

Clinical Paper

# Current Practice and Outcomes of Patients Undergoing Surgical Resection for Renal Cell Metastases to the Pancreas in Northern Ireland

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## ABSTRACT

Metastatic tumours to the pancreas are rare but most commonly arise from primary renal cell carcinoma (RCC). Contrary to other metastatic malignancies, metastatic RCC demonstrates indolent behaviour, with a long latency between primary tumour presentation and the development of metastasis, as well as a predilection to isolated pancreas-only disease. As such, pancreatic metastasectomy has evolved as a treatment option for patients with metastatic RCC; reported to associate with improved outcomes in selected patients.

The aim of this study was to describe the clinicopathological characteristics and patient outcomes in a series of patients undergoing pancreatic resection for metastatic RCC in a high volume, regional hepatopancreatobiliary (HPB) centre.

**Design** Retrospective review of all patients who underwent pancreatic metastasectomy for pathologically-confirmed metastatic RCC over an eighteen-year period. Clinicopathological characteristics and outcomes were collected and analysed.

**Results** Fifteen patients underwent pancreatic resection for metastatic RCC between October 2004 and October 2022. Two patients underwent synchronous nephrectomy and pancreatectomy. In thirteen patients, the pancreas was the only site of metastatic disease. For those with metachronous metastases, the median disease-free interval (DFI) was 126 months from initial nephrectomy.

Five-year disease-free and overall survival were 32.7 % and 63.3 %, respectively. No clinicopathological factor was found to associate with overall survival (OS); however, patients with synchronous metastatic disease had a significantly shorter disease-free survival ( $p = 0.029$ ). Similarly, patients with a longer DFI ( $\geq$  ten years) between RCC primary and the development of pancreatic metastases had a trend towards improved OS ( $p = 0.074$ ).

Post-operative morbidity and mortality rates were comparable to that of pancreatic surgery for primary pancreatic pathology.

**Conclusion** This case series supports the role of pancreatic resection in patients with metastatic RCC, with acceptable rates of morbidity and mortality and favourable patient outcomes. The long DFI between nephrectomy and pancreatic metastases highlights the importance of long-term

follow-up for patients diagnosed with RCC.

## Introduction

Metastatic tumours within the pancreas are rare; accounting for 2 – 5 % of pancreatic malignancy.<sup>1</sup> Renal cell carcinoma (RCC) is the most common primary tumour to metastasise to the pancreas, with studies reporting close to two-thirds of all pancreatic metastases arising from RCC.<sup>2</sup> RCC is the most common renal malignancy among adults. Approximately 20 – 30 % of patients have metastatic disease at presentation, while 30 – 50 % will develop metastases following potentially curative nephrectomy; of which 2 – 11 % may occur in the pancreas.<sup>3</sup>

Unlike other metastatic primary malignancies that present with disseminated disease, RCC metastases are frequently isolated to the pancreas alone. As such, they may be amenable to surgical resection and this has been reported to improve survival in selected patients with acceptable morbidity and mortality rates when performed in high volume, specialist centres.<sup>4</sup>

Overall, the five-year survival of patients with metastatic RCC has been reported as low as 10 – 15 %;<sup>1</sup> however, a recent systematic review on the outcomes of pancreatic resection for metastatic RCC has reported a five-year survival rate of 53.9 % (26 – 75 %).<sup>4</sup>

The aim of this study was to evaluate outcomes in patients undergoing pancreatic metastasectomy for metastatic RCC in the regional hepatopancreatobiliary (HPB) unit in Northern Ireland and determine if any clinicopathological variables influence outcome in these patients.

## Methods

### Study Design

This was a retrospective study of patients who underwent pancreatic resection for histologically-confirmed metastatic

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RCC in the regional HPB unit in Northern Ireland between October 2004 and October 2022.

The inclusion criteria comprised a diagnosis of RCC of any histological subtype, the presence of synchronous or metachronous pancreatic metastases and treatment of pancreatic metastases by surgical resection. Patients who met these criteria and had metastatic disease in other organs were also included. Eligible patients were identified from the centralised, regional pathology records. Patients who underwent exploratory-only surgery were excluded, as were patients who underwent pancreatic resection for local invasion from a synchronous, primary RCC.

#### Outcome variables

Clinicopathological data were collected including patient age, gender, presence or absence of extra-pancreatic metastases, and the interval between primary tumour resection and diagnosis of pancreatic metastases. Histopathology results of the RCC primary and the pancreatic secondary tumour were reviewed to include the International Society of Urological Pathology (ISUP) tumour grade, the number and size of pancreatic metastases, the resection margin (R) status, presence of lymphovascular (LVI) or perineural invasion (PNI) and the involvement of any resected regional lymph nodes.

With respect to the pancreatic resection; the nature of the pancreatic surgery performed, post-operative morbidity and 90-day mortality were collected, as well as the details of any adjuvant therapy received. Post-operative complications were classified according to the Clavien-Dindo classification system,<sup>5</sup> with grade 3 or higher considered as major morbidity. Post-operative pancreatic fistula (POPF) was classified and scored according to the 2016 International Study Group of Pancreatic Fistula (ISGPS) consensus,<sup>6</sup> with Grade B or C considered clinically relevant.

The primary outcome of overall survival (OS) was determined and defined as the time from pancreatic metastasectomy to the date of death from any cause, or most recent date of follow-up if the patient was still alive. Disease-free interval (DFI) was defined as the time from nephrectomy to the diagnosis of pancreatic metastasis, while disease-free survival (DFS) refers to the time between pancreatic metastasectomy and the diagnosis of recurrent disease on imaging. Local recurrence refers to that within the pancreatic bed, remnant or regional lymph nodes, whilst systemic recurrence refers to distant organ sites.

#### Statistical Analysis

Categorical variables are presented as frequency and percentage, and were compared using Chi-square test or Fisher's exact test, as appropriate. Continuous variables are described as median and interquartile range (IQR) and were compared using the Mann-Whitney U test. Median OS and DFS were calculated using Kaplan-Meier survival estimates

and survival curves compared using log-rank analysis. This was presented as median and IQR. Univariate analysis was used to determine if any clinicopathological variable influenced DFS or OS. Variables with a p-value < 0.05 were included in a Cox proportional multivariate hazards regression analysis to identify independent predictors of DFS or OS. Coefficients were reported as hazard ratios (HRs) and corresponding 95 % confidence intervals (CIs). A p-value < 0.05 was considered statistically significant and statistical analyses were performed using the SPSS for Windows<sup>®</sup> version 28.0 (SPSS Inc, Chicago, Ill, USA).

## Results

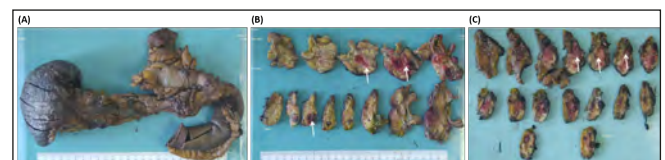
### Presentation

Between October 2004 and 2022, 15 patients underwent pancreatic resection for metastatic RCC, with a male-to-female ratio of 2:1. The median age at diagnosis of the primary RCC was 54 years (IQR 48 – 62 years), compared to 61 years (IQR 57 – 70 years) for the pancreatic metastasis. The clinicopathological characteristics of the primary tumour are summarised in Table 1 and those of the pancreatic secondary tumour are shown in Table 2.



**Figure 1**

Contrast-enhanced cross-sectional computed tomography (CT) image demonstrating a characteristic arterial enhancing lesion within the body of the pancreas.



**Figure 2**

Total pancreatectomy and splenectomy resection specimen performed for multifocal pancreatic RCC metastases.

(A) Posterior view of intact resection specimen.

(B) Sections through pancreatic head. Tumour indicated by white arrows.

(C) Sections through pancreatic tail. Tumour indicated by white arrows

All 15 patients underwent radical nephrectomy; with the majority of primary tumours located in the left kidney ( $n = 9$ , 60.0 %). Two patients presented with synchronous pancreas-only metastases (13 %) and underwent synchronous nephrectomy and pancreatic resection. Of the 13 patients with metachronous pancreatic metastases, the median DFI was 126 months (IQR 91 – 157 months).

Most patients with metastases to the pancreas were asymptomatic ( $n = 11$ , 73.3 %); diagnosed incidentally on surveillance imaging following nephrectomy (Table 2). Among the four who had symptoms, three presented with abdominal pain and one presented with painless, obstructive jaundice.

Prior to pancreatic resection, all patients had an abdominal computerised tomography scan (CT) demonstrating an arterial enhancing pancreatic lesion (Figure 1). Five (33.3 %) patients had an endoscopic ultrasound (EUS) performed, and two of these had a biopsy obtained confirming a diagnosis

of RCC metastasis prior to surgery. Thirteen (86.7 %) had isolated pancreas-only metastases while two (13.3 %) had renal recurrence in the contralateral kidney as well as pancreatic metastases.

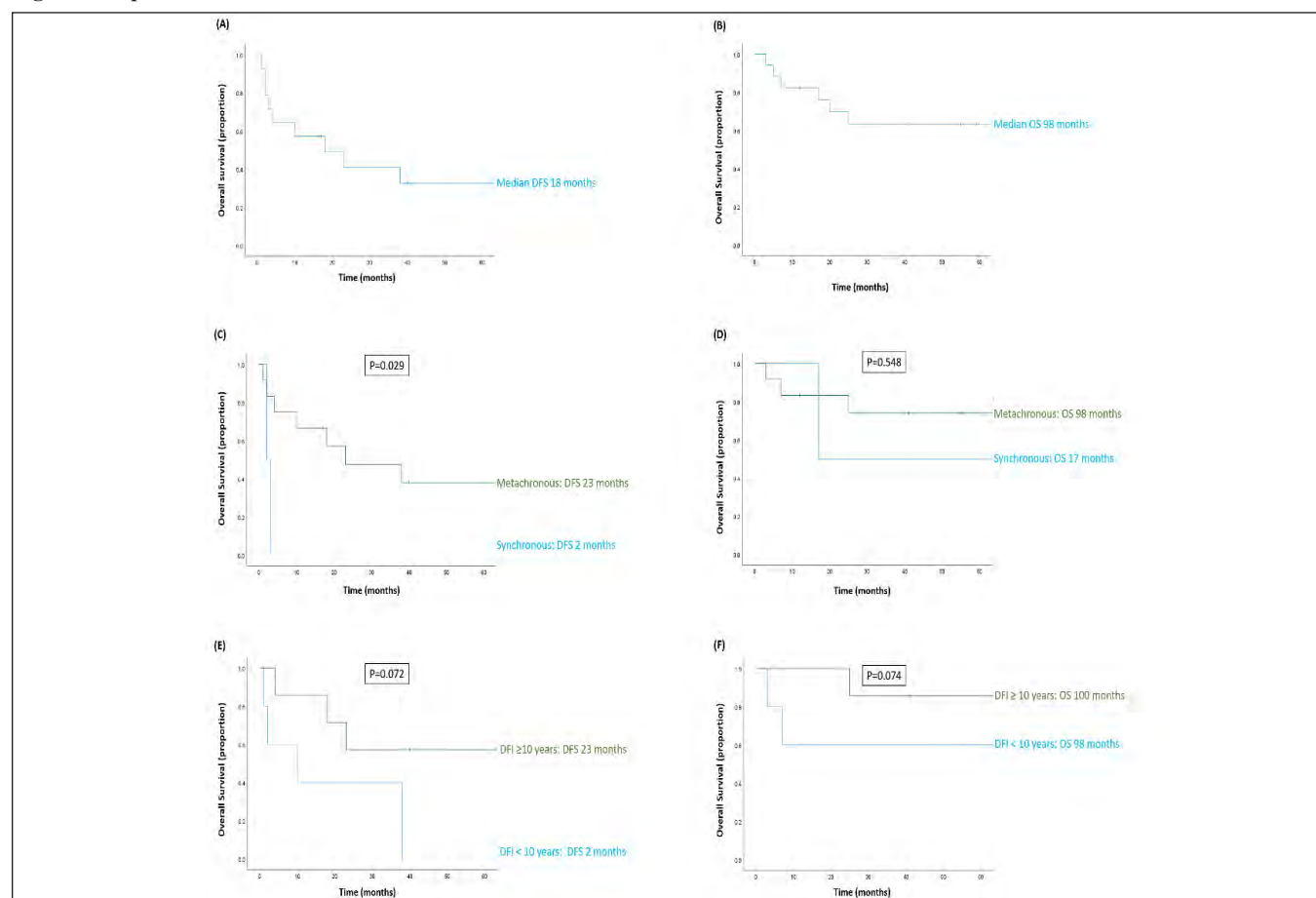
Metastases were located most frequently in the body or tail ( $n = 9$ , 60.0 %), followed by the head, neck or uncinate process ( $n = 3$ , 20.0 %) of the pancreas. Six patients had more than one pancreatic lesion, and in three patients these were located in more than one region of the pancreas ( $n = 3$ , 20.0 %) (Figure 2 A – C).

There was no association between the location of the primary RCC and the site of metastasis within the pancreas (Supplementary Table S1,  $p = 0.51$ ).

### Surgery

Based on tumour location, nine patients (60.0 %) underwent distal pancreatectomy (DP) with splenectomy, three (20.0 %) underwent a Whipple's pancreaticoduodenectomy and three

**Figure 3 Kaplan-Meier Survival Curves**



- (A) Median disease-free survival in patients who underwent pancreatic resection for metastatic RCC.
- (B) Median overall survival in patients who underwent pancreatic resection for metastatic RCC.
- (C) Median disease-free survival in patients with metachronous pancreatic metastases compared to those with synchronous pancreatic metastases.
- (D) Median overall survival in patients with metachronous pancreatic metastases compared to those with synchronous pancreatic metastases.
- (E) Median disease-free survival in patients stratified by disease-free interval.
- (F) Median overall survival in patients stratified by disease-free interval.





**Supplementary Table S1**

Primary tumour location and site of pancreatic metastasis.

Location of pancreatic metastases	Location of Primary RCC	
	Left kidney	Right kidney
Head/neck/uncinate	2	1
Body/tail	4	5
Multifocal	2	1

**Supplementary Table S2**

Statistical analysis of clinicopathological variables with respect to disease-free and overall survival.

	Disease-free survival (DFS)		Overall survival (OS)	
	Univariate Analysis Median DFS [months (IQR)]	p	Univariate Analysis Median OS [months (IQR)]	P
<b>Gender</b>				
Male (n=9)	23 (4 – 89)	0.426	100 (100-112)	0.156
Female (n=5)	10 (2 – 38)		98 (17 -98)	
<b>Age at pancreas resection</b>				
< 65 years (n=8)	10 (2 -23)	0.148	98 (17 -100)	0.396
≥ 65 years (n=5)	4 (1 – 4)		7 (5 out of 6 alive)	
<b>Primary tumour location</b>				
Left (n=9)	18 (3 – 38)	0.200	98 (25 – 112)	0.839
Right (n=5)	89 (10 – 89)		100 (17 -100)	
<b>Primary tumour Fuhrman grade</b>				
1 (n=0)	-	0.187	-	0.175
2 (n=5)	89 (23 -89)		100 (100 – 112)	
3 (n=5)	10 (3 – 18)		25 (17 -25)	
4 (n=4)	2 (1 -2)		7 (3 -7)	
<b>Primary tumour (T) stage</b>				
T1 (n=2)	23 (2 -23)	0.933	3 (-)	0.354
T2 (n=4)	18 (1 -89)		25 (7 -100)	
T3 (n=8)	10 (3 -10)		98	
T4 (n=0)	-		-	
<b>Primary tumour node (N) stage</b>				
N0 (n=4)	1 (1 – 3)	0.013	7 (-)	0.555
NX (n=10)	23 (10 -89)		100 (25 -112)	
<b>DFI (months)</b>				
< 120 months (n=5)	10 (2 – 38)	0.072	98 (7 – 98)	0.074
≥ 120 months (n=7)	89 (18 – 89)		100 (100-112)	
<b>Interval from primary to pancreatic metastasis</b>				
Metachronous (n=12)	2 (2 -3)	0.029	98 (25 – 100)	0.548
Synchronous (n=2)	23 (4 – 89)		17 (-)	
<b>Size of pancreatic metastasis</b>				
< 3cm (n=7)	18 (4 -23)	0.728	112 (25 -112)	0.869
≥ 3cm (n=4)	3 (1 -3)		7 (3 out of 4 alive)	
<b>Type of surgery</b>				
Whipples pancreaticoduodenectomy (n=2)	4 (4 -22)	0.352	- (both alive)	0.095
Distal pancreatectomy (n=9)	23 (10 -89)		98 (25 -100)	
Total pancreatectomy (n=3)	2 (1 -2)		7 (3 -7)	
<b>Pancreatic metastases Node (N) stage</b>				
N0 (n=11)	18 (2 -89)	0.774	100 (17 -100)	0.640
N1 (n=1)	10 (-)		-	
NX (n=2)	23 (23 -38)		98 (98 -112)	
<b>Pancreatic metastases margin (R) status</b>				
R0 (n=7)	38 (3 -38)	0.578	98 (25 -98)	0.157
R1 (n=4)	2 (1 -10)		7 (3 -7)	
<b>Lymphovascular invasion (LVI) status</b>				
LVI present (n=11)	10 (2 -23)	N/A	98 (17 -112)	N/A
LVI absent (n=0)	-		-	
Unknown (n=3)	-		-	
<b>Perineural invasion (PNI) status</b>				
PNI present (n=2)	4 (4 -10)	0.946	- (both alive)	N/A
PNI absent (n=3)	3 (1 -18)		25 (7 -25)	
Unknown (n=9)	-		-	
<b>Site of RCC metastases</b>				
Isolated pancreas only (n=12)	23 (2 -89)	0.333	98 (17 -100)	0.668
Extrapancreatic metastasis (n=2)	4 (4 -18)		25 (-)	
<b>Number of pancreatic metastases</b>				
Multifocal (n=6)	18 (3 -89)	0.208	98 (7 -112)	0.701
Single (n=8)	10 (2 -23)		100 (25 -100)	
<b>Clavien Dindo complication ≥3</b>				
Yes (n=3)	18 (18 -89)	0.333	100 (25 -100)	0.893
No (n=11)	10 (2 -10)		98 (17 -112)	

Table 1

Primary TUMOUR Characteristics		
	NUMBER	%
Gender (M:F)	10 : 5	66.7 : 33.3
Age at diagnosis (years)	54 (48 – 62)	
Location		
Left kidney	9	60.0
Right kidney	6	40.0
Radical nephrectomy	15	100
Histological subtype		
Clear cell	15	100
WHO/iSUP* grade		
1	0	0
2	4	26.7
3	7	46.7
4	4	26.7
AJCC Tumour (T) stage		
T1	2	13.3
T2	5	33.3
T3	8	53.3
T4	0	0
AJCC Node (N) stage		
N0	4	26.4
N1	0	0
NX	11	73.3
Interval to pancreatic metastases		
Synchronous	2	13.3
Metachronous	13	86.7

Table 2

Characteristics of Pancreatic Metastases		
	NUMBER	%
Age at diagnosis (years)	61 (57 – 70)	
Disease-free interval (months)	126 (91 – 157)	
Presentation		
Asymptomatic	11	73.3
Symptomatic	4	26.7
Investigations		
US	7	46.7
CT	15	100.0
MRI/MRCP	6	40.0
PET-CT	1	6.7
EUS	5	33.3
+ biopsy	2	13.3
Tumour Location		
Head/uncinate	3	20.0
Body/tail	9	60.0
Multifocal	3	20.0



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Table 2 continued

Type of surgery		
Whipple's pancreaticoduodenectomy	3	20.0
Total pancreatectomy & splenectomy	3	20.0
Spleen-preserving distal pancreatectomy	1	6.7
Distal pancreatectomy & splenectomy	8	53.3
<b>Resection of other organs</b>		
Subtotal gastrectomy	1	
Synchronous nephrectomy	2	
<b>Surgical approach</b>		
Open	13	86.7
Laparoscopic	2	13.3
<b>Tumour size (mm)</b>	25 (19 – 38)	
<b>Number of pancreatic metastases</b>		
Single	9	60.0
Multiple	6	40.0
<b>Lymphovascular invasion (LVI)</b>		
Yes	11	73.3
No	0	0
Unknown	4	26.7
<b>Perineural invasion (PNI)</b>		
Yes	2	13.3
No	3	20.0
Unknown	10	66.7
<b>Margin (R) status</b>		
R0	7	46.7
R1	5	33.3
R2	2	13.3
Unknown	1	6.7
<b>Lymph node status</b>		
Positive	1	6.7
Negative	14	93.3

had a total pancreatectomy with splenectomy (20.0 %). Open surgery was the most common approach, with laparoscopic distal pancreatectomy and splenectomy performed in two patients (20.0 %). One patient required a distal gastrectomy as well as distal pancreatectomy due to local invasion of the pancreatic metastasis into the distal stomach.

The overall post-operative morbidity rate was 40.0 %, with 26.7 % (n = 4) developing a Clavien-Dindo grade IIIa or higher complication. Significant morbidity most commonly followed the development of a post-operative pancreatic fistula (POPF) which was observed in six patients (40.0 %). According to the revised ISGPS definition for POPF,<sup>6</sup> 16.7 % (n = 3) developed a grade B fistula requiring insertion of a radiological drain, while the remaining three were grade C POPFs (16.7 %), two of whom required a reoperation for post-pancreatectomy haemorrhage. One patient with a grade C POPF died within 90 days of surgery, resulting in a 6.7 % 90-day mortality rate for the cohort.

### Pathology

Histological data for the primary RCCs and pancreatic metastases are summarised in Table 1 and Table 2, respectively. All primary RCCs demonstrated clear cell morphology, with the majority grade 3 according to the The World Health Organisation/International Society of Urological Pathology (WHO/ISUP) grading system for renal cell carcinoma. The median size of the metastatic pancreatic tumour was 25 mm (IQR 19 – 38 mm). Nine patients had a solitary pancreatic metastasis (60.0 %), while six had multifocal metastases within the pancreas (40.0 %). Only one patient was found to have metastatic disease within their resected regional lymph nodes (6.7 %).

### Survival

Excluding the 90-day post-operative mortality, median follow-up from pancreatic metastasectomy was 61 months (IQR 16 – 89 months), during which time ten (71.4 %)

patients developed recurrent disease and seven patients died (50.0 %).

The median DFS was 18 months (IQR 3 – 89), with 1-, 3- and 5-year DFS of 57.1 %, 40.8 % and 32.7 %, respectively (Figure 3A). Five of the ten patients (50.0 %) developed recurrence within six months of pancreatic surgery, of which two were alive at last follow-up.

Three patients developed recurrence at a single organ site; either the lung ( $n = 1$ ) or liver ( $n = 2$ ) and the remaining seven developed disseminated metastases. In order of frequency, the commonest sites of relapse were the liver ( $n = 7$ ), contralateral kidney ( $n = 7$ ), lung ( $n = 6$ ), bone ( $n = 3$ ) and pancreatic remnant ( $n = 2$ ). No patient underwent further surgical resection for disease relapse. Five patients (33.3 %) received systemic treatment for recurrent disease; two with Sunitinib monotherapy and three with combination targeted therapies. Locoregional therapies were utilised in four patients (40.0 %); with radiofrequency ablation (RFA,  $n = 2$ ) or cryo-ablation ( $n = 1$ ) used for renal recurrence, and combination transarterial chemoembolisation and RFA utilised in the same patient to manage their liver metastases.

Median OS was 98 months (IQR 25 - 100) from the time of pancreatic metastasectomy; 1-, 3- and 5-year overall survivals were 85.7 %, 70.1 % and 63.3 %, respectively (Figure 3B).

For patients presenting with synchronous, isolated pancreas-only metastases, their OS was 17 months from their synchronous nephrectomy and pancreatic resection, compared to 98 months for those who presented with metachronous pancreatic metastases (Figure 3C,  $p = 0.548$ ). These patients had a significantly shorter DFS compared to those with metachronous disease (DFS 2 months vs. 23 months,  $p = 0.029$ ).

Survival analysis was limited by the small number of cases. On univariate analysis, no clinicopathological variable was found to associate with OS (Supplementary Table S2). A trend towards improved survival was observed in patients with a longer DFI (Figure 3C - D,  $p = 0.074$ ). Only one patient had lymph node involvement at the time of pancreatic resection. Their median DFS was 10 months compared to 18 months in node negative patients, and 23 months in those whose nodes were not assessed ( $p = 0.774$ ). Despite a shorter time to disease relapse, the patient was still alive at last follow-up.

## Discussion

Renal cell carcinoma has a tendency to metastasise to the pancreas but displays relatively indolent behaviour in contrast to other metastatic tumours, making surgical resection a viable treatment option. Accordingly, pancreatic resection for metastatic RCC has now been reported in a number of published case series from specialist centres.<sup>1,3,7-9</sup> While case numbers are small, results from these series and systematic reviews suggest that pancreatic metastasectomy associates

with favourable survival outcomes, and with acceptable rates of morbidity and mortality.<sup>4,9</sup>

This study describes the outcomes of patients undergoing pancreatic resection for metastatic RCC in a specialist HPB centre in Northern Ireland over a consecutive eighteen-year period. Close to one patient per year underwent pancreatic resection for metastatic RCC, representing less than 2 % of all pancreatic resections performed in the region per annum. Results confirm encouraging long-term outcomes in patients undergoing surgery for metastatic disease, with a five-year survival rate of 63 % and a median OS exceeding eight years.

The vast majority of pancreatic RCC metastases are metachronous, with synchronous metastases observed in just two patients in this study. A long latency period between primary nephrectomy and development of pancreatic metastasis is well recognised; with an estimated mean DFI of 105 months based on systematic reviews.<sup>4</sup> In our cohort, we observed a DFI of 126 months following nephrectomy, highlighting the importance of long-term surveillance of patients up to, and even beyond, ten years post-nephrectomy. This is particularly important when we consider that over 70 % of these patients were asymptomatic and had their metastases diagnosed on surveillance investigations.

Radiologically, pancreatic RCC metastases may be difficult to distinguish from primary pancreatic adenocarcinoma. A high index of suspicion is necessary when a solid, hypervascular pancreatic mass is detected on CT or MRI in a patient with a history of RCC (Figure 1). Differential diagnoses include other hypervascular neoplasms such as neuroendocrine tumours. For the majority, an oncological history aids the correct diagnosis. However, most cases are amenable to endoscopic ultrasound (EUS) and biopsy when the diagnosis is uncertain.

Evidence to support the role of surgery in the management of RCC pancreatic metastases is based on small case series, with a lack of randomised or case-control series comparing surgical and non-surgical treatment options. Non-matched controlled cohorts<sup>10</sup> and systematic reviews<sup>2,4</sup> suggest that surgery associates with prolonged DFS and OS compared to conservative management.

Similar to surgery for primary pancreatic malignancy, the aim of pancreatic metastasectomy is to excise the tumour with clear margins whilst preserving as much normal pancreatic parenchyma as possible. The nature of surgery performed depends on the location of the metastatic tumour and whether it is solitary or multifocal, with lesions within the head or uncinate process requiring a Whipple's pancreaticoduodenectomy, while lesions within the body or tail may be resected with a distal pancreatectomy. Enucleation has been described in small isolated lesions<sup>1,3,11</sup> but was not performed in our cohort. This approach is generally avoided due to the high risk of tumour recurrence and significant risk of POPF.<sup>1,11</sup> While metastases may often be multifocal within the pancreas, a total pancreatectomy is not always





necessary provided a clear margin can be achieved. Although a total pancreatectomy does not carry the risk of POPF, this approach is avoided where possible due to the lasting impact of the resulting insulin-dependent brittle diabetes on quality of life.<sup>12</sup> Furthermore, it has been shown that a radical total pancreatectomy or the addition of a splenectomy does not appear to reduce recurrence or associate with improved OS.<sup>4</sup> In our study, the three patients who underwent total pancreatectomy had multifocal metastases throughout the gland. One patient was identified on preoperative CT to require a total pancreatectomy for clearance, while for the remaining two this decision was made intraoperatively.

Unlike primary pancreatic adenocarcinoma, involvement of the regional lymph nodes is an uncommon feature of metastatic RCC and was observed in just one case (6.7 %). Standard oncological resections require excision and assessment of the regional lymph nodes to provide prognostic information and to reduce the risk of disease recurrence. A survival benefit of peripancreatic lymphadenectomy in metastatic RCC has not been established<sup>4</sup> and given the low rates of lymph node involvement associated with pancreatic RCC metastases, routine lymphadenectomy may be of limited value.

Traditionally, pancreatic surgery associates with significant morbidity and mortality rates. Recent advances in surgical approach and post-operative care have led to a reduction in these rates.<sup>11</sup> The overall morbidity rate of 44.4 % in our study is comparable to that published in a recent systematic review,<sup>9</sup> with rates ranging from 12.5 % to 61.9 %. Morbidity rates as low as 38.5% and mortality rates of less than 5 % have been observed in specialist units performing high numbers of pancreatic resections.<sup>2-4</sup>

Despite improvements in the morbidity associated with major pancreatic resection, not all patients will be suitable for major surgery. Furthermore, recurrence rates following metastasectomy are high; ranging from 39 – 100 % across various single and multicentre studies.<sup>3,4,9</sup> As such, many advocate systemic therapy over surgery. Traditionally, RCC response rates to chemotherapy and radiotherapy have been poor. However, the development of targeted therapies, such as tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, and immune checkpoint inhibitors has led to improved response rates; but non-response remains a problem.<sup>13</sup> As such, combination systemic therapy is recommended.<sup>14</sup>

While no study has compared surgery to immune checkpoint inhibitor therapy, similar survival outcomes with tyrosine kinase inhibitors have been demonstrated compared to metastasectomy.<sup>13</sup> However, surgery has the advantage that it may achieve disease-free control in a proportion of patients compared to systemic therapy, but at the expense of higher morbidity and mortality rates.<sup>13</sup>

Ultimately, due to its low incidence, there is a lack of

prospective, randomised or case-control evidence to support surgery over systemic therapies. Formal discussion involving both urological and hepatopancreatobiliary multidisciplinary teams is crucial and findings from our series would suggest that case-selection for metastasectomy is important. While the small numbers have limited identification of prognostic factors in metastatic RCC, we observed a significantly shorter DFS in those with synchronous metastases, and a trend towards improved OS in those with a longer latency period between nephrectomy and development of pancreatic metastases. This is a finding that has been observed by others,<sup>4,9,15</sup> and suggests that synchronous metastases or a short DFI heralds a more aggressive tumour biology. A strategy of selective upfront systemic therapy in these high-risk patients to assess biological response may be more appropriate and avoid pancreatic resection with its associated morbidity in those at risk of early disease relapse. Although not demonstrated in our study, other factors that have been shown to associate with high recurrence rates and worse prognosis include: the presence of extra-pancreatic metastases prior to pancreatic metastases<sup>15,16</sup> and the presence of vascular invasion<sup>11</sup> or lymph node metastases.<sup>11,16</sup>

Despite high recurrence rates, prolonged survival can still be achieved in patients with metastatic RCC. Our recurrence rate was 71.4 % (n = 10) over a median follow-up of 61 months, with a DFS of 18 months. Contrary to other reports of a predilection to single organ recurrence, 70 % of cases in our cohort had disease relapse at more than one site. Despite the high recurrence rate and short DFS observed in this study, the median OS was 98 months and 5-year survival 63.3 %; similar to rates reported by others.<sup>6</sup> These findings highlight that prolonged survival can still be achieved in patients with relapsed metastatic RCC utilising combinational systemic therapies, as well as locoregional treatments to manage oligometastatic disease. Radiofrequency ablation in particular has emerged as a safe and effective modality to manage relapse in the contralateral kidney,<sup>17</sup> as well as the pancreatic remnant,<sup>18</sup> liver<sup>19</sup> or lung.<sup>20</sup>

### *Conclusion*

Our results show that surgery for RCC metastases to the pancreas carries comparable morbidity and mortality rates to that of pancreatic resection for primary pancreatic cancer, yet with a more favourable overall prognosis. The indolent biology of RCC, with long DFI and isolated single site metastases mean that metastatic RCC does not carry the poor prognosis associated with other primary abdominal malignancies. Despite high recurrence rates and a short DFS, prognosis for these patients is favourable. Locoregional therapies may now be added to the armamentarium of surgery, tyrosine kinase and immune checkpoint inhibitors. Similar to the evolution of metastatic colorectal cancer management, a multidisciplinary, multimodal approach may be utilised to control metastatic RCC and achieve excellent patient outcomes.



**Key words:** Pancreatic metastases, renal cell carcinoma

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