Pulmonary resection for metastasis from renal cell carcinoma

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Abstract

The treatment of metastatic renal cell carcinoma still represents a widely debated issue due to the introduction of several immunotherapies. To confirm again a role for resection of pulmonary metastases for such tumors, we reviewed our institutional experience. Between 1992 and 2007, eight patients with pulmonary metastases from renal cell carcinoma underwent complete pulmonary resection. All patients had undergone curative resection of their primary renal cell carcinomas and also had obtained or had obtainable locoregional control of their primaries. Various perioperative variables were investigated retrospectively. Disease-free interval varied from 25 to 156 months, with a median of 73 months. In three patients, lung metastases were found to be unilateral and solitary. Four patients presented two metastases in the unilateral lungs. One patient showed five metastases in the bilateral lungs. Six patients underwent wedge resection or segmentectomy, while two patients underwent more than lobectomy. Five patients showed recurrence after pulmonary metastasectomy. Five-year and 10-year overall survival rate was 83.3% and 41.7%, respectively, while 3-year and 5-year disease-free survival rate was 35.0% and 17.5%, respectively. Our study suggested that pulmonary metastasectomy for renal cell carcinoma might be well justified.

Keywords: Renal cell carcinoma; Pulmonary metastasis; Metastasectomy

1. Introduction

Renal cell carcinoma accounts for approximately 2% of all cancers, and nearly 50% of all patients with renal cell carcinoma will eventually present with metastatic disease that requires individual treatment decision. Patients with untreated metastatic disease have a 5-year survival of 0%-18% [1]. Pulmonary metastasectomy has become the standard therapy for various metastatic malignancies to the lungs [2]. Many reports suggest a role for pulmonary metastasectomy in managing metastatic renal cell carcinoma [1, 3–5], but inconsistency among reports has led to confusion in many respects, such as important factors associated with survival. Furthermore, due to the introduction of immunotherapy the treatment of metastatic renal cell carcinoma still represents a widely debated issue. On the other hand, non-surgical therapy for metastatic renal cell carcinoma is of limited efficacy, despite addition of immunotherapy to traditional chemotherapeutic regimens [6, 7]. To confirm again a role for resection of pulmonary metastases for such tumors, we reviewed our institutional experience.

2. Patients and methods

A retrospective analysis of patients with lung metastases from renal cell carcinomas, who were referred for pulmo-

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nary resection to Kyoto University Hospital between January 1992 and December 2007, was performed. In this period, complete resection of pulmonary metastases from renal cell carcinomas was performed on eight patients. Chest X-rays or CT-scans were considered positive if they showed new, rounded pulmonary lesions without calcifications in patients previously known to have renal cell carcinomas. All specimens obtained from metastasectomies were reviewed by several pathologists. The pulmonary lesions were only considered metastatic if the pathologists could exclude the possibility of a primary lung malignancy and define the tumor as metastatic based upon histologic similarity to the primary tumor. In every patient we collected data on primary treatment, and on the interval between primary surgical treatment for the primary esophageal lesions and the detection of pulmonary metastases (disease-free interval—DFI). Further data were collected on the characteristics of metastases, on the method of treatment, and on details concerning the metastasectomy.

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 lungs, and (3) locoregional control of their primary renal lesions was obtained or obtainable. Five patients met these criteria and metastasectomy was performed. Complete clinical and pathological data were reviewed.
3. Results

Eight patients with pulmonary metastases from primary renal cell carcinoma underwent a thoracotomy and resection. Seven patients were male and one was female (Table 1). The median age was 61 years, with a range of 58–77 years. In all cases, the primary cancers had been completely resected. No patients received chemotherapy before the nephrectomy, and only one patient received immunotherapy with IFN (interferon-α). No patients showed the lymph node involvements in the primary lesions. In three patients, pathological data were unknown since nephrectomy was performed at other hospitals. DFI varied from 25 months to 156 months, with a median of 73 months (Table 2). In no patient, recurrence of renal cell carcinoma was observed before the detection of pulmonary metastases. In seven patients, lung metastases were found to be unilateral. Three patients had a solitary pulmonary metastasis, while four patients had two metastases in the unilateral lung. One patient had five metastases bilaterally, but several detailed data were missing. The number of metastases which was evaluated preoperatively by CT was consistent with that confirmed intraoperatively. The median diameter of the largest metastasis was 30 mm (range, 8–40 mm). Since seven patients had unilateral tumors, they underwent a unilateral thoracotomy. One patient with bilateral lesions underwent staged bilateral thoracotomies. An attempt was made to conserve as much lung tissue as possible. This was reflected by the fact that wedge resection was the most common procedure performed; however, in two patients more than lobectomy was performed because of the size or the location of the tumors (Table 3). In three patients, wedge resection was performed by video-assisted thoracoscopic surgery, while the other patients underwent ordinary thoracotomy. No patients died directly of surgery and all the patients were discharged home without any lesions after surgery. Five patients received immunotherapy with IFN after the pulmonary metastasectomy. In two patients (Patient 1 and 2), immunotherapy had not been applied at that time. One patient (Patient 8) did not receive immunotherapy because he suffered brain infarction after the pulmonary metastasectomy and needed rehabilitation.

Three patients remained free of disease after their first thoracic operation, while five patients developed recurrences. To be specific, Patient 1 developed ipsilateral rib metastasis 18 months after the pulmonary metastasectomy.

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Kidney surgery</th>
<th>Pathological stage of renal cell carcinoma</th>
<th>Immunotherapy pre-/post-nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62/M</td>
<td>Left nephrectomy</td>
<td>Unknown</td>
<td>No/no</td>
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<tr>
<td>2</td>
<td>77/F</td>
<td>Right nephrectomy</td>
<td>T2N0M0</td>
<td>No/no</td>
</tr>
<tr>
<td>3</td>
<td>59/M</td>
<td>Right nephrectomy</td>
<td>T2N0M0</td>
<td>No/no</td>
</tr>
<tr>
<td>4</td>
<td>41/M</td>
<td>Right nephrectomy</td>
<td>T3bN0M0</td>
<td>No/IFN</td>
</tr>
<tr>
<td>5</td>
<td>61/M</td>
<td>Right nephrectomy</td>
<td>T1N0M0</td>
<td>No/no</td>
</tr>
<tr>
<td>6</td>
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<td>Left nephrectomy</td>
<td>Unknown</td>
<td>No/no</td>
</tr>
<tr>
<td>7</td>
<td>60/M</td>
<td>Right nephrectomy</td>
<td>Unknown</td>
<td>No/no</td>
</tr>
<tr>
<td>8</td>
<td>58/M</td>
<td>Left nephrectomy</td>
<td>T2N0M0</td>
<td>No/no</td>
</tr>
</tbody>
</table>

DFI, disease-free interval.

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>DFI (month)</th>
<th>Tumor laterality</th>
<th>Tumor number</th>
<th>Tumor size maximum (mm)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>84</td>
<td>Bilateral</td>
<td>5</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>Unilateral</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>Unilateral</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>Unilateral</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>156</td>
<td>Unilateral</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>Unilateral</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>Unilateral</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>Unilateral</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

DFI, disease-free interval.

He received irradiation and then underwent a resection of the rib. Since he did not come to our outpatient clinic, he was censored four months later. Patient 3 presented a multiple lung metastasis and left renal metastasis 24 months after the pulmonary metastasectomy. He received immunotherapy with IFN, but he presented right adrenal metastasis 20 months later and multiple brain metastasis 65 months later. Finally, he died of disease 101 months after the pulmonary metastasectomy. Patient 4 received immunotherapy with IFN for six months after the right nephrectomy, but 49 months later he developed two metastases in the right lower lobe. He resumed immunotherapy with IFN, but he did not continue immunotherapy due to a side effect. Then, he received pulmonary metastasectomy, but he developed brain metastasis five months later. He died of disease 15 months after the pulmonary metastasectomy. Patient 5 developed contralateral pulmonary metastasis 46 months after the first pulmonary metastasectomy, and received left upper segmentectomy. He has been well without recurrence for three years. Patient 6 developed pulmonary metastasis and underwent pulmonary metastasectomy 25 months after nephrectomy. However, he developed local recurrence on the right chest wall and received its resection seven months later. Then, he developed multiple bone metastases four months later, but he is presently alive with multiple metastases 17 months after the first pulmonary metastasectomy.

Disease-free survival time ranged between 5 and 189 months with a mean of 16 months, while overall survival time ranged from 5 to 189 months with a mean of 20 months. Five-year and 10-year overall survival rate was 83.3% and 41.7%, respectively, while 3-year and 5-year disease-free survival rate was 35.0% and 17.5%, respectively.

IFN, interferon-α.
Fig. 1. Overall survival and disease-free survival of patients with pulmonary metastasectomy for renal cell carcinoma.

(Fig. 1). The sites of tumor recurrence were lungs in two cases, brain in two cases, bone in two cases, kidney in one case, and adrenal gland in one case. Currently, five patients are alive without evidence of disease, one patient is alive with disease, and two patients died of disease.

4. Discussion

Many studies have been performed for pulmonary metastasectomy for various primary cancers, such as colorectal cancer, breast cancer, and osteosarcoma [2]. Pulmonary metastasectomy has become the standard therapy for various metastatic malignancies to the lungs. The lung is one of the most frequently affected metastatic sites (second after the liver) in patients with renal cell carcinoma. Many reports suggest a role for pulmonary metastasectomy in managing metastatic renal cell carcinoma [1, 3–5], but inconsistency among reports has led to confusion in many respects. To help clarify the role of pulmonary metastasectomy and possibly confirm published inconsistencies, we reviewed our institutional experience.

Patients with lung metastases were once considered untreatable, but nowadays they can benefit from surgery and adjuvant systemic therapies with cytokines have shown good results in recently published clinical trials [8]. However, the treatment of metastatic renal cell carcinoma still represents a widely debated issue. Although no effective chemotherapeutic or hormonal agents have been introduced to date, adoptive immunotherapy and the administration of cytokines seem to represent the most effective treatment. However, their efficacy and toxicity still need to be confirmed in large studies and more accurate patient selection is needed.

In our study, 5-year and 10-year overall survival rate was 83.3% and 41.7%, respectively. In many reports, 5-year survival for complete resection of pulmonary metastasis from renal cell carcinoma was up to 60% [3–5, 9]. Although the number of patients is small, our study suggested that the current therapy for the pulmonary metastasis from renal cell carcinoma might be well justified. Our data also suggested that aggressive treatment including repetitious resection and systemic immunotherapy might be considered for the recurrent patients, since we experienced a long-term survival of patients with the recurrence after pulmonary metastasectomy (Patient 3 and 5). Patients with longer DFI seemed to have longer survival in pulmonary resection of several metastatic malignancies [10, 11]. Cerfolio et al. also reported that patients with DFI more than 3.4 years had better survival rates [12]. However, some authors reported that late renal cell carcinoma metastases are often combined with rapid disease progression [13, 14]. Late relapses after nephrectomy and prolonged stabilization of disease in the absence of systemic treatment may suggest that host immune mechanisms are important in regulating tumor growth, but these mechanisms have not yet been fully explored [15]. In our study, among five patients with more than 5 years of DFI, three patients lived longer than almost 7 years, while one patient with pT3b disease died 15 months after the pulmonary metastasectomy. From our limited experience, longer DFI might lead to a better survival.

There are several limitations to our analysis. The biggest limitation is the size of the study in number. 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 with many institutions is absolutely required. Furthermore, our treatment strategy was heterogeneous because a combination of surgery and immunotherapy was highly individualized based on unique patient.

In conclusion, current practice of pulmonary metastasectomy for renal cell carcinoma in our institution is seemingly justified since we experienced patients with long-term survival; however, the accumulation of cases is necessary to evaluate a prognostic factor properly and to determine the selection criteria for resection.
References


References

