: 0.20-0.97) (Fig. 1). One patient received additional treatment 4 months after undergoing the pulmonary metastasectomy, but almost all five patients without recurrence did not receive additional treatment and had long-term survival. Among the patients experiencing recurrence, multiple surgeries and/or chemotherapy resulted in long-term survival in four patients (Table 2). The death of the single patient who died was due to multiple brain and lung metastases; the death occurred 28 months after the patient underwent the pulmonary metastasectomy.

*Prognostic factors of recurrence after pulmonary metastasectomy.*　　We compared the median DFS duration for each factor. Based on the population medians, the following cut-off values were set: for age, 75 years; for the DFI, 36 months; and for the size of

Table 1    Patient characteristics

| Age | |
|---|---|
| median (range) | 75.5 (60–83) years |
| **Sex** | |
| male | 8 |
| female | 2 |
| **Histology of renal cell carcinoma** | |
| clear cell carcinoma | 10 |
| **Initial tumor size of renal cell carcinoma** | |
| pT1 | 8 |
| >pT1 | 2 |
| **Initial nodal status of primary tumor** | |
| pN0 | 10 |
| **Disease free interval** | |
| median (range) | 40.5 (0–149) months |
| 0 month | 2 |
| –36 months | 2 |
| 36–60 months | 3 |
| 60– months | 3 |
| **Number of metastases** | |
| single | 7 |
| multiple | 3 |
| two | 1 |
| three | 2 |
| **Size of metastases** | |
| median (range) | 12.9 (5–42.2) mm |
| –12 mm | 4 |
| >12 mm | 6 |
| **Surgical procedure** | |
| partial resection | 7 |
| segmentectomy | 3 |

metastases, 12 mm. The factors with significant differences at the median duration of DFS were sex, DFI, and size of metastases. Female sex, a long DFI, and small size of metastases were significantly associated with a long duration of DFS ($p = 0.047$, $p = 0.017$, and $p = 0.014$, respectively) (Table 3, Fig. 2).

We classified the patients as the 3F group (with all three of the above significant factors, n = 2), the 1-2F group (with one or two factors, n = 5), and the 0F group (without any factor, n = 3), and a further analysis revealed a difference in the recurrence rate among these groups. Two patients in the 3F group had no

recurrence, whereas all three patients in the 0F group experienced recurrence. The recurrence rates were as follows: the 3F group, 0%; the 1-2F group, 40%; and the 0F group, 100%.

## Discussion

Surgical resection is generally performed for the treatment of pulmonary metastases from various cancers. According to the annual report by the Japanese Association for Thoracic Surgery, 8,950 procedures were performed in Japan in 2017 for metastatic pulmonary tumors, which was the third most common disease followed by the procedures performed for primary lung cancer (44,140 cases) and pneumothorax (14,499 cases). Among the metastatic pulmonary tumors, RCC (746 cases) was the second most frequent diagnosis, followed by colorectal cancer (4,240 cases) [12]. Several research groups have reported that surgery for pulmonary metastases from colorectal cancer and a pulmonary metastasectomy are established as treatment strategies for stage IV colorectal cancer [13-17]. Similarly, in RCC, some recent studies have indicated that a pulmonary metastasectomy could result in long-term survival in patients with stage IV RCC [1-7]. In the present study, the 5-year OS rate after surgery for pulmonary metastases from RCC was 80%, which is a good clinical outcome. In addition, the median patient age of the present population (75.5 years) is older than those in previous studies (range 57.7-68 years) [1,2,4-7]. Our findings demonstrate that pulmonary metastasectomy was safe and resulted in long-term survival, even in elderly patients.

Notably, our recurrence-free patients had a particularly better prognosis and long-term survival by only a first pulmonary metastasectomy. This result suggests that surgery was especially useful in some patients. We thus investigated the clinical factors that could be used to predict disease recurrence. The following have been reported as prognostic factors: complete resection, nodal status, DFI, number of metastases, size of metastases, surgical procedure, decreased preoperative forced expiratory volume in 1 second (FEV1), synchronous metastases, and pleural infiltration (Table 4) [1, 2,4-7]. In particular, all studies involving incomplete resection identified complete resection as a prognostic factor. There is no doubt that complete resection is a prognostic factor. At our institution, surgical indica-
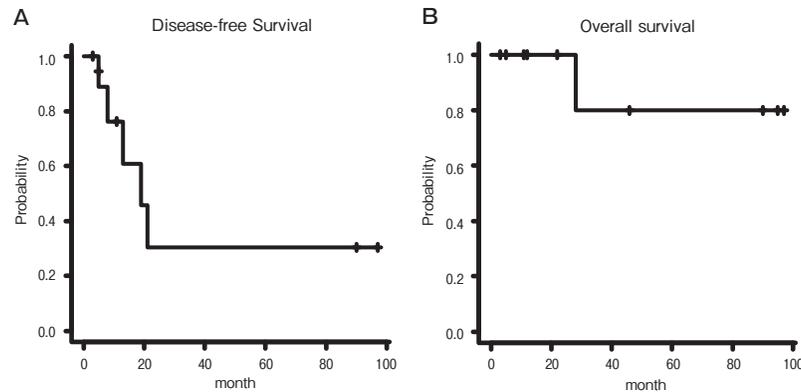
**Fig. 1**   Disease-free survival (DFS) and overall survival (OS) after surgical resection for pulmonary metastases from renal cell carcinoma (RCC). **A**, The 5-year DFS rate was 30.5% (95%CI: 0.045-0.63); **B**, The 5-year OS rate was 80% (95%CI: 0.20-0.97).

**Table 2**   Clinical courses of all ten patients

| Case | Age (years) | Sex | DFI (months) | The number of metastases | Size of metastases (mm, maximum) | Diagnostic modalities before pulmonary surgery | PS at pulmonary surgery | Surgical procedure | Recurrence | Treatment for recurrence | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 60 | F | 38 | multiple | 6.4 | CT, PET-CT | 0 | segmentec-tomy | no | | alive |
| 2 | 76 | M | 43 | single | 6.2 | CT | 0 | partial | lung, rib | multiple surgeries (three times) molecular target drug nivolumab | alive |
| 3 | 64 | F | 99 | single | 5 | CT, Bone scan | 0 | partial | no | | alive |
| 4 | 83 | M | 149 | single | 42.2 | CT, PET-CT | 2 | segmentec-tomy | no | | lost follow |
| 5 | 83 | M | 0 | single | 26 | CT, PET-CT Bone scan | 1 | partial | lung, brain | molecular target drug nivolumab | death |
| 6 | 75 | M | 103 | single | 13 | CT | 1 | partial | lung | multiple surgeries (three times) | lost follow |
| 7 | 75 | M | 11 | single | 11.6 | CT, PET-CT | 1 | partial | no | | lost follow |
| 8 | 77 | M | 31 | multiple | 12.8 | CT | 1 | partial | lung | molecular target drug | alive |
| 9 | 82 | M | 50 | multiple | 17 | CT, PET-CT | 0 | partial | no | | lost follow |
| 10 | 73 | M | 0 | single | 18 | CT, Bone scan | 0 | segmentec-tomy | lymph node | lpilimumab + nivolumab | alive |

RCC, renal cell carcinoma; DFI, disease-free interval; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; PS, performance status

Table 3    Comparison of the median duration of disease-free survival (log-rank test)

| Factor | | n | | Follow-up period until recurrence or censoring (months) | Median duration of DFS (months) | |
|---|---|---|---|---|---|---|
| | | all | recurrences | | | |
| Age | ≤75years | 5 | 2 | 5–97 | NA | p = 0.28 |
| | >75years | 5 | 3 | 3–21 | 13 | |
| Sex | female | 2 | 0 | 90–97 | NA | p = 0.047 |
| | male | 8 | 5 | 3–21 | 13 | |
| DFI | ≥36months | 6 | 2 | 3–97 | 21 | p = 0.017 |
| | <36months | 4 | 3 | 5–13 | 10.5 | |
| Number of metastases | single | 7 | 4 | 5–90 | 19 | p = 0.77 |
| | multiple | 3 | 1 | 3–97 | 8 | |
| Size of metastases | <12 mm | 4 | 1 | 11–97 | NA | p = 0.014 |
| | ≥12 mm | 6 | 4 | 3–19 | 13 | |
| Surgical procedure | segmentectomy | 3 | 1 | 5–97 | NA | p = 0.79 |
| | partial resection | 7 | 4 | 3–90 | 19 | |

DFS, disease-free survival; DFI, disease-free interval.
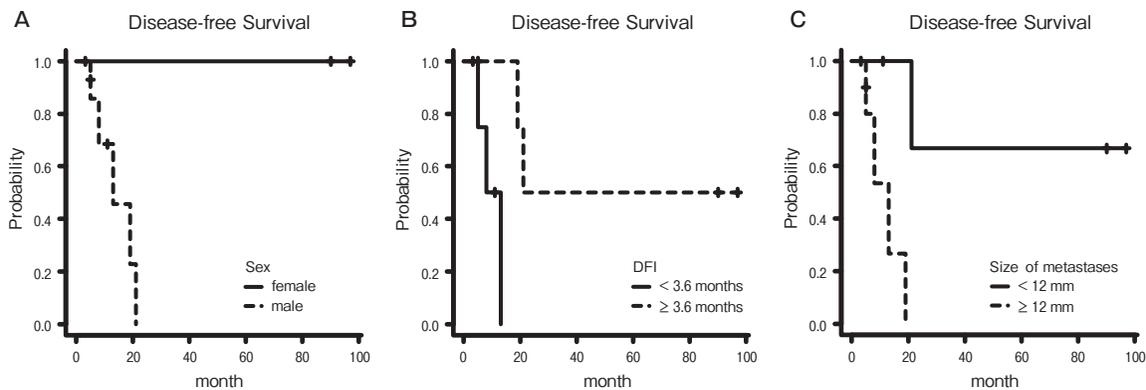


Fig. 2    Comparison of DFS after surgical resection for pulmonary metastases from RCC. The median duration of DFS was significantly longer in the female patients ($p = 0.047$) (**A**), the patients with a disease-free interval (DFI) ≥36 months ($p = 0.017$) (**B**), and the patients with metastases <12 mm ($p = 0.014$) (**C**).

tions are determined based on the criteria proposed by Kondo *et al.* [11], which include "the pulmonary lesions are thought to be completely resectable;" therefore, all patients in our study underwent a complete resection. Regarding other clinical factors, we compared the median duration of DFS for each factor to determine the factors associated with a good clinical outcome, and three factors (sex, DFI, and size of metastases) were identified as prognostic factors.

The DFI and the size of metastases have been reported as prognostic factors, and the cut-off values of these factors differed depending on the studies [1-7]. In our present investigation, the cut-off values were based on the population medians: the DFI cut-off was 36 months, and that of the size of metastases was 12 mm. As a result, a long DFI and small metastases were con-

**Table 4**   Previous studies

| Reporter | Year | The number of cases (Incomplete resection) | Median age | The 5-year survival rate (Complete resection) | Prognostic factors |
|---|---|---|---|---|---|
| Hayashi *et al* | 2019 | 23 (0) | 62 | 91.3% (91.3%) | surgical procedure |
| Yanagisawa *et al* | 2010 | 14 (0) | 68 | 35% (35%) | DFI |
| Piltz *et al* | 2002 | 105 (17) | 59 | 40% (40%) | complete resection, N, size of metastases |
| Pfannschmidt *et al* | 2002 | 191 (42) | 57.7 | 36.9% (41.5%) | complete resection, N, DFI, number of metastases |
| Murthy *et al* | 2005 | 92 (29) | 60 | 31% (42%) | complete resection, N, DFI, number of metastases, size of metastases, decreased preoperative $FEV_1$ |
| Meimarakis *et al* | 2011 | 202 (27) | 59.5 | 39% (45%) | complete resection, N, size of metastases, synchronous metastases, pleural infiltration |

DFI, disease-free interval; N, nodal status; $FEV_1$, forced expiratory volume in 1 second.

firmed to be associated with the recurrence-free cases. Although patients with a long DFI were considered to have better prognoses, it should be emphasized that a long follow-up observation after a pulmonary metastasectomy is necessary because one of our patients with recurrence experienced pulmonary metastasis 103 months after the nephrectomy. This patient underwent a pulmonary metastasectomy three times because of recurrence. The patient's post-surgery follow-up and early intervention for pulmonary metastases resulted in long-term survival.

Sex was not identified as a prognostic factor in the above-cited studies [1-7]. The two female patients in our study had no recurrence, and their durations of survival after pulmonary metastasectomy were 97 and 90 months, respectively. These two patients also met the above two factors (long DFI and small metastases), which also suggests that these two factors are associated with good clinical outcomes. However, one of the male patients had a long DFI and small metastases and experienced recurrence. These results suggests that a patient's sex might influence the prognosis. A further accumulation of cases might determine whether sex is a prognostic factor.

Some of the relevant studies focused on laboratory data, but we could not investigate these due to some patients' missing data. The Clinical Practice Guideline for Renal Cancer recommends C-reactive protein (CRP) as a prognostic factor for RCC. Karakiewicz *et al.* reported that CRP is a promising prognostic marker in patients at various stages of RCC [18], and a study by Saito *et al.* revealed that a non-elevated CRP group and a post-treatment normalized CRP group had significantly better outcomes than a non-normalized CRP group: the 2-year survival rates were 69%, 55%, and 4%, respectively [19]. Other investigations have indicated that the neutrophil-to-lymphocyte ratio was associated with survival in patients with RCC [20,21]. It has been estimated that the prognosis after resection for pulmonary metastases from RCC is associated with inflammatory parameters [18-21], and further studies are warranted to elucidate their association.

This study has several limitations. It was a retrospective analysis of patients treated at a single institution. We could not perform multivariate analyses because of the insufficient number of patients, and there were some missing data for the analyses. In addition, the urology surgeons were asked whether they referred patients to our department; the study thus included few patients with multiple metastases. This might be at least part of the reason for the good clinical outcomes in our study. Further cases of multiple metastases should be gathered and examined to establish the prognostic factors.

In conclusion, we report a good clinical outcome after surgery for pulmonary metastases from RCC. Pulmonary metastasectomy was performed safely even in elderly patients, and the 5-year survival rate was 80%. Female sex, a long disease-free interval (DFI), and small metastases were identified as beneficial prog-

nostic factors, and surgery can be recommended for patients with these factors. However, further studies are needed to establish the prognostic factors.

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