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Case Series

Pancreatectomy for metastatic renal cell carcinoma: twenty years of experience at a tertiary centre

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ABSTRACT

Renal Cell Carcinoma (RCC) accounts for approximately 90% of primary renal malignancies, of which the clear cell subtype is most common. While metastatic disease is common at the time of diagnosis and generally confers a poor prognosis, metastatic RCC may demonstrate relatively indolent behaviour and present many years after resection of the primary tumour, including to the pancreas. The available literature suggested that surgical resection was appropriate for select patients, including those with a solitary pancreatic metastasis, minimal comorbidities and uncomplicated progress from initial treatment of their primary renal malignancy. A retrospective case series of patients presenting with RCC metastases to the pancreas, managed via surgical resection at a tertiary teaching hospital was reviewed. Analysis of patient demographics, investigations, management and outcomes were performed, with a focus on post-operative morbidity and overall survival. Between 2000 and 2020, 7 patients underwent pancreatic resection of RCC metastases at our tertiary teaching hospital with curative intent. Median age at time of resection was 66 years. No post-operative mortality or major morbidity was experienced by the 7 patients, although 4 patients developed some degree of pancreatic insufficiency. Four patients experienced recurrent metastatic RCC, with median time to recurrence of 3.5 years. This was the largest local study to describe an Australian experience of the surgical management of RCC pancreatic metastases. These patients are frequently afforded prolonged survival following pancreatic resection, but often develop other distant sites of disease and second renal tumours.

Keywords: Pancreatectomy, Metastatic renal cell carcinoma, Tumour

INTRODUCTION

RCC account for approximately 90% of primary renal malignancies with a peak incidence in the sixth to eighth decades of life. Since it was first reported in the 1970s, incidence rates have slowly increased over time from 7 per 100,000 population in 1975 to 15 per 100,000 in 2016, likely secondary to the growing prevalence of obesity, a known RCC risk factor.[1,2,5]

There are greater than ten separate histological and molecular subtypes of RCC, of which the most common are clear cell, papillary and chromophobe. Each subtype exhibits distinct oncological behaviour relating to its metastatic potential and prognosis.[1,2,5] Metastasis occurs in roughly one third of patients with RCC, with 5-year survival estimated at less than 10% when left untreated. However, delayed metastases may occur with disease-free intervals greater than 20 years. Such presentations

have been postulated to be explained by the phenomenon of tumour regression.[6-8]

RCC is the most common source of metastatic lesions of the pancreas, making up 20-50% of such lesions.[9,10] Metastases to the pancreas from other primary malignancies are rare, comprising only 2-3% of all pancreatic neoplasms. Due to the sometimes-indolent behaviour of RCC metastases, surgical resection of metastases may confer a significant survival benefit. Pancreatic resections for metastases from other primary malignancies is more controversial, due to the poorer prognosis associated with these conditions.[10,11]

CASE SERIES

We described a case series of seven patients treated with resection of RCC metastases to the pancreas at a tertiary teaching hospital from 2000 to 2021. The choice of procedure for metastasectomy was dependent on the site of the metastatic disease. Permission was granted by each individual patient for their de-identified case to be published.

Patient 1

A 65-year-old man was found to have a new distal body pancreatic lesion detected on surveillance imaging 14 years after left nephrectomy for clear cell RCC. An EUS-guided biopsy was performed, with histological findings suggestive of metastatic RCC. Subsequent gallium-68 PET scan confirmed a localised lesion and the decision was made to proceed with a distal pancreatectomy and splenectomy. The operation was performed without complications and the patient was discharged home 10 days postoperatively. He remained well and was disease free at his 2 years follow up appointment.

Patient 2

A 65-year-old lady with a background of a previous right nephrectomy for RCC 15 years ago was referred for the management of multiple pancreatic lesions on her Gallium-68 DOTATATE PET scan and raised CGA levels suggestive of multiple pancreatic neuroendocrine lesions. She underwent concurrent treatment for distant recurrent disease, including resection of a left femoral lesion and radiofrequency ablation of two left renal lesions.

A total pancreatectomy and splenectomy were performed for presumed multifocal pancreatic neuroendocrine tumours and the patient recovered without any major complications. The histopathological was consistent with metastatic RCC of the clear cell subtype. Approximately 12 months later, she developed primary lung cancer, which was treated with partial lung resection. Unfortunately, she passed away 4 years after her total pancreatectomy due to incurable local recurrence of her lung cancer.

Patient 3

A 70-year-old lady was referred for management of new peripancreatic lymphadenopathy consistent clear cell RCC. She was originally treated 10 years ago with a right nephrectomy, with subsequent metastasectomies. This included a left hemithyroidectomy one year post initial diagnosis of RCC and subsequently distal pancreatectomy and splenectomy 2 years later. After extensive investigations, the patient underwent a pancreaticoduodenectomy, with preservation of a small remnant of pancreas. Histological examination confirmed RCC. Unfortunately, she developed recurrent disease in her left kidney, pulmonary and cerebellar metastases and died 5 years after her second pancreatic resection.

Patient 4

A 56-year-old man was found to have a 2.7 cm mass in the pancreatic head on surveillance imaging two years after undergoing a left nephrectomy for clear cell RCC. Biochemically, his Chromogranin A was 102 mg/dl, CEA was 1.5 mg/dl and CA 19.9 was 7 mg/dl. PET scan found mild uptake in the pancreatic head mass. Endoscopic ultrasound and fine needle biopsy findings were suggestive of metastatic clear RCC and the patient proceeded to undergo a pancreaticoduodenectomy, from which he recovered without significant complications. Histopathology confirmed metastatic renal cell cancer with clear margins and no lymph node involvement. 2 years later, he developed new metastatic disease in the liver and contralateral kidney. Discussions regarding further management options are ongoing.

Patient 5

A 56-year-old man was diagnosed with a new lesion in the tail of the pancreas on surveillance imaging 18 years after right nephrectomy for clear cell RCC. The patient underwent a distal pancreatectomy and splenectomy. Six months later, he developed hepatic metastases and is currently being treated with palliative intent. He remained alive at the most recent follow-up one year post pancreatic resection.

Patient 6

A 52-year-old man was diagnosed with two new pancreatic lesions on surveillance imaging seven years after his right nephrectomy for clear cell RCC. These lesions were further investigated with EUS and subsequently managed with a subtotal distal pancreatectomy. Histological examination confirmed the presence of metastatic clear cell RCC with clear margins and no lymph node involvement. He developed RCC metastases in his thyroid 6 years later, which was managed with a right hemithyroidectomy, followed by completion total thyroidectomy. Four years later he developed new pancreatic, hepatic and pulmonary metastases, which have been treated with palliative

chemotherapy. He is currently 12 years post his pancreatic resection and remains on palliative management at latest review in January 2021.

Patient 7

A 72-year-old lady undergoing investigations for her normochromic, normocytic anaemia, was found to have multiple pancreatic lesions on CT imaging. Her background history was significant for a right nephrectomy 12 years prior for clear cell RCC. EUS confirmed echogenic masses in the neck and body of the pancreas, and an FNA biopsy of the lesions demonstrated metastatic clear cell RCC. The patient underwent a subtotal distal pancreatectomy and had an uncomplicated recovery. Histological examination of the resected specimen confirmed the presence of metastatic clear cell RCC with clear margins. She remains disease free 5 years after her pancreatic resection.

Seven patients underwent pancreatectomy for resection of metastatic RCC with curative intent, including 4 distal pancreatectomies, 2 pancreaticoduodenectomies and 1 total pancreatectomy. Mean age at time of pancreatic resection was 65.9 years (SD=6.47), with a median age of 66 years. All seven patients had previous nephrectomy, 5 of which were right-sided and 2 of which were left-sided. Median interval between nephrectomy and pancreatectomy was 12 years (range=2-19 years). Diagnosis in 5 patients was due to routine surveillance imaging; while one patient had their recurrence diagnosed incidentally, and the remaining patient was diagnosed as a result of investigation of anaemia.

There was no post-operative mortality or major morbidity experienced by any of the 7 patients. Four patients developed pancreatic insufficiency, with two developing a new insulin requirement, one developing exocrine pancreatic enzyme supplementation, and one patient requiring both.

Median follow-up was 5 years (range 1-12 years), with 5 (71.4%) patients alive at the time of writing. Of the two patients deceased within the study period, one died of an unrelated cause (primary lung cancer) 4 years after pancreatic resection, and the other from multifocal recurrent RCC metastases 5 years after pancreatic resection. 4 (57.1%) patients experienced recurrent metastatic RCC, with median time to recurrence of 3.5 years (range 6 months to 6 years).

Table 1: Summary of patient details and post-operative outcomes. Disease free interval refers to time between nephrectomy for incident diagnosis of RCC and distant recurrence with metastasis to the pancreas. Survival, endocrine and exocrine insufficiency refer to outcomes following pancreatic resection of metastases.

Patients	Disease Free Interval (years)	Pancreatic Resection	Survival status	Survival (months)	Endocrine insufficiency	Exocrine insufficiency
Patient 1	14	Distal pancreatectomy and splenectomy	Alive	23	No	No
Patient 2	15	Total pancreatectomy and splenectomy	Deceased	48	Yes	Yes
Patient 3	10	Pancreaticoduodenectomy	Deceased	67	No	Yes
Patient 4	2	Pancreaticoduodenectomy	Alive	24	No	No
Patient 5	18	Distal pancreatectomy	Alive	23	Yes	No
Patient 6	7	Distal pancreatectomy	Alive	126	No	No
Patient 7	12	Distal pancreatectomy	Alive	63	Yes	No

DISCUSSION

Various retrospective studies have demonstrated a survival benefit associated with resection of pancreatic metastases from RCCs, likely owing to the sometimes-indolent behaviour of RCC.[10] Overall 5-year survival rates after resection of pancreatic RCC metastases range from 60-70%; compared to less than 15% in the absence of resection.[12,13] In contrast to metastasectomy for other primary malignancies, post pancreatectomy outcomes show comparatively good survival rates. RCC metastases to other distant organ sites appeared to confer a poorer prognosis, with 5-year overall survival of 43% following pulmonary metastectomy and 38-62% following hepatic metastectomy.[14]

If considering medical therapy only, RCCs were conventionally thought to be refractory to traditional cytotoxic chemotherapies, posing an ongoing therapeutic dilemma in comparison to other solid malignancies. Before 2005, the mainstay of medical management of metastatic RCCs was limited to immunotherapy via interleukin-2 (IL-2) and interferon-α (IFN-α).[15,16] Overall survival during this era of management centered around immunotherapy was estimated to be around 1 year. Subsequent to this molecular targeted agent have been developed, significantly improving metastatic RCC survival. These agents can be broadly summarised to act via inhibition of the VEGF pathway, the mammalian target of rapamycin pathway and immune checkpoints. Median survival of metastatic RCCs with these new

therapies have subsequently improved to about 2.5-3 years.[15-17]

The survival outcomes of our local series of seven patients were consistent with that previously reported in international COHORTs, in which mean survival had been reported at 9 years.[14] Anderson et al in 2020 found median overall survival rates post nephrectomy to be 17.6 years.[18] All seven patients were alive at the minimum follow-up time of 23 months, and the two patients to have died within the study period achieving an overall survival of 48 and 67 months. Three patients had survived beyond 5 years at the time of last follow-up, with another three still eligible to achieve this milestone. Overall, our series suggests that good long-term survival can be achieved with aggressive surgical management of RCC metastases to the pancreas in selected patients, particularly those with metachronous metastatic disease following a prolonged disease-free interval, and with minimal comorbidities.

CONCLUSION

Pancreatectomy for RCC metastases is associated with good oncological outcomes including long term overall and disease-free survival. Postoperative quality of life may be affected by the development of endocrine and exocrine insufficiency; however, these long-term complications can be effectively controlled with medical management. Patients fit to undergo major pancreatic resection should be considered for aggressive surgical management of RCC metastases in sub-specialised centres experienced with the care of such patients.

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