Refining indications for contemporary surgical treatment of renal cell carcinoma metastatic to the pancreas

Aram N. Demirjian1, Charles M. Vollmer1, David F. McDermott2, John T. Mullen1, Michael B. Atkins2 & Mark P. Callery1

1Department of Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA and 2Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Abstract

Background: The pancreas is a rare location for metastatic disease, with only 2–11% of all pancreatic tumours being of non-primary origin. It is also uncommon for renal cell carcinoma (RCC) to metastasize to the pancreas (1–3% of cases) and, when it does, it typically occurs substantially after index nephrectomy. It is not known whether all pancreatic metastases need be resected because today’s chemo- and biological therapies are increasingly effective in controlling advanced disease.

Methods: Six patients with a variety of symptoms are discussed. Four patients presented with recurrent gastrointestinal bleeding, ranging from occult to life-threatening in severity.

Results: The four patients with gastrointestinal bleeding had RCC metastases that had eroded into the duodenum and were successfully controlled by palliative pancreaticoduodenectomy or completion pancreatectomy. The other two patients were treated using different chemotherapeutic or biological agents.

Conclusions: Renal cell carcinoma metastases to the pancreas typically occur long after index nephrectomy. Although clinical presentation is variable, palliative resection should be reserved for those who develop complications, such as upper gastrointestinal bleeding, and, in other series, obstructive jaundice. Routine debulking resections do not appear to be indicated because current biological therapies effectively and reliably control disease over long periods.

Keywords
renal cell carcinoma, pancreatic metastases, operative palliatively

Received 27 August 2008; accepted 30 November 2008

Correspondence
Charles M. Vollmer, Department of Surgery, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Stoneman 9, Boston, MA 02215, USA. Tel: +1 617 667 2633. Fax: +1 617 667 7756. E-mail: cvollmer@bidmc.harvard.edu

Introduction

Metastases to the pancreas are rare, comprising only 2–11% of malignancies involving the organ.1 Of resected pancreatic tumours, 0.25–3.00% of specimens are pathologically determined to be renal cell carcinoma (RCC), depending on the series.2,3 There is often a prolonged interval between the resection of the primary renal tumour and the subsequent appearance of pancreatic metastases, with reported median periods of 7–10 years,2,3 and as long as 23 years in one case.1 Symptoms of pancreatic involvement are variable, ranging from none (incidental abdominal imaging findings) to abdominal pain, evidence of biliary obstruction, vomiting, anaemia, weight loss, new-onset diabetes and upper gastrointestinal (UGI) bleeding.2,3,4

In the absence of systemic disease or major co-morbidities, pancreatic resection has become an accepted treatment modality for such patients, as well as for other non-pancreatic primary tumours, such as malignant fibrous histiocytoma, and pancreaticoduodenectomy, distal pancreatectomy and total pancreatectomy have all been performed to this end.1,4 In fact, recently, pancreatic resection has gained acceptance for treatment of isolated metastases with manageable systemic burden.2,5

We present a contemporary series of six patients with metastatic RCC to the pancreas referred for surgical evaluation at our institution. Ultimately, four of these patients required pancreatic
resection; however, the other two were managed with solely medical therapy. It is important to note that each of the patients undergoing resection required emergency or semi-emergency surgical intervention for tumour-related haemorrhage. In describing this series of patients, we propose that not all pancreatic metastases of renal cell origin need to be aggressively resected. Given the efficacy of emerging chemo- and biological therapies currently applied for advanced disease, radical surgical resections may best be withheld.

**Materials and methods**

**Overview**

This series of patients was drawn from a 10-year period at a multidisciplinary, tertiary care medical centre with both a high-volume specialty practice in hepato-pancreato-biliary surgery and a busy medical oncology practice with a strong focus on RCC. The median time for appearance of metastatic disease following resection of the primary tumour in this series was just under 10 years (range 0–19 years). Consistent with other published reports, the median age of patients in this series at the time of discovery of pancreatic involvement was 69 years.3

Specific patient characteristics and results, accrued from chart review, are summarized below. Our series reflected a broad range of presenting ailments. Our subjects included asymptomatic patients, whose disease was discovered by radiographic surveillance, and patients with physical symptoms, such as pain, fatigue, jaundice and upper or lower gastrointestinal bleeding.

**History and presentation**

**Patient 1**

A 69-year-old woman presented with a left parotid mass. This proved to be a synchronous metastasis from a right RCC. Following simultaneous parotid and renal resections carried out after presentation, she remained in good health for 9 years until a computed tomography (CT) scan performed for right lower quadrant discomfort revealed pancreatic lesions typical in appearance of metastatic RCC (Fig. 1).

**Patient 2**

A 68-year-old man underwent a right radical nephrectomy for RCC in 1989. He maintained good health for 15 years until late 2004, when he developed fatigue and began passing melena. Evaluation with axial imaging led to the discovery of two masses in the head of the pancreas (Fig. 2).

**Patient 3**

A 48-year-old woman was diagnosed with RCC in 1995 and underwent right radical nephrectomy at the time. She was subsequently treated with interleukin-2 (IL-2) for concurrent metastatic ovarian disease. She was well for 5 years, until a surveillance CT scan revealed a 2 × 3-cm lesion in the tail of the pancreas, and a distal pancreatectomy and splenectomy were performed. These were followed by induction of adjuvant biological therapy using IL-12 and Bayer 43-9006. Later CT scans showed lesions in the liver, as well as a progressively enlarging lesion in the head of the pancreas.

**Patient 4**

A 75-year-old man with a remote history of RCC, who was asymptomatic, was found incidentally to have a pancreatic mass during a screening CT scan. Repeat imaging showed multiple hypervascular pancreatic lesions, which, on the basis of the subject’s previous right nephrectomy for RCC 19 years earlier, was concluded to be consistent with multifocal metastatic RCC (subsequently proven by biopsy).

**Patient 5**

Eleven years after an index nephrectomy for RCC, a 67-year-old man presented with a small ampullary lesion identified by
endoscopy carried out for occult UGI bleeding. Imaging studies revealed diffuse metastatic involvement of the pancreas.

**Patient 6**
An 87-year-old, otherwise healthy woman presented initially with jaundice and abdominal pain. She was found to have synchronous masses in the pancreas and left kidney, which were proven to be RCC of clear cell type upon endoscopic ultrasound-guided biopsy. Her biliary obstruction was palliated with endoscopic stenting.

**Results**

**Elective pancreatic resection**
One patient in this series underwent an elective surgical procedure as the initial step once metastatic disease to the pancreas became apparent. A distal pancreatectomy and splenectomy were performed in patient 3 when a CT scan detected metastatic disease in the pancreas. She did, however, develop recurrent disease shortly thereafter.

**Urgent pancreatic resection**
Three patients required semi-urgent or urgent pancreaticoduodenectomy. In all these cases this resulted from tumour erosion through the wall of the duodenum, leading to haemodynamically significant, transfusion-dependent UGI bleeding.

Patient 1 was admitted for UGI bleeding with a drop in haematocrit to 18.9. An emergency Whipple procedure for uncontrolled duodenal bleeding was performed and it was discovered intraoperatively that a 5-cm mass had eroded through the wall of the first and second portions of the duodenum. Pathological analysis demonstrated a 6.7-cm metastatic RCC of clear cell type, involving both the duodenum and the pancreas.

Patient 2 presented to a referring hospital with significant UGI bleeding that required transfusion. Esophagogastroduodenoscopy (EGD) showed a 10-mm ulcer in the second portion of the duodenum. The bleeding could not be controlled and the patient was transferred to our institution, where he underwent an emergency Whipple resection.

Over time, patient 3, whose initial metastatic disease had been managed operatively (see above: distal pancreatectomy/splenectomy), developed increasing fatigue, shortness of breath and black stools, prompting an EGD. A friable and actively bleeding mass was seen in the third portion of the duodenum, which could not be controlled endoscopically and led to a significant drop in haematocrit despite multiple transfusions. The decision was made to proceed with a completion pancreatectomy (pylorus-preserving). Pathology later showed metastatic RCC to the head of the pancreas, which had eroded through the duodenal wall.

**No pancreatic resection**
Because of the multifocal nature of patient 4’s disease, in conjunction with his lack of symptoms, it was decided that it would be imprudent to proceed with a radical pancreatic resection or total pancreatectomy. High-dose IL-2 was not considered a possibility secondary to the patient’s co-morbidities, but it was thought that he might do well on Sorafenib.

Patient 5 underwent an exploratory laparotomy, which showed widespread metastatic involvement of the pancreas. It was decided at the time not to perform a total pancreatectomy. The patient was initially started on the epidermal growth factor receptor inhibitor cetuximab (ABX-EGF), but was switched to IL-2 secondary to disease progression. The disease remained stable for some time until a second bout of UGI bleeding led to the discovery of an infra-ampullary duodenal mass, which was resected because of resultant bleeding and perforation. The patient recovered nicely and was started on Avastin for control of his disease.

Patient 6 was not interested in operative interventions at the age of 87 years. She therefore underwent endoscopic management of her biliary obstruction, which proved to be secondary to a metastatic pancreatic lesion discovered at the same time.

**Discussion**
Renal cell carcinoma has long been notorious for its lack of response to conventional chemoradiotherapy, with response rates typically in the range of 4–6%. Compounding this problem is the apparent rise in incidence of this cancer, which is reported to be as much as 126% over the past 50 years. Although any metastatic disease to the pancreas is rare, when it does occur, a renal cell primary has long been recognized as a potential culprit. The dually fascinating and confounding hallmark of this disease entity is the degree of latency between the identification and resection of the primary tumour, and the diagnosis of a pancreatic metastasis, between which there is a median time interval of 7–10 years. By comparison, it is far less common to have synchronous metastastic disease: one meta-analysis places the incidence of synchronous disease at 12%.

The management of metastatic RCC to the pancreas has become, by consensus, largely surgical. Multiple case reports, case series and meta-analyses suggest that aggressive surgical resection confers a significant survival advantage in this situation.

Law et al. found that 11 of 14 patients who underwent pancreatic resection were alive at 32 months of follow-up, although only seven of them were disease-free. It is important to note, however, that five patients were operated for reasons secondary to symptoms of their disease, not as a matter of protocol. The authors noted that proving a survival benefit in asymptomatic patients would be a difficult task.

As previously mentioned, until recently, results of traditional chemoradiotherapy in this disease have been abysmal. The immunomodulators interferon-alpha (IFN-α) and IL-2 have been in use for some time, and the current standard in the treatment of metastatic disease is IL-2. These drugs have now been used in
combination, and at low doses, to successfully control widespread disease, suggesting a synergistic effect that also avoids the toxicity associated with high-dose IFN-α. Better understanding of RCC and its biology has led to multiple new targeted therapies, which are in varying states of study and/or clinical use.14 Hainsworth et al. published results from a series of 63 patients with metastatic RCC treated using the vascular endothelial growth factor (VEGF) inhibitor bevacizumab and the tyrosine kinase inhibitor erlotinib. Their data showed that disease either regressed or stabilized in 86% of patients receiving this therapy. Another study of 63 patients treated with a small molecule inhibitor of the VEGF and platelet-derived growth factor (PDGF) receptors, sunitinib malate (SU11248), demonstrated a 67% rate of response or disease stabilization.16

Given the successes achieved using some of these new biological therapeutic agents, and the relatively indolent behaviour of RCC metastatic to the pancreas, it may be relevant to revisit current treatment recommendations. A distinction must be made between isolated pancreatic metastases and widespread RCC. The biology of this tumour naturally blurs this distinction and the certainty with which one can judge a metastatic deposit in the pancreas to be representative of truly isolated disease is suspect. In their series of 23 patients, Zerbi et al. noted a 34.8% rate of multifocal pancreatic metastases by pathological examination, but preoperative imaging had predicted multiple lesions far less often.17 As most of these series are small and their follow-up generally limited, their power must also be questioned. In addition, some distinction must be made between the management of asymptomatic and asymptomatic patients. It is difficult to argue that pancreatic resection should not be undertaken (if possible) in asymptomatic patients, especially in cases of bleeding or obstruction, as it is also difficult to prove unambiguous survival benefit in those with asymptomatic disease.2,18

Conclusions
Renal cell carcinoma metastases to the pancreas typically occur long after index nephrectomy. Given the heterogeneity of RCC biology and the difficulty of accurately identifying the full extent of disease spread preoperatively,17 palliative resection should be reserved for those who develop complications such as UGI bleeding and, in other series, obstructive jaundice. Routine or radical debulking resections do not appear to be indicated as today’s new biological therapies effectively and reliably control disease over long periods. Although the morbidity of major pancreatic resection is quite low, especially in high-volume centres, postoperative quality of life must be compared with quality of life achieved by non-operative management. This represents a potential area for further study.

Conflicts of interest
None declared.

References