

## The Role of Surgery in Renal Cell Carcinoma with Pancreatic Metastasis

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Metastasis of renal cell carcinoma to the pancreas is uncommon and, in most cases, presents as a single pancreatic mass that shows a more favorable prognosis than primary pancreatic tumors. We examined patients with renal cell carcinoma metastatic to the pancreas, and discuss the clinical findings, treatment administered, and final outcomes. The present study is a retrospective analysis of renal cell carcinoma patients with pancreatic metastasis. Pancreatic tumor specimens were obtained by surgical excision, surgical biopsy, fine-needle biopsy, or endoscopic ultrasound biopsy. The surgical approaches included distal splenopancreatectomy, total pancreatectomy, or distal pancreatectomy. The physician determined the postoperative treatment regimen with interferon- $\alpha$  or targeted therapy on the basis of patient's performance. A total of six patients with median age of 50 years were included in the study. The median time from the primary nephrectomy to the development of pancreatic metastasis was 16 years. In the biopsy-only group, the mean stable disease period was 16.5 months. In the patients treated with surgery combined with interferon- $\alpha$  or targeted therapy, the mean stable disease period was 29.5 months. The patients treated with repeat mastectomy showed a mean stable disease period of 33.3 months. Aggressive surgical management is more effective than observation or immunotherapy. Recent advances in the design of targeted therapies may provide alternative treatment strategies. Combination therapy may play an important role in the future. Considering patient compliance and cost-effectiveness, resection of pancreatic metastasis is currently the first choice of treatment. (*Biomed J* 2015;38:173-176)

**Key words:** nephrectomy, pancreatic metastasis, pancreatic tumor, renal cell carcinoma

Renal cell carcinoma (RCC) is one of the most common malignancies of the genitourinary tract. It accounts for 2-3% of all adult cancers.<sup>[1]</sup> Radical nephrectomy remains the treatment of choice for localized renal tumors. However, recurrence occurs in approximately 20-30% of patients with localized tumors, and in most cases, it occurs within a period of 3 years.<sup>[2]</sup> The most common sites of recurrence are the lungs, liver, brain, and bones.<sup>[3]</sup>

Metastasis to the pancreas is uncommon in RCC patients. Most patients present with a single pancreatic mass that shows a more favorable prognosis than primary pancreatic tumors.<sup>[4]</sup> In the present study, the medical records of six patients with RCC metastatic to the pancreas were reviewed and the clinical findings, treatment administered, and the final outcomes are discussed.

### METHODS

After receiving internal review board's approval, the data of six RCC patients who were treated at our hospital for metastasis to the pancreas between 2005 and 2011 were retrospectively analyzed. All the data were obtained from the medical records. Tumor staging was performed according to the 2002 American Joint Committee on Cancer TNM classification. The diagnosis of pancreatic metastasis was based on the clinical findings and image data, including abdominal computed tomographic (CT) or magnetic resonance imaging (MRI) scans. The final diagnosis of metastatic RCC was confirmed by the histological examination. Pancreatic tumor specimens were obtained by surgical excision, surgical biopsy, fine-needle biopsy, or endoscopic ultrasound biopsy.

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Surgical procedures, which included distal spleno-pancreatectomy, total pancreatectomy, or distal pancreatectomy, were determined by the surgeon. Postoperative immunotherapy with interferon- $\alpha$  or targeted therapy was administered according to the performance of the patients and was determined by the physician.

## RESULTS

Table 1 summarizes the characteristics of the patients. A total of six patients, with a median age of 50 years (range, 43-57 years) were included in the study. All the patients underwent primary nephrectomy. All the tumors were diagnosed as clear cell carcinoma. The median time from the primary nephrectomy to the diagnosis of pancreatic metastasis was 16 years (range, 2-27 years). Four patients had metastases to other organ: One to the liver, duodenum, lung, and brain; one patient had left adrenal gland metastasis; one had left kidney involvement; and one had spleen and left retroperitoneal metastasis. One patient received total pancreatectomy, three patients received distal pancreatectomy combined with metastasis site excision, and two patients received endoscopic or echo-guided biopsy of the pancreas. The mean follow-up period from the time of confirmation of pancreatic metastasis was 36.8 months (range, 3-60 months), and two patients died during this period. All the patients received targeted therapy with sunitinib or sorafenib, and three patients were treated with interferon- $\alpha$  before receiving targeted therapy.

In the biopsy-only group, one patient received short-term (3 months) sorafenib therapy, and died after 3 months. One patient received short-term interferon- $\alpha$  therapy owing to poor tolerance and was found with multiple metastases to the lungs and para-aortic lymph nodes at the 30-month follow-up. The patient received targeted therapy with sunitinib for 3 months and was followed-up at our hospital. The mean stable disease period in the biopsy-only group was 16.5 months (range, 3-30 months).

In the surgery group, one patient died during the follow-up period and two patients received targeted therapy. One of the two patients underwent distal pancreatectomy and adrenalectomy and was treated with sorafenib for 11 months. The other patient received distal pancreatectomy and left nephrectomy owing to tumor invasion and was followed-up regularly with close observation. After 51 months, the patient had recurrence of pancreatic metastasis and liver metastasis and was treated with sunitinib for 3 months. Of the two patients treated with interferon- $\alpha$  and targeted therapy, one underwent total pancreatectomy followed by 45 months of interferon- $\alpha$  therapy, which was changed to sorafenib for 1 month because of tumor progression. The patient died 3 month later. The other patient received distal pancreatectomy, local tumor excision, and splenectomy and then regular follow-up without adjuvant treatment [Figure 1]. Twelve months later, the patient was found with right RCC, which was treated with cryotherapy. Recurrence of metastasis to the head of the pancreas and duodenum was detected after 22 months, and the patient received short-term interferon- $\alpha$

**Table 1:** Summarizes the patients characteristics of RCC with pancreatic metastasis

Patient no.	Age/sex	Primary RCC site/ stage	Time to pancreas metastasis, years	Combination with other metastasis at diagnosis	Surgical method	Adjuvant therapy (period)	Outcome
1	57/M	Right/ unknown	15	Liver, duodenum, lung brain	Biopsy	Sorafenib (3 months)	Die
2	50/F	Left/ T3aN0M0	2	Nil	Biopsy	Interferon- $\alpha$ 2 times → observation 30 months → sorafenib (4 months)	Alive
3	43/M	Left/ T2N0M0	16	Nil	Total pancreatectomy	Interferon- $\alpha$ (45 months) → Sorafenib (1 month)	Die
4	55/F	Left/ T3aN1M0	6	Adrenal gland	Distal pancreatectomy+ adrenalectomy	Sorafenib (11 months)	Alive
5	45/F	Right/ T1aN0M0	27	Left kidney	Distal pancreatectomy+left nephrectomy	Observation (51months) → sunitinib (3 months)	Alive
6	55/F	Left/ T2N0M0	16	Spleen, left retroperitoneal	Distal pancreatectomy+ splenectomy+local excision	→ Observation (12 months) → right kidney cryotherapy → observation (10 months) → pancreas recurrent → Interferon- $\alpha$ (3 months) → Whipple operation → observation (27 months) → right kidney RCC recurrent → sunitinib (8 months)	Alive

Abbreviations: RCC: Renal cell carcinoma; M: Male; F: Female

therapy (3 months) followed by a Whipple procedure and regular follow-up without local recurrence. Twenty-seven months later, the patient had local RCC recurrence and was treated with sunitinib for 8 months. The patient was still alive and was followed-up at our clinical department at the time of the study. For the patients treated with surgery combined with interferon- $\alpha$  or targeted therapy, the mean stable disease period was 29.5 months (range, 10-51 months). In the patients receiving repeat metastasectomy, the mean stable disease period was 33.3 months (range, 10-51 months).

## DISCUSSION

The pancreas is a rare site for tumor metastasis, and approximately 2-3% of all pancreatic tumors are metastatic.<sup>[5]</sup> Metastasis to the pancreas occurs mostly from kidney, lung, breast, colon, and skin cancers, and is often associated with diffuse systemic disease.<sup>[6]</sup> Although RCC can metastasize to any organ through the venous and lymphatic systems, the most common sites of metastasis are the lungs, bones, liver, and brain.<sup>[3]</sup> In the present study, only six cases with metastatic pancreatic cancer were identified.

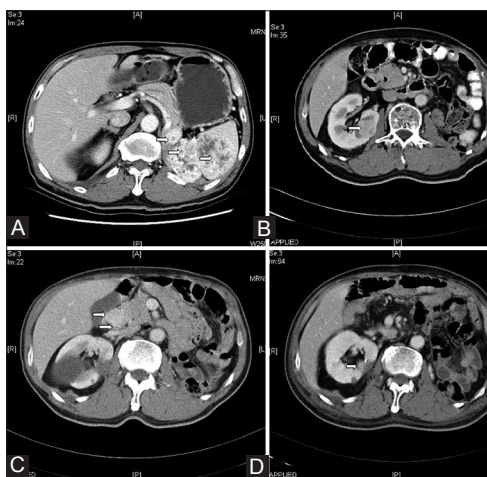
Local recurrence or late distant metastasis is common in RCC. McNichols *et al.*, reported that 11% of patients undergoing primary nephrectomy will develop metastatic disease after 10 years.<sup>[7]</sup> The longest period between the primary cancer and the development of pancreatic metastasis was 15-22 years.<sup>[5,8]</sup> In the present study, the longest period was 27 years. Wente *et al.*, suggest that the follow-up period in patients with early-stage RCC should extend be-

yond 20 years for the detection of recurrence or metastatic disease.<sup>[8]</sup>

The current approaches to the treatment of metastatic RCC include immunotherapy with interferon- $\alpha$ , targeted therapy, or one of these therapies combined with metastasectomy. Motzer *et al.*, reported that the median progression-free survival with interferon- $\alpha$  was 5 months and the response rate was 6%.<sup>[9]</sup> In our study, one patient received immediate post-operative adjuvant therapy with interferon- $\alpha$  until disease progression (45 months). On the other hand, short-term interferon- $\alpha$  therapy in one patient after biopsy resulted in a stable disease period of 36 months. In two patients treated with surgery and observation only, the disease-free periods were 12 and 51 months, respectively. In one patient was pancreas recurrence received surgery and remained disease-free for 27 months. The present data revealed that the patients treated with or without immunotherapy maintained a long stable- disease period.

Targeted therapy for the treatment of metastatic RCC was introduced in recent years. Most of these drugs are used for the treatment of clear cell type RCC. Motzer *et al.*, reported a partial response rate for sunitinib of 34-40% and a median progression-free survival of 8.3-8.7 months.<sup>[10,11]</sup> For sorafenib therapy, Escudier *et al.*, reported that the progression-free survival was 5.5 months and the median overall survival rate was 19.3 months.<sup>[12]</sup> In a study on the effect of bevacizumab, Escudier *et al.*, showed that the combination of the inhibitor with interferon- $\alpha$  resulted in a progression-free survival period of 10.2 months and a response rate of 31%.<sup>[13]</sup> Temsirolimus therapy has been mostly used for the treatment of RCC patients with poor prognosis, and the median overall survival rate was 10.9 months in a study by Hudes *et al.*, which was superior to that of interferon- $\alpha$  therapy (7.3 months).<sup>[14]</sup> Everolimus was used for the treatment of patients who failed to respond to tyrosine kinase inhibitor, and the median progression-free survival was 4 months.<sup>[15]</sup> Despite the effectiveness of these drugs for the short-term control of disease progression, they have been associated with serious adverse events.<sup>[9,13-15]</sup> In addition, the high cost of targeted therapy is an important limiting factor for the patients and the health insurance administration. Targeted therapy may therefore be more suitable for the treatment of patients with multiple metastases that cannot be complete eliminated surgically.

Another important issue in RCC with metastasis to the pancreas is whether pancreatic metastasectomy is indicated or not. Zerbi *et al.*, reported favorable disease control and survival rates in patients who underwent surgery compared with nonsurgical patients, with 5-year survival rates of 88% and 47%, respectively and median disease-free survival periods of 44 and 27 months, respectively.<sup>[16]</sup> In a recent review, Tanis *et al.*, reported that the 2-and 5-year



**Figure 1:** (A) A 55-year-old man with left RCC received left radical nephrectomy and showed local tumor recurrence at the tail of the pancreas, spleen, and left retroperitoneum (arrow). (B) Twelve months later, right renal RCC was diagnosed (arrow). (C) Twenty-two months later, recurrence at the head of the pancreas and metastasis to the duodenum were observed (arrow). (D) After a Whipple operation (pancreaticoduodenectomy) and regular follow-up without local recurrence for 27 months, recurrence at the right kidney was found (arrow).

overall survival rates were 80.6% and 72.6%, respectively, in patients undergoing surgery, whereas they were 41% and 14%, respectively, in a nonoperative group, respectively.<sup>[17]</sup> In our study, the patients undergoing excision of the pancreatic tumor and adjacent organs in combination with interferon- $\alpha$  or targeted therapy or observation only showed a mean stable disease period of 29.5 months. In case of tumor recurrence to other areas treated with aggressive surgery, the mean stable disease period was 33.3 months. The patients receiving biopsy only had a mean stable disease period of 16.5 months. These results are significant because they show that the patients who were treated aggressively with extensive surgery showed improved disease control compared with those receiving biopsy only. The relatively favorable outcome of patients with metastatic RCC to the pancreas compared with those with other metastasis and the limited role of traditional immunotherapy and radiotherapy in the treatment of metastatic RCC indicate that aggressive treatment with metastatectomy is effective for prolonging survival in certain patients.

## Conclusions

RCC with metastasis to the pancreas is uncommon, and aggressive surgical management is more effective than observation or immunotherapy. However, recent advances in the design of targeted therapies may provide alternative treatment strategies, and combination therapy with surgery may play an important role in the future. Considering patient compliance and cost-effectiveness, resection of pancreatic metastasis is currently the first choice of treatment.

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