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Pancreatic metastases from renal cell carcinoma. Postoperative outcome after surgical treatment in a Spanish multicenter study (PANMEKID)

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ABSTRACT

Background: Renal Cell Carcinoma (RCC) occasionally spreads to the pancreas. The purpose of our study is to evaluate the short and long-term results of a multicenter series in order to determine the effect of surgical treatment on the prognosis of these patients.
Methods: Multicenter retrospective study of patients undergoing surgery for RCC pancreatic metastases, from January 2010 to May 2020. Variables related to the primary tumor, demographics, clinical characteristics of metastasis, location in the pancreas, type of pancreatic resection performed and data on short and long-term evolution after pancreatic resection were collected.
Results: The study included 116 patients. The mean time between nephrectomy and pancreatic metastases' resection was 87.35 months (ICR: 1.51–332.55). Distal pancreatectomy was the most performed technique employed (50 %). Postoperative morbidity was observed in 60.9 % of cases (Clavien-Dindo greater than IIIa in 14 %). The median follow-up time was 43 months (13–78). Overall survival (OS) rates at 1, 3, and 5 years were 96 %, 88 %, and 83 %, respectively. The disease-free survival (DFS) rate at 1, 3, and 5 years was 73 %, 49 %, and 35 %, respectively. Significant prognostic factors of relapse were a disease free interval of less than 10 years (2.05 [1.13–3.72], p 0.02) and a history of previous extrapancreatic metastasis (2.44 [1.22–4.86], p 0.01).
Conclusions: Pancreatic resection if metastatic RCC is found in the pancreas is warranted to achieve higher overall survival and disease-free survival, even if extrapancreatic metastases were previously removed. The existence of intrapancreatic multifocal compromise does not always warrant the performance of a total pancreatectomy in order to improve survival.

1. Introduction

Pancreatic metastases are uncommon, with their prevalence ranging from 2 to 5% of all malignancies found in the pancreas [1–4]. As for the types of cancer known to produce pancreatic metastases, renal cell carcinomas (RCC) are markedly the most common [5], followed by colorectal cancer, melanomas, sarcomas, and lung cancer [6]. Often patients remain asymptomatic and lesions are discovered incidentally or during follow-up. Secondary tumors may develop up to many years after the initial diagnosis and treatment of the primary cancer; therefore, they should be considered when a patient with a cancer history presents with a isolated pancreatic mass. Although pancreatic metastases of non-renal malignancies are typically only seen when patients have a generalized systemic disease, the RCC frequently spreads to the pancreas alone, thus being susceptible to surgical resection [7].

Most published studies look at isolated cases or small retrospective series, not allowing to draw consistent conclusions on which patient subgroups could potentially benefit from surgical resection and for which others surgery would not be indicated.

The purpose of our study is to evaluate the short and long-term results of a multicenter series in order to determine the effect of surgical treatment on the prognosis of these patients.

2. Materials and methods

2.1. Data collection

This is a multicenter retrospective study of patients undergoing surgery for pancreatic metastases, from January 2010 to May 2020. The study was carried out at the Hepato-Pancreato-Biliary Surgery Departments of 40 hospitals in Spain.

Inclusion criteria: Patients with RCC pancreatic metastases, as corroborated upon surgery, were considered suitable for inclusion in the study. Exclusion criteria: Patients with other pathological diagnoses and patients who underwent additional pancreatic resections after a first surgery for metastatic RCC were excluded.

Each participating center appointed a local manager to carry out the data collection and to liaise with the general study coordinator. All the data were collected by this local manager. Researchers collected information from electronic health records, whereas the project coordinator had access to medical data only. The study was approved by the Hospital Universitario de Badajoz Research Ethics Committee and confirmed by the other hospitals' Research Ethics Committees. An informed consent from the patient was not required since the study was retrospective and observational, and entailed no risk.

2.2. Preoperative assessment

Diagnostic management included establishment of a medical history, performance of clinical examination, and imaging tests, including computerized tomography (CT), to confirm the tumor's location within the pancreas and its size, as well as any infiltration of adjacent structures. In case of doubt, an abdominal MRI was also performed. These tests also ruled out distant metastases and allowed us to assess resectability and the possibility of reconstruction depending on the location.

2.3. Definitions

Multiple lesion refers to the existence of more than one tumor in the pancreas while multifocal disease is also the existence of more than one tumor and they are located in different regions of the pancreas, for example the head and body of the pancreas.

The type of surgery performed was defined as pancreaticoduodenectomy (PD) classic or using the preservation of the pylorus technique [8,9], distal pancreatectomy (DP), total pancreatectomy (TP), or other pancreas-sparing resections (local excision, central pancreatectomy).

The resection margins of the surgical specimen were categorized according to the definitions of the Royal College of Pathologists: R0 (margin to the tumor $\geq$ 1 mm), R1 (margin to the tumor < 1 mm), and R2 (macroscopically positive margin) [10]. Complications were assessed at 90 days using the Clavien-Dindo (CD) classification, and those defined as Clavien-Dindo grade IIIa or higher were considered major [11]. For the recording of complications, the medical and nursing notes from the patients' electronic records were referred to. When it came to the specific complications of the pancreatic surgeries, definitions by the International Study Group on Pancreatic Surgery (ISGPS) of delayed gastric emptying [12], post-pancreatic hemorrhage [13], bile leak [14], and pancreatic fistula [15] were used.

Follow-up regimen: Long-term patient follow-up included physical examination and chest-abdomen-pelvis CT scan every three months for the first two years, twice a year up to five years, and then annually. Local recurrence was defined as the return of a tumor within the surgical field or regional lymph nodes, while systemic recurrence was defined as recurrent disease elsewhere.

2.4. Variables

2.4.1. The following variables were studied

Related to primary tumor: Date of resection, tumor size (cm), side (right or left), Furhman classification [16]. Epidemiological: age, sex, past medical history, medication, the American Society of Anesthesiologists (ASA) Classification. Clinical: symptoms. Diagnostic: serological tests: hemoglobin (gr/dl), leukocytes, neutrophils, lymphocytes, platelets, LDH, albumin, calcium (mg/dL), bilirubin (mg/dl), albumin (g/dl), ALT (U/L), AST (U/L), calcium (mg/dL). Radiological and endoscopic diagnostic tests performed, preoperative biliary drainage if necessary, and preoperative biopsy. Related to the metastasis: The size, location within the pancreas, the existence of a single or multiple lesion(s), and the involvement of one or more pancreatic region(s), surgical approach (type of resection and reconstruction), and intraoperative complications were recorded. The following details of the postoperative course were collected: morbidity and mortality (according to the Clavien-Dindo Classification, re-operation, hospital length of stay, readmission, and operative mortality [up to 90 days post-surgery]). The histological data retrieved were: TNM, tumor size and lymph nodes harvested, R status, and degree of differentiation. Among the key long-term data recorded were time of relapse, disease-free and overall survival, cause of death and postoperative follow-up (in months).

2.5. Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were analyzed for Gaussian distribution by the Shapiro-Wilk test; those with normal distribution were presented as means and standard deviations (SD), and non-normal variables were reported as median and interquartile range (IR). The Chi-squared analysis or Fisher's exact probability test was used to compare categorical variables. Non-parametric tests were used to compare medians. Kaplan-Meier survival analysis was performed to model all-cause mortality and relapse-free survival from the day of surgery. The Cox proportional hazards model was used to assess the effect of study variables in both univariate and multivariate survival analyses.

Data were analyzed using IBM SPSS v22.0. The level of significance was set at 0.05.

3. Results

The study encompassed 116 patients (51 women and 65 men) who underwent pancreatic resections due to RCC metastases. The mean age was 68 years (ICR 61–74). All other demographic data are recorded in Table 1.

Primary tumor characteristics are recorded in Table 1. The mean amount of time between nephrectomy and pancreatic metastases' resection was 87.35 months (ICR: 1.51–332.55).

In 2 cases (1.7 %) the pancreatic surgery and the nephrectomy were performed simultaneously. Nineteen (19) patients (16.4 %) had had a previous resection to remove the metastasis from an organ other than the pancreas, specifically the lung, adrenal gland, ovary, thyroid gland, contralateral kidney, jejunum, and cavum (from most to least frequent).

Table 1
Demographic and primary tumor characteristics.

Characteristic	Number	%
Age, years	68 [61–74]	
Median (IQR)		
Sex (M: F)	51:65	44:56
Von Hippel Lindau	1	0.86
ASA Classification		
Unreported	2	1.7
1	9	7.8
2	54	46.6
3	49	42.2
4	2	1.7
Tumor size (cm)	8 [2.5–45]	
Median (IQR)		
Location		
Right	58	50
Left	54	46.6
Unreported	4	3.4
Type of nephrectomy		
Radical	109	94
Partial	3	2.6
Unreported	4	3.4
Margin status	88	95.7
R0	88	75.9
R1	4	3.4
Unreported	24	20.7
Histology		
CCRCC	112	96.6
Papilar pattern	2	1.7
Sarcomatoid pattern	2	1.7

CCRCC: clear cell renal cell carcinoma.

Most patients were asymptomatic at the time of diagnosis of the pancreatic metastasis, which was typically found incidentally during the follow-up stage of their cancer. Of those who experienced symptoms, the most common was abdominal pain (10.3 %). Only 2 patients (1.7 %) experienced jaundice as part of their clinical presentation. Two (2) others had weight loss. Diagnostic tests performed, and size and tumor location are detailed in Table 2.

Prior to the surgery, 5 patients (4.3 %) received systemic treatment consisting of interleukin-2, sumatinib, sorafenib, sunitinib, INF-α (interferon).

In order of frequency, the metastases were found in the following pancreatic regions: head and uncinate process (32 patients, 27.6 %), pancreatic body (27 patients, 23.3 %), tail (24 patients, 20.7 %), and neck (4 patients, 3.4 %). It is worth mentioning that 30 patients (25.9 %) presented with more than one pancreatic mass, 23 of whom (19.8 %) experienced metastases in more than one pancreatic region. The mean metastatic diameter was 2.4 cm (ICR: 1.5–4 cm).

At the time of surgery, 93.1 % of patients had a secondary lesion isolated to the pancreas whereas in 8 cases, there was also extrapancreatic involvement (liver, left or right adrenal glands, axilla, pelvic node, subcutaneous cellular tissue, and gallbladder). All but one of them were synchronously resected at the time of the metastatic surgery, with the exception being an axillary adenopathy which was biopsied, confirming the secondary disease.

The most common surgical approach was open surgery, while laparoscopy was performed in 18.1 % of cases. DP was the most performed technique (50 %), followed by PD (24.1 %). Enucleation was performed in 5 patients (4.3 %). Subtotal PD was only performed in 1 patient (0.9 %), whereas TP was performed in 19 patients (19.1 %) as a first intervention (Table 2). Out of 21 patients in whom we performed a laparoscopic approach, 18 underwent distal pancreatectomy, one patient underwent central pancreatectomy, and the remaining two patients underwent enucleation. In the open approach group, we performed 28 pancreaticoduodenectomies, 40 distal pancreatectomies, 19 total pancreatectomies, and some other type of resection in the remaining 8 patients.

Seven (7) patients (6.1 %) required further resection involving adjacent organs (colon, left adrenal gland, stomach, diaphragm).

Postoperative morbidity was observed in 60.9 % of cases (Clavien-Dindo greater than IIIa in 14 %) (Table 3). Postoperative pancreatic fistula (POPF) was the most common complication. POPF occurred in 28 patients. According to the ISGPS definition, 11 patients presented a biochemical leak. Type B and C fistulas occurred in 15 (12.9 %) and 2 (1.7 %) patients, respectively. Postpancreatectomy hemorrhage was present in 12 (10.3 %) patients (two of them grade A, and 10 others grade B). Only one patient experienced delayed gastric emptying (grade A).

The postoperative mortality rate (within 90 days) was 3.5 %. The median length of stay was 12 days (ICR 7–22.5 days).

Regarding pathologic characteristics, there was no lymph node involvement in 96.6 % of cases. The median of total removed lymph nodes was 6 (2–12).

The median follow-up time was 43 months (13–78). During follow-up we detected relapse in 62 patients with the following location: loco-regional in 7 (11.3 %) patients, pancreatic in 17 (27.4 %) patients, distant metastasis in 29 (46.8 %) patients, multiple sites in 5 (8.1 %) patients, and unspecified in 4 (6.5 %) patients. The treatment in relapsed cases was as follows: observation in 4 (6.5 %) patients, surgical treatment in 31 (50 %) patients, systemic therapy in 19 (30.6 %) patients, unspecified in the remaining 8 (12.9 %) patients. Pancreatic relapse was treated in most cases by pancreatic resection. Pancreatectomy was performed in 13 (76.5 %) patients. Of the remaining 4 patients, 2 of them received systemic therapy, and for 2 others we have no data on treatment. None of the patients who had multiple pancreatic lesions in different regions and underwent pancreas-sparing surgery had recurrence in the remaining pancreas during follow-up.

The median overall survival (OS) rate was 105 months (91.56–118.43), and the disease-free survival (DFS) rate was 33 months (8.07–57.93). OS rates at 1, 3, and 5 years were 96 %, 88 %, and 83 %, respectively (Fig. 1). The disease-free survival (DFS) rate at 1, 3, and 5 years was 73 %, 49 %, and 35 %, respectively (Fig. 1).

There was no relation found between the side where the primary tumor was found and the side for the pancreatic metastases (p 0.121). Similarly, no significant differences were observed when looking at the relation between the side where the primary tumor was found and the occurrence of single or multiple metastases.

Prognostic factors of overall survival and disease free survival are listed in Table 4. Performance of TP as the first line of treatment

Table 2
Characteristics of pancreatic metastases.

	Number	%
Patient presentation		
Asymptomatic	100	86.2
Symptomatic	16	13.8
Diagnosis		
CT	105	91.3
MRI	17	14.8
PET-CT	29	25.7
EUS	63	54.3
Biopsy	67	57.8
Tumor size (cm)		
Median (IQR)	2.4 [1.5–4]	
Location		
Head-uncinate	33	28.4
Body-tail	62	53.4
Multifocal disease	21	18.1
Multiple lesions	30	25.9
Extrapancreatic disease	8	6.9
Type of surgery		
PD	28	24.1
DP	58	50
TP	19	16.4
Others	11	9.5
Splenectomy	59	50.9
Vascular resection	3	2.6
Venous	2	1.7
Arterial	1	0.8
Resection of other organs	7	6.1
Surgical approach		
Open	95	81.9
Laparoscopic	21	18.1
Margin status		
R0	105	90.5
R1	10	8.6
Unreported	1	0.9
Peripancreatic tissue involvement	17	14.6
Lymph node positive	4	3.4

CT: computerized tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; PD: pancreaticoduodenectomy; DP: distal pancreatectomy; TP: total pancreatectomy; others: pancreas-sparing resections (local excision, central pancreatectomy).

Table 3
Postoperative morbidity. Clavien-Dindo classification.

No complications	45 (38.8 %)
Grade I	10 (8.6 %)
Grade II	32 (27.6 %)
Grade IIIa	12 (10.3 %)
Grade IIIb	11 (9.5 %)
Grade IVa	0
Grade IVb	1 (0.9 %)
Grade V	4 (3.4 %)
Lost	1 (0.9 %)

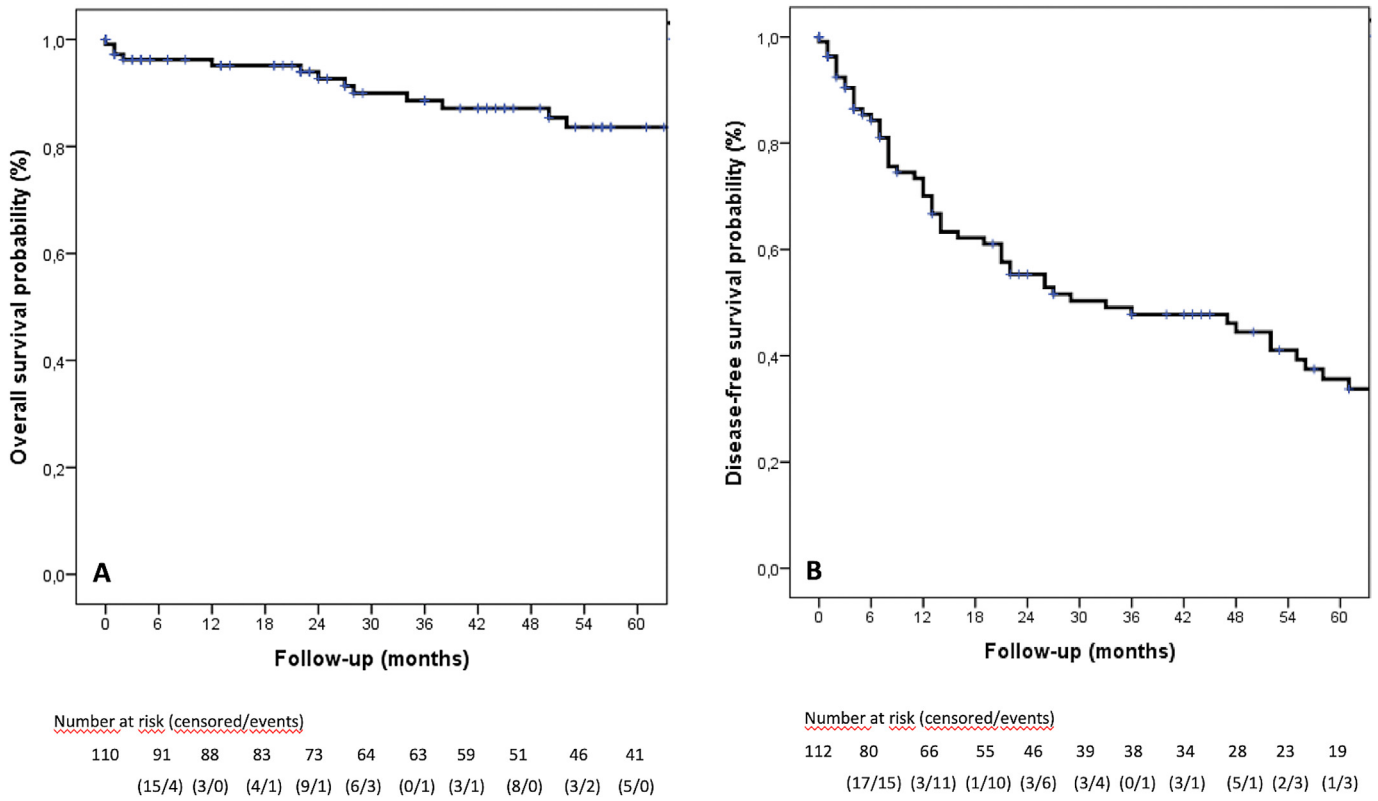

Fig. 1. (A) Kaplan–Meier survival curve of Overall survival (OS) following pancreatic resection. (B) Kaplan–Meier survival curve of Disease-free survival (DFS) following pancreatic resection.

(p 0.386) and the addition of a splenectomy (p 0.933) did not impact OS (Table 4).

An analysis of the outcomes for patients with multiple lesions and in different pancreatic regions reported no significant differences in the OS according to whether TP was the first line of treatment or not (127.7 vs 102 months; p 0.686); no differences were observed either in the DFS rate (56.04 vs 46.8 months; p 0.895) (Table 5).

Table 4
Prognostic factors of overall survival and disease free survival.

	Overall survival (OS)				Disease free survival (DFS)			
	Univariate		Multivariate analysis		Univariate		Multivariate analysis	
	HR (CI 95 %)	p < 0.05	HR (CI 95 %)	p < 0.05	HR (CI 95 %)	p < 0.05	HR (CI 95 %)	p < 0.05
Gender male	0.89 (0.41–1.97)	0.78			0.69 (0.41–1.16)	0.16		
Age (years)	1.04 (0.99–1.09)	0.08			0.99 (0.96–1.01)	0.38		
DFI (months)	1.00 (1.00–1.01)	0.06	1.01 (1.00–1.01)	0.03	0.99 (0.99–1.00)	0.20	2.05 (1.13–3.72)	0.02
- DFI 60 months	2.01 (0.80–5.05)	0.13			1.09 (0.64–1.86)	0.76		
- DFI 120 months	1.48 (0.67–3.25)	0.32			1.55 (0.91–2.65)	0.11		
EPM	1.16 (0.34–3.90)	0.81			2.09 (1.14–3.82)	0.02	2.44 (1.22–4.86)	0.01
Primary tumor size (cm)	0.98 (0.86–1.11)	0.73			0.93 (0.86–1.01)	0.08		
Primary tumor location (left)	1.43 (0.63–3.27)	0.39			1.51 (0.89–2.57)	0.13	1.35 (0.79–2.33)	0.27
Radical nefrectomy	4.68 (1.07–20.42)	0.04			7.00 (0.86–56.94)	0.07		
Syncronic	0.04 (0.00–98.31)	0.43			0.36 (0.05–2.64)	0.32		
Multiple metastases	1.11 (0.45–2.78)	0.81			1.06 (0.59–1.91)	0.84		
Pancreatic location	0.80 (0.62–1.03)	0.08			0.92 (0.78–1.09)	0.35		
Isolated metastases	2.40 (0.89–6.42)	0.08			1.07 (0.42–2.75)	0.89		
Type of surgery	0.70 (0.48–0.99)	0.05	0.65 (0.45–0.95)	0.02	0.87 (0.68–1.10)	0.24		
Initial TP	0.57 (0.17–1.92)	0.36			0.53 (0.24–1.17)	0.12		
Postoperative morbidity	0.65 (0.28–1.49)	0.31			0.78 (0.46–1.31)	0.35		
Pancreatic fistula	0.88 (0.35–2.23)	0.78			1.10 (0.61–2.01)	0.75		
Size of metastases (cm)	1.04 (0.86–1.26)	0.69			0.91 (0.79–1.05)	0.21		
Lynphadenectomy	0.90 (0.37–2.15)	0.81			1.04 (0.59–1.82)	0.89		

DFI: disease-free Interval.
EPM: extrapancreatic resected metastases previously.
TP: total pancreatectomy.

Table 5
Comparative of median overall survival (OS) and disease free survival (DFS) attending to different variables.

	Median of overall survival	p < 0.05	Median of DFS	p < 0.05
	105 months (91.56–118.43)		33 months (8.07–57.93)	
Gender (female/male)	134.91 (100.39–169.43) vs 98.43 (85.26–111.51)	0.78	59.85 (41.41–78.30) vs 43.94 (31.85–56.02)	0.16
DFI 10 yrs	117.08 (97.59–136.58) vs 121.62 (84.95–158.29)	0.32	44.74 (31.47–58.00) vs 61.28 (44.07–78.49)	0.11
EPM	127.27 (101.74–152.81) vs 96 (76.63–115.37)	0.81	56.58 (43.81–69.36) vs 24.89 (11.62–38.16)	0.01
Primary tumor location (left/right)	133.40 (104.75–162.05) vs 89.83 (75.52–104.14)	0.39	60.70 (44.52–76.89) vs 38.68 (28.60–50.76)	0.13
Multiple metastases	127.44 (99-46-155.43) vs 116.10 (85.92–149.27)	0.81	51.06 (38.10–64.02) vs 46.92 (31.66–62.18)	0.84
Isolated metastases	88.86 (35.08–142.63) vs 115.30 (98.67–131.93)	0.08	54.86 (9.46–100.26) vs 50.34 (38.57–62.12)	0.89
Initial TP	116.89 (90.69–143.09) vs 138.51 (108.39–168.64)	0.36	45.91 (35.65–56.16) vs 74.84 (40.66–109.02)	0.12
Splenectomy	111.85 (91.73–131.97) vs 129.38 (91.55–167.20)	0.96	46.93 (32.72–61.14) vs 54.82 (39.29–70.35)	0.50

DFI: disease-free Interval.
EPM: extrapancreatic resected metastases previously.
TP: total pancreatectomy.

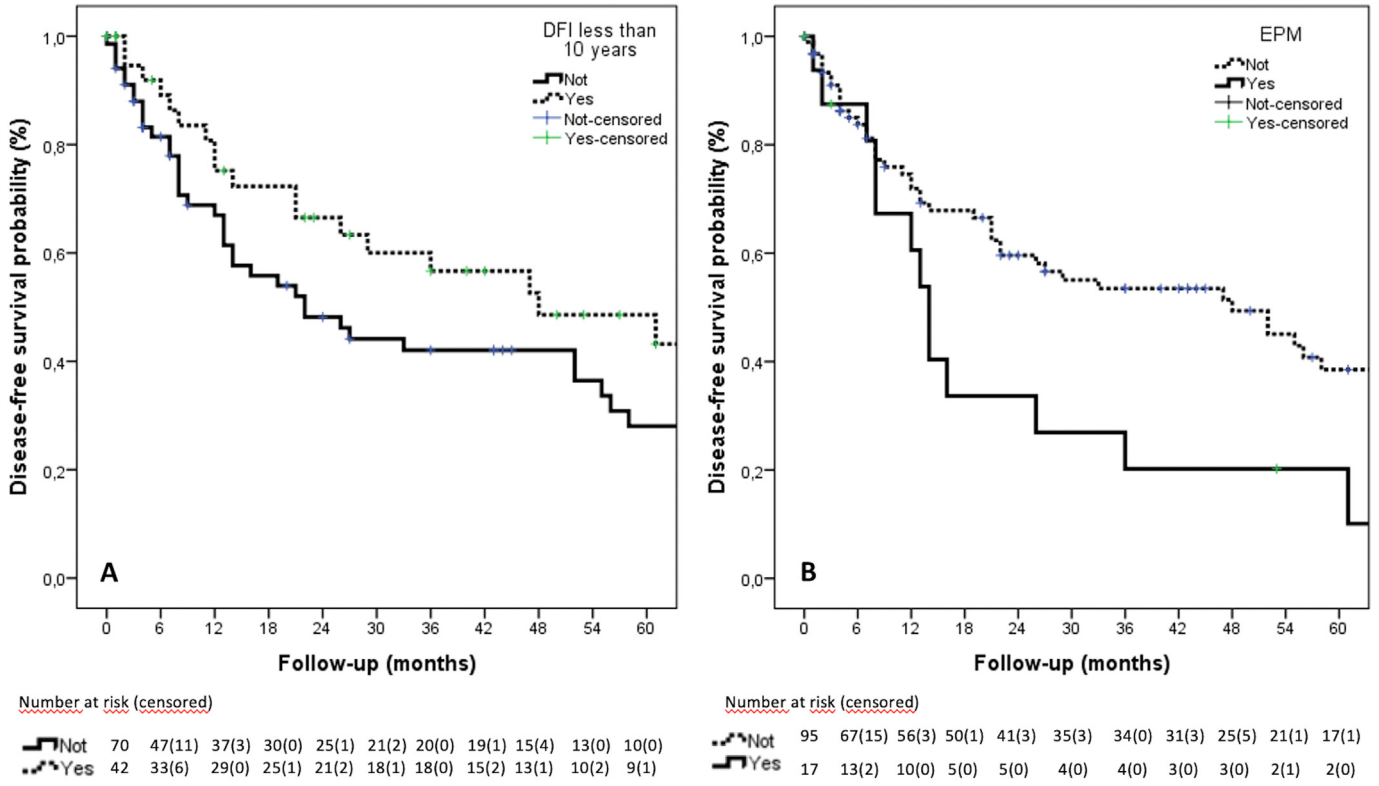

Fig. 2. (A) Kaplan–Meier survival curve of Disease-free survival (DFS) following pancreatic resection grouped by DFI. (B) Kaplan–Meier survival curve of Disease-free survival (DFS) following pancreatic resection grouped by previously resected EPM.
DFI: Disease free interval
EPM: Extrapancreatic metastasis.

In the multivariate analysis, significant factors associated with the OS rate were the disease-free interval (DFI) between the primary tumor and the pancreatic metastasis (1.01 [1.00–1.01], p 0.03), and the type of surgery performed (0.65 [0.45–0.95], p 0.02). Significant prognostic factors of relapse were a DFI of less than 10 years (2.05 [1.13–3.72], p 0.02) and a history of previously resected extrapancreatic metastasis (2.44 [1.22–4.86], p 0.01) (Table 5) (Fig. 2).

4. Discussion

Pancreatic resection due to metastasis is not frequent and RCC is considered the most common primary source [17,18]. The medical literature on pancreatic resection due to metastasis is limited to isolated cases or retrospective series. However, in select patients, there seems to be a benefit to survival when they undergo surgery, especially in cases where RCC is the primary tumor [3,7,19–21]. However, in select patients, there seems to be a benefit to survival when they undergo surgery, especially in cases where RCC is the primary tumor [3,7,19–21].

Given that most institutions dealing with pancreatic surgery have isolated cases or few cases of pancreatic resection due to metastatic RCC in their series, we decided to carry out a multicenter study for the purpose of gathering a larger number of cases in order to try to draw more solid conclusions. We ended up with 116 patients in our series, who underwent 131 pancreatic resections; however, we have only analyzed cases of first-time pancreatic resection, excluding re-operations. To our knowledge, it is the

largest published series on pancreatic resection due to metastatic RRC to this date.

Pancreatic metastasis from RCC appear after a long follow-up interval, that is 87.35 months in our series (1.51–332.55). This is similar, although somewhat lower, than the interval previously reported by other authors. In a systemic review including 21 articles with more than 5 patients each, for a total of 354 patients, the mean interval for the development of RCC pancreatic metastasis was 105.11 months (0–361.6). A recent study conducted by the University of Verona and Memorial Sloan Kettering Cancer Center, including 69 patients, the mean interval was 109 months. This slow-growing tumor has a peculiar tropism for the pancreas, in that the ratio of metastases increases in a time-dependent manner, reaching a plateau well beyond 10 years from nephrectomy [20,22–24].

When it comes to the characteristics of the primary tumor, most patients had undergone radical resection, with tumors reaching large dimensions, and with no signs of predominance of one side over the other (right 51.8 % vs left 48.2 %), similar to what other authors had observed before [25]. We found no relation in our series between the location of the primary tumor and the location of the metastasis within the pancreas, or with the OS or DFS rates after pancreatic resection either.

These lesions frequently are non-specific, and usually appear as single, asymptomatic tumors, which are often diagnosed by routine imaging tests during follow-up of kidney cancer patients. The described symptoms are non-specific; abdominal pain, gastrointestinal hemorrhage or anemia, weakness, jaundice, and weight loss [19]. Most patients in our series were asymptomatic. Of those who experienced symptoms, the most common was abdominal pain (10.3 %) followed by jaundice and weight loss, although both symptoms were relatively rare (1.7 % of cases).

The type of surgery performed varied widely depending on the location of the tumor, with PD being the one seen more often. Atypical resection was performed in just 5 patients (4.3 %), which differs from other studies in which this rate has been higher [19,20].

The postoperative morbidity rate was 60.9 %. Despite the high rate, it should be noted that only 14 % of patients had major complications and that the medical literature registers the rate of complications somewhere between 12.5 % and 61.9 % [21,26]. Postoperative pancreatic fistula was the most common complication, as is the norm for patients undergoing pancreatic resection [15]. Postoperative mortality rate (within 90 days) was 3.5 %, which is within the range found in literature (0%–12.5 %) [27,28].

The five-year OS after pancreatic metastasis resection is greater than 50 % (22–88 %), according to literature [19]. In our series, the OS rate at the 1, 3, and 5-year mark was 96 %, 88 %, and 83 %, respectively, and the DFS rate at 1, 3, and 5 years was 73 %, 49 %, and 35 %, respectively.

We have not established any connection between the location within the pancreas and the long-term prognosis. As for the type of surgery performed, we have been able to verify that the existence of multiple pancreatic metastases does not warrant a total pancreatectomy, as long as the tumors are removed through a less radical surgery; when we looked at the patients in our series with multiple lesions and lesions in different pancreatic regions, we found no difference in the OS based on whether a total pancreatectomy was performed in the first intervention or not (p 0.686). No differences were observed in the DFS either. In none of the patients who had multiple pancreatic lesions in different regions and underwent pancreas-sparing surgery did we observe recurrence in the remaining pancreas during follow-up. Therefore, we are arguing that a total pancreatectomy is not required to prevent recurrence. In a recent article on total pancreatectomy for pancreatic cancer, the authors conclude that there are no differences in survival between patients in whom total pancreatectomy is performed and those in whom part of the pancreas is preserved; however, the quality of life is better among the latter [29].

Resection of other organs in addition to pancreatic resection was not common in our series, but one could argue that, as long as a radical treatment is feasible, it could be warranted, as demonstrated by one recent systemic review of a case of a pancreatic tumor and confirmed by other authors [30–32].

OS after pancreatic resection has been prolonged spanning to 105 (91.56–118.43) months, with OS rates at 1, 3, and 5 years at 96 %, 88 %, and 83 % respectively, one of the highest we have found in literature. In a recent systematic review, the 3 and 5-year OS was 69.3%and 53.9 %, respectively [19]. Other authors have also reported somewhat lower OS rates, though prolonged [25]. In contrast, an Italian multicentric study analyzed the results of 44 patients who underwent a pancreatic resection versus 59 patients who received tyrosine kinase inhibitor (KTI) therapy concluding that surgery did not improve survival [33]. It is worth noting that the side effects of prolonged treatment would be avoided with resection. In addition, surgery increases the chances of having a prolonged DFS, something that is not attainable with systemic treatment. Therefore, with a longer follow-up of patients, the OS is expected to increase [19].The Malleo et al. [20] study analyzed the survival of patients with greater than 10 years of follow-up, and concludes that the 10-year cumulative incidence of disease-specific death was 25.5 %. The DFI between the primary tumor resection and the finding of pancreatic metastasis has shown to have an impact on OS in our series ($p = 0.03$), as well as in other published studies, such as the one by Alzahrani et al. [34], which determined that the 94-month mark was the cutoff point. In terms of the DFS, one of the significant factors we found was the presence of previously-treated extrapancreatic metastases (EPM) before the development of pancreatic metastasis, with a DFS of 24.9 (11.6–38.2) vs 56.6 (43.8–69.4) months ($p = 0.013$). Other authors have established a similar relation; for example, Swartz et al. [25], in a French-Belgian multicenter study with 62 patients, found that lymph node involvement and the existence of EPM before pancreatic metastasis were associated with poor OS. For patients with N0, Nx, or N + status, 5-year OS rates were 70 %, 55 %, and 33 %, respectively, while 10-year OS rates were 48 %, 26 %, and 0%, respectively ($p = 0.009$). Prognosis was impacted in cases of EPM before pancreatic metastases, with 5 and 10-year OS rates of approximately 25 % and 12%, respectively ($p = 0.03$). In our series, 70.7 % of patients underwent a lymphadenectomy. We did not establish a significant connection between the OS and lymph node involvement, although only 3.4 % of our patients experienced lymphatic infiltration. Most clinical series previously published indicate that lymph node involvement in metastatic pancreatic malignancy is unusual [4,35,36]. However, in the aforementioned Swartz el al. series, lymph node involvement was not rare, affecting 27 % of patients.

Our study has some limitations: It is a retrospective series, which could mean occasionally missing some information and follow-up. Since the series encompasses many institutions, most of them have included less than 3 cases. Additionally, since our study looks at an extended period of time, we could not assess the role of more recent drugs in patient survival.

5. Conclusions

Pancreatic resection if metastatic renal cell carcinoma is found in the pancreas is warranted in select cases to achieve higher overall survival and disease-free survival, even if extrapancreatic metastases were previously removed.

The existence of intrapancreatic multifocal compromise does

not always warrant the performance of a total pancreatectomy in order to improve survival.

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Data statement

I confirmed that the relevant data is real and you can get them by consulting correspondence author.

Ethical approval

The study was approved by the Ethical Committee of our institution.

CRediT authorship contribution statement

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Declaration of competing interest

All authors state that they have no conflict of interest.

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