

Survival benefit of pancreatic metastasectomy of clear cell renal cell carcinoma

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The clear cell renal cell carcinoma (ccRCC) appears to have a predilection for metastasizing to the pancreas.^[1] In the recent years, there are increasing numbers of clinical series from Europe and the United States that demonstrate encouraging survival results of pancreatic metastasectomy,^[2] but there are a few clinical data or only some case reports from East Asian population,^[3] and there are no specific guidelines regarding the appropriate management. The objective of this study was to present our experience of pancreatic metastasectomy from ccRCC by reporting the peri-operative and survival outcome.

The Ethical Committee of Zhongshan Hospital, Fudan University approved this study. The patients signed the informed consent for research at the time of the surgery. We used a prospectively maintained surgical database to identify all ten patients with pancreatic metastasis of ccRCC from July 15, 2007 to April 9, 2019. The data retrieved included patient demographics, origin of the primary tumor, time interval prior to pancreatic metastasectomy, type of pancreatic surgery, post-operative complication, and survival. Overall survival after pancreatic surgery was calculated from the time of the pancreatic metastasectomy surgery to cancer-related death or the last follow-up day. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows, version 20.0 (SPSS, Inc., Chicago, IL, USA). Survival analysis was implemented using life tables and Kaplan-Meier analysis.

The primary ccRCC lesions including right kidney in six patients and left kidney in four patients, with six males and four females, were resected in all cases. The median size of the ccRCC was 5.5 cm (2–10 cm), with nine TNM (tumor, node, metastasis) stage II and one stage III patients. Only one patient accepted the interferon treatment after renal

surgery. Cases 8 and 10 were diagnosed as recurrent contralateral ccRCC and treated with partial nephrectomy at 2.0 and 65.9 months before the pancreatic metastasis. Moreover, solitary left lung metastasis was developed in case 7, 4.1 months before the pancreatic metastasis, and it was treated with left upper lobectomy.

The proportion of pancreatic metastasis of ccRCC in all the pancreatic malignancies from 2007 to 2019 was about 0.5% (10/2000). The median age of the total ten patients was 58.7 years (range: 51.0–68.0 years) at the time of pancreatic surgery. Only two of them had the chief complaint of upper abdominal pain, the rest eight of them were asymptomatic and diagnosed based on the routine abdominal imaging surveillance. All the computed tomography imaging showed the hyper-vascular and intense homogeneous contrast enhancement in the arterial phase, greater than normal pancreatic parenchyma, and a tendency to pass undetected in more delayed post-contrast phases.

Clinicopathologic characteristics of the ten cases of pancreatic metastatic ccRCC are shown in Table 1. The median time interval from the initial renal carcinoma surgery to the emergence of the pancreatic metastasis was 73.4 months (range: 4.4–182.7 months). Pancreatic metastasis was solitary in nine cases and multifocal in one case and existed in the head in four cases, body-tail in five cases, head with body-tail in one case. The median size of the pancreatic metastasis was 2.4 cm (range: 0.9–4.9 cm). Operative procedure was R0 resection, with distal pancreatectomy in five cases, pancreaticoduodenectomy in four cases, total pancreatectomy in one case. Grade B and grade C of post-operative pancreatic fistula were observed in case 2 and case 5, respectively. There was no peri-operative mortality. From the immunohistochemistry

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Table 1: Clinicopathologic characteristics of the ten patients with pancreatic metastatic ccRCC.

No. of patients	Time after ccRCC (months)	Age at pancreatic surgery (years)/gender	Site of tumor	Size (cm)	Symptom	Surgery	Post-operative treatment	Follow-up
1	34.1	58/M	Head	4.5	Asymptomatic	PD	Observation	Died 99.1 months after surgery
2	86.0	65/M	Head & distal	3.0 & 1.5	Asymptomatic	TP	Chemotherapy: 5-FU+Gemcitabine	Died 62.1 months after surgery
3	75.2	57/F	Distal	4.5	Asymptomatic	DP	Liver metastasis 3.5 months after surgery and TACE	Died 76.8 months after surgery
4	36.0	51/M	Head	1.6	Abdominal pain	PD	Observation	Died 61.3 months after surgery
5	87.2	68/M	Head	1.5	Asymptomatic	PD	Observation	Alive, disease free
6	71.6	60/F	Distal	2.0	Asymptomatic	DP	Observation	Alive, disease free
7	67.0	63/F	Distal	2.7	Asymptomatic	DP	Sorafenib	Alive, disease free
8	4.4	52/M	Distal	0.9	Asymptomatic	DP	Observation	Alive, disease free
9	182.7	59/F	Head	4.9	Abdominal pain	PD	Observation	Alive, disease free
10	124.6	54/M	Distal	2.0	Asymptomatic	DP	Pazopanib	Alive, disease free

ccRCC: Clear cell renal cell carcinoma; PD: Pancreaticoduodenectomy; TP: Total pancreatectomy; DP: Distal pancreatectomy; M: Male; F: Female; 5-FU: 5-Fluorouracil; TACE: Transarterial chemoembolization.

staining, carbonic anhydrase 9 (CA-9[+]) and paired box gene 8 (PAX8[+]) were indicative of ccRCC, while synaptophysin (SYN[-]), neuronal cell adhesion molecules 56 (CD56[-]), and chromogranin A (CGA[-]) could differentiate from the neuroendocrine tumors.

The median follow-up time was 59.6 months (range: 0.7–99.1 months). Three and a half months after the pancreatic surgery was performed, liver metastasis existed in the patient (case 3) and was treated by transarterial chemoembolization. In case 2 with the multifocal pancreatic metastasis, six cycles of chemotherapy of 5-fluorouracil combined with gemcitabine was implemented, while in case No. 7 sorafenib and case No. 10 pazopanib was orally taken respectively. All the other patients did not receive any post-operative treatment. Until the last follow-up day, six patients still alive and four patients died. The median overall survival after pancreatic metastasectomy was 77 months, with 1-, 3-, and 5-year survival rate 100%, 100%, and 60%, respectively.

The survival of our study revealed that six of the total ten patients still alive, the median survival after pancreatic metastasectomy was 77 months, indicating the very significant survival benefit of the surgical resection. Moreover, an Italian large-sample multicenter study of 103 patients turned out that there was no significant survival difference between pancreatic resection versus tyrosine kinase inhibitors.^[4] Therefore, more large-sample, multi-institutional studies should be implemented to confirm the survival benefit of surgical resection over non-surgical treatment.

Moreover, the peri-operative outcomes in the current study were satisfactory with no peri-operative mortality and only two patients had the complication, with morbidity only 2/10. Therefore, it is considered feasible and safe to perform the pancreatic metastasectomy especially in the high-volume pancreatic centers. However, whether or not to perform the typical or atypical

pancreatic surgery is still controversial, because some studies showed that only digging out the metastatic lesions could protect the exocrine and endocrine function of the pancreas,^[5] let alone the relatively indolent tumor phenotype of metastatic ccRCC.

Besides, this study has some limitations. Firstly, because pancreatic metastasis from ccRCC is a rare disease, it is difficult to implement the clinical trial in a prospective manner. Secondly, the post-operative regimen both after the primary renal surgery and pancreatic metastasectomy were not standard. Thirdly, due to the single-center experience and relatively small sample size, it is difficult to analyze the prognostic risk factors.

In summary, long-term survival may be achieved in some patients of ccRCC pancreatic metastasis through pancreatic metastasectomy with satisfactory morbidity. However, the decision of pancreatic metastasectomy should be carefully and systematically evaluated according to the specific condition of the patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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