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Repeated pancreatic resection for pancreatic metastases from renal cell Carcinoma: A Spanish multicenter study (PANMEKID)

Adela Rojas-Holguín [a,b], Constantino Fondevila-Campo [c,ab], Alfonso Sanjuanbenito [d], Joan Fabregat-Prous [e], Luís Secanella-Medayo [e], Fernando Rotellar-Sastre [f], Fernando Pardo-Sánchez [f], Mikel Prieto-Calvo [g], Héctor Marín-Ortega [i], Santiago Sánchez-Cabús [h], Luis Diez-Valladares [i], Óscar Alonso-Casado [j], Carmen González-Serrano [k], Juan Carlos Rodríguez-Sanjuan [l], Gabriel García-Plaza [m], Isabel Jaén-Torrejimeno [b], Miguel Ángel Suárez-Muñoz [n], Antonio Becerra-Massare [o], Paula Senra-del Rio [p], Elizabeth Pando [q], Rafael López-Andújar [r,s], Elena Muñoz-Forner [t], Mario Rodriguez-López [u], Fernando Pereira [v], Alejandro Serrablo-Requejo [w], Víctor Sánchez Turrión [x], Manuel Jiménez Garrido [x], Fernando Burdío [y], Elena Martín-Pérez [z], Rafael Estevan-Estevan [aa], Diego López-Guerra [a,b], José Castell-Gómez [ab], Javier Salinas-Gómez [ab], José Ángel López-Baena [ac], Santiago López-Ben [ad], Lorena Solar-García [ae], Alejandro J. Pérez-Alonso [o,af], Luis Alberto Martínez-Insfran [ag], Juan Luis Blas [ah], Marian Cornejo [ai], Alberto Gutierrez-Calvo [aj], Carlos Domingo-del Pozo [ak], Federico Ochando-Cerdan [al], Luis Muñoz-Bellvís [am], José Rebollar-Saenz [an], Belinda Sánchez [ao], José María Jover [ap], Miguel Ángel Gómez-Bravo [aq], José M. Ramia [s,ar], Gerardo Blanco-Fernández [a,b,*]

[a] Universidad de Extremadura, Departamento de Terapeútica Médico Quirúrgica, Facultad de Medicina y Ciencias de la Salud, Badajoz, Spain
[b] Department of HBP Surgery and Liver Transplantation, Hospital Universitario de Badajoz, Badajoz, Spain
[c] Department of Surgery, Hospital Clinic, Barcelona, Spain
[d] Department of Surgery, Hospital Universitario Ramón y Cajal, Madrid, Spain
[e] Department of Surgery, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Spain
[f] Department of Surgery, Clínica Universitaria de Navarra, Pamplona, Spain
[g] Department of Surgery, Hospital Universitario Cruces, Baracaldo, Spain
[h] Department of Surgery, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[i] Department of Surgery, Hospital Clínico Universitario San Carlos, Madrid, Spain
[j] Department of Surgery, MD Anderson Cancer Center Madrid, Spain
[k] Department of Surgery, Hospital Universitario Basurto, Bilbao, Spain
[l] Department of Surgery, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[m] Department of Surgery, Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain
[n] Department of Surgery, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain
[o] Department of Surgery, Hospital Universitario Virgen de las Nieves, Granada, Spain
[p] Department of Surgery, Hospital Alvaro Cunqueiro, Vigo, Spain
[q] Department of Hepato-pancreato-biliary and Transplant Surgery, Hospital Universitario Vall d'Hebron, Barcelona, Spain
[r] CIBERehd, Instituto de Salud Carlos III, Madrid, Spain
[s] Hepatology, HBP Surgery and Transplants, IIS La Fe, Hospital La Fe, Valencia, Spain
[t] Department of Surgery, Hospital Clínico Universitario de Valencia, Valencia, Spain
[u] Department of Surgery, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
[v] Department of Surgery, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain
[w] Department of Surgery, Hospital Universitario Miguel Servet, Zaragoza, Spain
[x] Department of Surgery, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain
[y] Department of Surgery, Hospital del Mar, Barcelona, Spain

* Corresponding author. Universidad de Extremadura, Departamento de Terapeútica Médico Quirúrgica, Facultad de Medicina y Ciencias de la Salud, Avda de Elvas s/n, 06006, Badajoz, Spain.
E-mail address: gerardoblanco@unex.es (G. Blanco-Fernández).

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[z] Department of Surgery, Hospital Universitario de La Princesa, Madrid, Spain
[aa] Department of Surgery, Fundación Instituto Valenciano de Oncología, Valencia, Spain
[ab] Department of Surgery, Hospital Universitario La Paz, Madrid, Spain
[ac] Department of Surgery, Hospital Gregorio Marañon, Madrid, Spain
[ad] Department of Surgery, Hospital Universitari Dr Josep Trueta, Girona, Spain
[ae] Department of Surgery, Hospital Universitario Central de Asturias, Oviedo, Spain
[af] Department of Surgery, Complejo Hospitalario de Jaén, Jaén, Spain
[ag] Department of Surgery, Hospital Universitario San Juan de Alicante, Alicante, Spain
[ah] Department of Surgery, Hospital Royo Villanova, Zaragoza, Spain
[ai] Department of Surgery, Hospital Marina Baixa, Villajoyosa, Alicante, Spain
[aj] Department of Surgery Hospital Universitario Principe de Asturias. Alcalá de Henares, Madrid, Spain
[ak] Department of Surgery, Hospital Dr. Peset, Valencia, Spain
[al] Department of Surgery, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain
[am] Department of Surgery, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain
[an] Department of Surgery, Hospital Universitario de Álava, Álava, Spain
[ao] Department of Surgery, Hospital Regional de Málaga, Málaga, Spain
[ap] Department of Surgery, Hospital Universitario de Getafe, Getafe, Madrid, Spain
[aq] Department of Surgery, Hospital Universitario Virgen del Rocío, Sevilla, Spain
[ar] Department of Surgery, Hospital General Universitario de Alicante, Alicante, Spain

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ABSTRACT

Background and objectives: Recurrent isolated pancreatic metastasis from Renal Cell Carcinoma (RCC) after pancreatic resection is rare. The purpose of our study is to describe a series of cases of relapse of pancreatic metastasis from renal cancer in the pancreatic remnant and its surgical treatment with a repeated pancreatic resection, and to analyse the results of both overall and disease-free survival.

Methods: Multicenter retrospective study of patients undergoing pancreatic resection for RCC pancreatic metastases, from January 2010 to May 2020. Patients were grouped into two groups depending on whether they received a single pancreatic resection (SPS) or iterative pancreatic resection. Data on short and long-term outcome after pancreatic resection were collected.

Results: The study included 131 pancreatic resections performed in 116 patients. Thus, iterative pancreatic surgery (IPS) was performed in 15 patients. The mean length of time between the first pancreatic surgery and the second was 48.9 months (95 % CI: 22.2–56.9). There were no differences in the rate of postoperative complications. The DFS rates at 1, 3 and 5 years were 86 %, 78 % and 78 % vs 75 %, 50 % and 37 % in the IPS and SPS group respectively ($p = 0.179$). OS rates at 1, 3, 5 and 7 years were 100 %, 100 %, 100 % and 75 % in the IPS group vs 95 %, 85 %, 80 % and 68 % in the SPS group ($p = 0.895$).

Conclusion: Repeated pancreatic resection in case of relapse of pancreatic metastasis of RCC in the pancreatic remnant is justified, since it achieves OS results similar to those obtained after the first resection.

1. Introduction

Among the lesions that may occur in the pancreas, metastases are relatively rare; the rates range from 2 % to 5 % of all malignancies found in this organ [1–4]. As for the types of cancer known to produce pancreatic metastases, renal cell carcinomas (RCC) are by some distance the most common [5], followed by colorectal cancer, melanomas, sarcomas, and lung cancer [6]. Often lesions are discovered incidentally or during follow-up, and patients remain asymptomatic. Secondary tumors may develop many years after the initial diagnosis and treatment of the primary cancer; therefore, the possibility of a secondary tumor should be considered when a patient with a history of cancer presents with an isolated pancreatic mass. Although pancreatic metastases of non-renal malignancies are typically only seen when patients have generalized systemic disease, RCCs frequently spread to the pancreas alone, and are thus susceptible to surgical resection [7].

Surgical treatment in cases of isolated metastases in the pancreas has shown very favorable results for overall and disease-free survival [8,9]. When the disease recurs after pancreatic resection, it usually disseminates and is found in other organs such as the lung; in exceptional cases it may recur in the pancreatic remnant [8]. The scientific evidence available on treatment in cases of isolated pancreatic recurrence is very limited. The objective of the present study is to describe a series of cases of relapse of pancreatic metastasis from renal cancer in the pancreatic remnant and its surgical treatment with an iterative pancreatic resection, and to analyse the results of both overall and disease-free survival.

2. Material and methods

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 undergoing surgery for pancreatic metastasis of renal cancer confirmed by postoperative histopathological study. Exclusion criteria: Patients with other pathological diagnoses and patients who underwent any additional organ resections.

Each participating center appointed a local manager responsible for data collection and for liaising with the general study coordinator. All the data were recorded by this local manager. Researchers collected information from electronic health records, while 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 ethics committees of the other hospitals. Patients' informed consent was not required since the study was retrospective and observational, and entailed no risk.

2.1. Preoperative assessment

The diagnostic management procedure comprised a medical history, clinical examination, imaging tests (computerized tomography, CT), to confirm the tumor location in the pancreas and its size, and to assess any possible infiltration of adjacent structures. An abdominal MRI was also performed in case of doubt. In addition, these tests ruled out the possibility of distant metastases, and evaluated resectability and the

feasibility of reconstruction, depending on the location.

2.2. Definitions

The surgical procedure performed was pancreaticoduodenectomy (PD), either classic or with preservation of the pylorus [10,11], distal pancreatectomy (DP), total pancreatectomy (TP), or other pancreas-sparing resections such as local excision or central pancreatectomy.

The resection margins of the specimen were classified according to the Royal College of Pathologists' definitions: R0 (margin to tumor ≥ 1 mm), R1 (margin to tumor < 1 mm), and R2 (macroscopically positive margin) [12]. Complications at 90 days were assessed with the Clavien-Dindo (CD) classification, and those rated as grade IIIa or above were defined as major [13]. Complications were assessed on the basis of the medical and nursing notes in the patients' electronic records. Complications specific to pancreatic surgeries were defined using the criteria of the International Study Group on Pancreatic Surgery (ISGPS) as delayed gastric emptying [14], post-pancreatic hemorrhage [15], bile leak [16], and pancreatic fistula [17].

Follow-up regimen: Long-term patient follow-up included a general physical examination and chest-abdomen-pelvis CT scan four times a year in the first two years, twice a year until five years, and once a year thereafter. Local recurrence was defined as the reappearance of a tumor inside the surgical field or regional lymph nodes, and systemic recurrence as reappearance at a different site.

2.3. Variables

The following variables were assessed:

Primary tumor-related variables: Date of resection, size (cm), side (left or right), Fuhrman classification [18]. Epidemiological variables: sex, age, past medical history, medication, the American Society of Anesthesiologists (ASA) Classification. Clinical variables: symptoms. Diagnostic variables: serological tests: hemoglobin (gr/dl), neutrophils, leukocytes, lymphocytes, platelets, LDH, albumin (g/dl), bilirubin (mg/dl), ALT (U/L), AST (U/L), calcium (mg/dL). Radiological and endoscopic diagnostic tests performed, preoperative biliary drainage (when necessary), and preoperative biopsy. Variables related to the first intervention to treat the pancreatic metastasis: size, location inside the pancreas, presence of a single or multiple lesion(s), involvement of more than one pancreatic region(s), surgical procedure (type of resection and reconstruction), and intraoperative complications. With regard to the postoperative course, morbidity (according to the Clavien-Dindo Classification) and mortality rates, re-operation, length of hospital stay, re-admission, and operative mortality (i.e., up to 90 days post-surgery). The histological data recorded were: TNM, tumor size and lymph nodes harvested, R status, and degree of differentiation. With regard to the surgical intervention to treat the pancreatic recurrence, the same variables as for the first pancreatic resection were recorded.

The most salient long-term data recorded included time of recurrence, overall and disease-free survival, cause of death and post-operative follow-up (in months).

2.4. Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables were analysed for Gaussian distribution using the Shapiro-Wilk test; normally distributed variables are presented as means and standard deviations (SD), and non-normally distributed variables as medians and interquartile ranges (IR). The Chi-squared test or Fisher's exact probability test was applied to compare categorical variables. Non-parametric tests were used to compare medians.

Kaplan-Meier survival analysis was used to model all-cause mortality and relapse-free survival post-surgery.

Data were analysed using IBM SPSS v22.0. A ¨p¨ level of 0.05 was considered significant.

3. Results

One hundred and thirty-one pancreatic resections performed in 116 patients were included in the study. Thus, iterative pancreatic surgery (IPS) was performed in 15 patients (six men and nine women). The median age was 70 years (IQR 70–77). All other demographic data are recorded in Table 1.

Characteristics of the primary tumor and first metastatic disease are recorded in Table 1. In 12 of the 15 patients who underwent IPS, the primary tumor was more frequently located on the left side than in patients who had undergone a single surgery (80 % vs 43.3 %, $p = 0.008$). Radical nephrectomy had been performed in all patients.

The median length of time between nephrectomy and the first resection for pancreatic metastasis was 98.7 months (IQR: 80.9–166.5) and between the first pancreatic surgery and the second 48.9 months (IQR: 22.2–56.9).

As for the type of surgery performed, three patients underwent enucleation, six distal pancreatectomy and the other six pancreaticoduodenectomy. The approach was open surgery in all cases.

Most patients were asymptomatic at the time of diagnosis of the pancreatic metastasis. In most cases the metastasis was detected incidentally during follow-up of their cancer. Only one patient (6.7 %) presented weight loss.

After the first pancreatic resection, the resection margin was R0 in 10 patients, R1 in one, and not described in four.

The appearance of the first pancreatic metastasis was in the head/uncinate process in 27 cases (26.7 %) in the single pancreatic surgery (SPS) group vs 8 cases (53.3 %) in the IPS group ($p = 0.04$). Other variables analysed in relation to the first pancreatic surgery in both groups of patients are presented in Table 2. Postoperative morbidity was observed in 40 % of cases compared with 60.9 % of cases after the first pancreatic resection ($p = 0.314$). Pancreatic fistula was observed in one case and hemorrhage in two. No biliary fistulas were observed. Complications according to the Clavien-Dindo classification after the first and second pancreatic resection are presented in Table 3.

The 90-day postoperative mortality rate was 0 % in patients with iterative resection, compared with 3.5 % after the first pancreas resection ($p = 0.628$).

The median disease-free survival (DFS) time after pancreatic resection was 33 months (95 % CI: 10.86–55.13) in the SPS group compared with 84 months (95 % CI: 0–176.14, $p = 0.195$) in the IPS group (After last pancreatic resection). The DFS rates at 1, 3 and 5 years were 86 %, 78 % and 78 % in the IPS group vs 75 %, 50 % and 37 % in the SPS group ($p = 0.179$) (Fig. 1).

Overall survival (OS) after the first pancreatic resection presented a median of 106 months (95 % CI: 90.7–121.2). In the IPS group (after the first pancreatic resection) it was 116.4 months (95 % CI: 92.7–139.6) and in the SPS group (After the single pancreatic resection) 102.4 months (95 % CI: 82–122.9); $p = 0.07$ (Fig. 2). Median OS after the last pancreatic resection surgery was 85 months (95 % CI 64–105.9) in the IPS group (Fig. 3). OS rates at 1, 3, 5 and 7 years were 100 %, 100 %, 100 % and 75 % in the IPS group vs 95 %, 85 %, 80 % and 68 % in the SPS group ($p = 0.895$) (Fig. 3).

4. Discussion

The literature on pancreatic metastases is scarce and is normally limited to the reporting of isolated cases or retrospective series with a small number of patients. However, in selected patients, surgical resection of metastases seems to have an impact on survival, especially if the primary tumor is an RCC [3,6,8,9,19–21]. After resection of the pancreatic metastasis, recurrence in the pancreas is extremely rare; there are very few reports in the literature of iterative pancreatic resection in cases of recurrence of pancreatic metastasis of renal origin

Table 1
Patient characteristic.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Age (yrs)	73	51	61	76	70	80	72	79	78	70	70	82	77	70	67
Sex	F	M	M	M	F	F	F	M	F	F	M	F	F	M	F
Symptomatic	–	–	No	Yes	No	–	No	No	No	No	No	No	No	No	–
Localitation in pancreas	Multifocal	Body-tail	Head-uncinate	Head-uncinate	Head-uncinate	Body-Tail	Head-uncinate	Head-uncinate	Head-uncinate	Body-Tail	Head-uncinate	Body-Tail	Body-Tail	Head-uncinate	Body-Tail
Primary tumor size (mm)	80	120	120	35	90	70	–	160	–	76	40	–	80	–	90
Localitation	Left	Left	Left	Right	Left	Left	Left	Left	Left	Left	Left	Left	Right	Left	Right
Secondary metastasis size (mm)	–	70	7	8	25	–	20	10	35	–	8	9	11	–	5
First surgery	PD	DP	DP	DP	DP	PD			DP						
Second surgery	DP	DP	PD	PD	PD	DP	PD	Enuc	PD	DP	Enuc	DP	DP	PD	Enuc
Surgical approach	Open	Open	Open	Open	Open	Open	Open	Open	Open	Open	Open	Open	Open	Open	Open
Reintervention	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No
Postoperative morbidity (Clavien- Dindo score)	No	–	IIIa	No	IIIb	–	–	II	No	–	No	No	II	–	No
Postoperative stay (days)	6	–	17	10	–	–	9	13	–	–	9	6	14	–	7
Relapse	No	Yes (multiple)	Yes (Lung)	No	No	Yes (Liver)	No	Yes (Kidney)	No	Yes	No	No	No	Yes (Lung)	No
Disease- free survival (months)	21.03	2.04	62.82	39.20	0.56	19.78	45.50	10.94	1.84	94.29	25.20	30.26	36.99	84.96	41.20
Overall survival (months)	21.03	71	65.87	39.20	0.56	84.11	80.03	50.94	1.84	94.29	25.20	30.26	36.99	84.96	41.20
Status	NED	DOD	AWD	NED	NED	AWD	NED	NED	NED	DOD	NED	NED	NED	DOD	NED

M: male; F: female; PD: pancreaticoduodenectomy; DP: distal pancreatectomy; Enuc: enucleation; AWD: Alive with disease; NED: No evidence of disease; DOD: Died of disease; DOC: Died of other causes.

Table 2
Comparison of the characteristics of presentation and first pancreatic resection in the two groups of patients.

	SPS group (n = 101) n (%)	IPS Group (n = 15) (n/%)	p
Single nodule inside the pancreas	75 (74.3 %)	13 (86.7 %)	0.518
Isolated metastases	93 (92.1 %)	13 (86.7 %)	0.616
Location on head/uncinate	27 (26.7 %)	8 (53.3 %)	0.305
Synchronous resection of other sites of metastases	8 (7.9 %)	2 (13.3 %)	0.616
Prior systemic treatment	4 (4 %)	1 (1.15 %)	0.385
Vascular resection	3 (3 %)	1 (1.15 %)	0.430
Adjacent organ resection	7 (7 %)	0 (0 %)	0.290
Pancreaticoduodenectomy	26 (25.7 %)	8 (53.3 %)	0.060
Splenectomy	53 (52.5 %)	3 (20 %)	0.019

SPS: Single pancreatic resection; IPS: Iterative pancreatic resection.

Table 3
Postoperative complications.

	First pancreatic resection: n (%)	Iterative pancreatic resection n (%)	p
Clavien Dindo			
I	10 (8.6 %)	0 (0 %)	0.87
II	32 (27.6 %)	2 (13.3 %)	
IIIA	12 (10.3 %)	1 (6.7 %)	
IIIB	11 (9.5 %)	1 (6.7 %)	
IV	1 (0.9 %)	0 (0 %)	
V	4 (3.4 %)	0 (0 %)	
Pancreatic Fistula	28 (24.1 %)	1 (6.7 %)	0.11
Bile Leak	7 (6.0 %)	0 (0 %)	0.42
Hemorrhage	8 (6.9 %)	2 (13.3 %)	0.32
Wound infection	1 (0.9 %)	0 (0 %)	0.89
Surgical Site Infection (Deep)	5 (4.3 %)	0 (0 %)	0.54
Postoperative pancreatic failure (Endocrine and/or exocrine)	3 (2.6 %)	0 (0 %)	0.69

[22–25]. Given that most centers with experience in pancreatic surgery treat only isolated cases, we decided to form a multicenter working group, PANMEKID, to gather together our experience of resection surgery for pancreatic metastases of renal origin. In our series, the results obtained after resection in these patients, excluding cases of iterative surgery, were very encouraging: the OS rates at the 1, 3, and 5-year marks were 96 %, 88 %, and 83 % respectively, and the DFS rates at 1, 3, and 5 years were 73 %, 49 %, and 35 % [8]. In view of these positive results, our objective was to analyse whether good survival rates could be obtained after iterative pancreatic surgery in cases of metastatic relapse in the pancreatic remnant. Although not very numerous, to our knowledge, this is the largest series of cases of repeated resection due to pancreatic metastases of renal origin published in the literature. Our series comprised 15 patients who underwent IPS, representing 12.9 % of the total patients in the multicenter series. This rate seems significant to us and argues in favor of surgical treatment in these patients, given its curative potential.

Compared with the SPS group, the IPS group presented a greater number of cases of primary tumor located in the left kidney (80 % vs 43.3 %, p = 0.008). We do not have an explanation for this finding, since previous reports have not indicated an influence of the laterality of the primary tumor on the presentation of pancreatic metastasis [8,26].

In our series, the mean time between nephrectomy and first pancreatic metastasis resection was 98.7 months (IQR: 80.9–166.5) and between the first pancreatic surgery and the second 48.9 months (IQR: 22.2–56.9). The disease-free interval from the primary tumor to pancreatic resection has been shown to have a prognostic value [8,27]. In our previous study, this interval was 87.35 months [8]. The long interval between the primary tumor and the appearance of metastasis

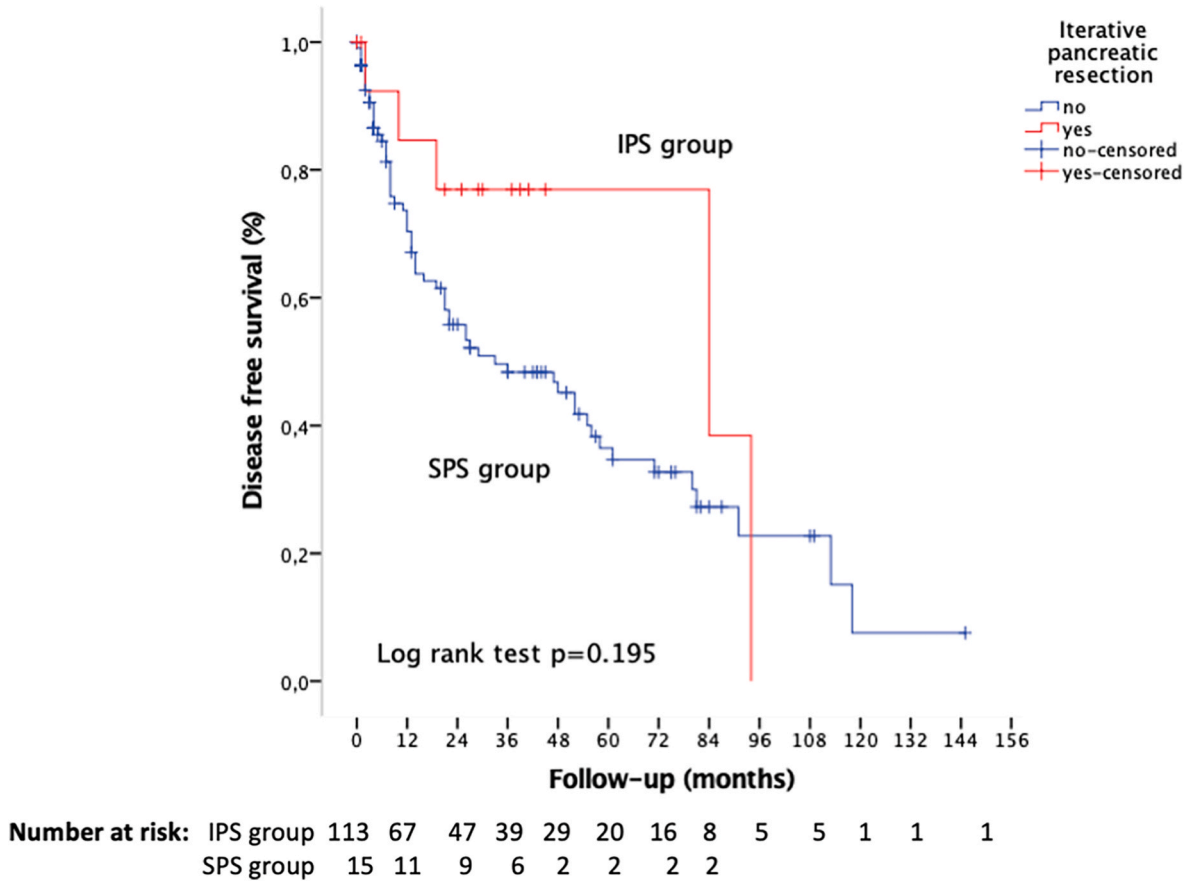

Fig. 1. Disease-free survival after pancreatic resection according to whether patients underwent a single pancreas resection or iterative surgeries.

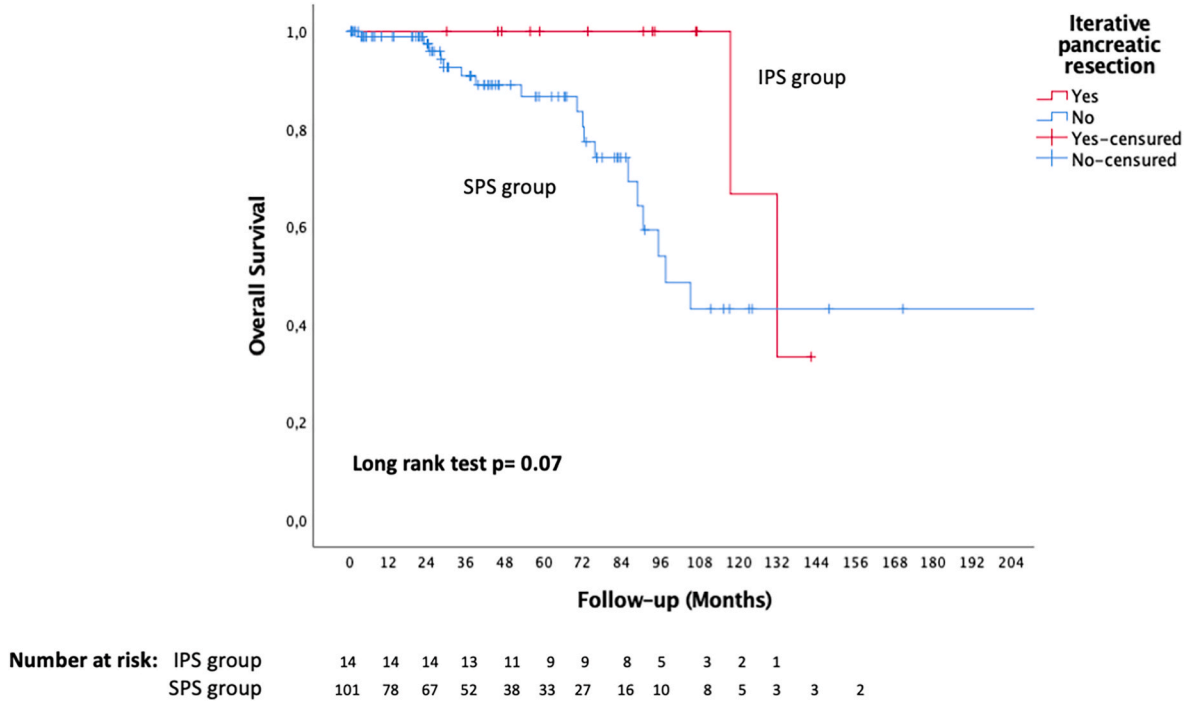

Fig. 2. Overall Survival after first pancreatic resection according to whether patients underwent a single pancreas resection or iterative surgeries.

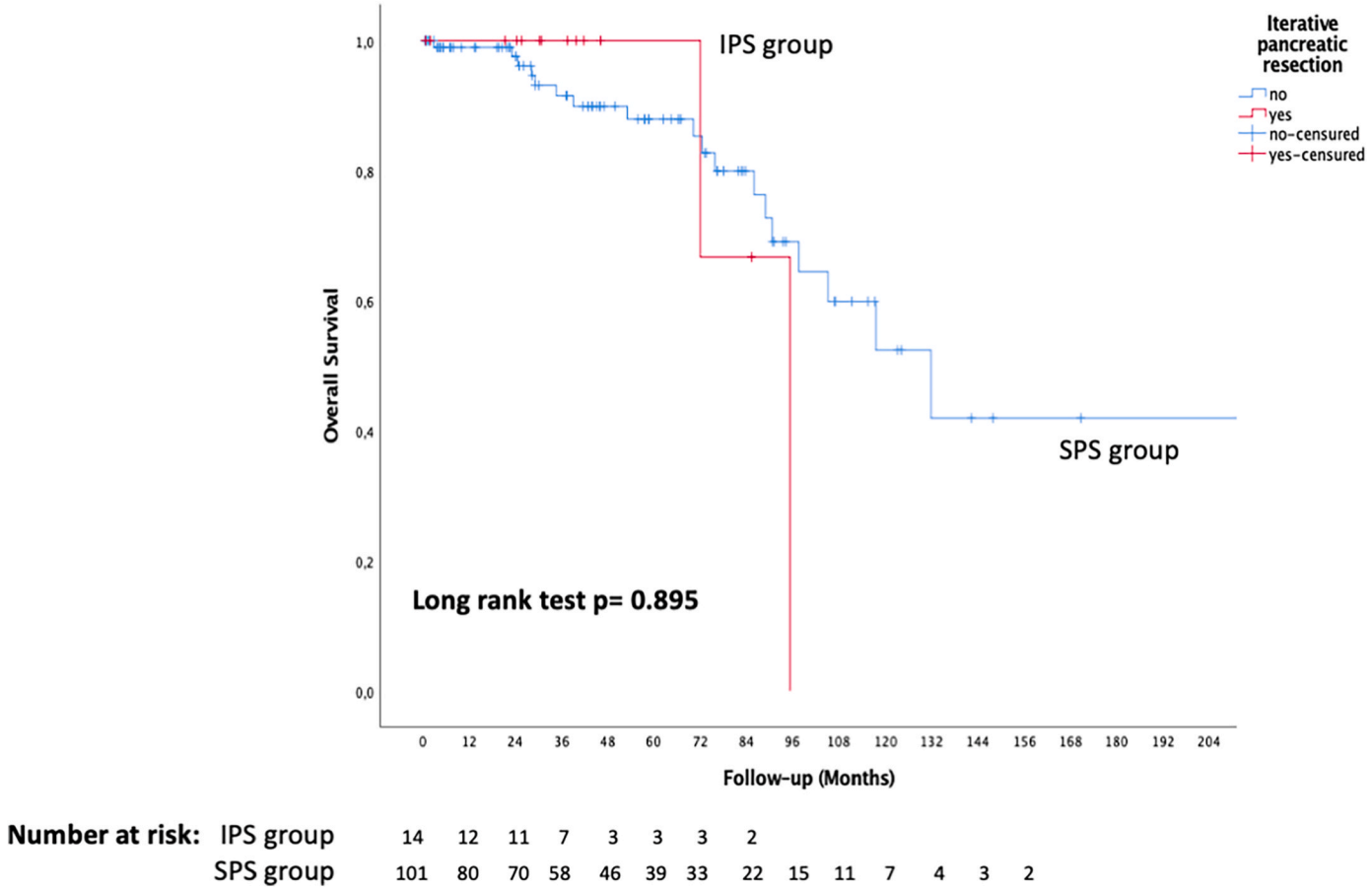

Fig. 3. Overall Survival after last pancreatic resection according to whether patients underwent a single pancreas resection or iterative surgeries.

suggests a favorable tumor biology, which may also explain the existence of a long period between the first pancreatic surgery and the second (48.9 months, IQR: 22.2–56.9. Other authors who have reported cases of repeated pancreatic resection have also reported intervals of up to nine years between the first and second pancreatic resection [23]. In most cases the first pancreatic resection was R0 and therefore the relapse could not generally be attributed to an incomplete resection. In a recent systematic review, the authors found three patients out of 44 who had local pancreatic recurrence after primary enucleation (25). In all patients, the recurrence was distant from the previous enucleation and the initial enucleation was R0; the authors hypothesized that the recurrence might have been undetected residual disease and that intraoperative ultrasound might have helped prevent the complication. We grant that this may occur in some cases but, given the long interval until relapse, undetected synchronous disease is high unlikely; most cases will be a metachronous recurrences.

The choice of surgery performed is determined by the previous pancreatic resection, the location of the lesion within the pancreatic remnant, and the number of nodules (one or more). In our series, PD was performed in six cases, DP in six more, and enucleation in the remaining three. The use of enucleation in these patients is controversial. In a review including 56 patients who underwent enucleation for pancreatic metastases of renal origin, Brozzetti et al. [25] concluded that this procedure obtained similar figures of overall and disease-free survival and lower rates of postoperative morbidity and mortality compared with standard resections. However, these same authors argue against enucleation for cases of recurrent pancreatic metastases given the high relapse rate (4 out of 7 patients) [25]. The main rationale for its implementation would be to improve the quality of life due to the avoidance of endocrine and/or exocrine pancreatic insufficiency. One might also assume that avoiding resection using PD or DP in a previously operated patient would be associated with less morbidity, given that repeated surgery on the pancreas is a challenge and requires extensive experience. However, in our analysis, we did not find higher rates of complications or mortality than after the first pancreatic resection. In the literature there are few studies with large series that have analysed this issue [28–30]. Müller et al. reported higher mortality rates in patients who underwent primary total pancreatectomy (6 %) than in those who underwent elective total pancreatectomy after pancreatic head or tail resection (0 %), while the surgical morbidity rates were similar (25 % vs. 20.8 %) [31]. Similarly, in a series of 114 patients included in a project run by the Japanese Society of Hepato-Biliary-Pancreatic Surgery, highly promising results were found after the resection for recurrent pancreatic cancer in the pancreatic remnant after pancreatectomy, with Clavien-Dindo morbidity rates of III or higher in only 8.9 % of patients, and a 90-day mortality rate of 1.1 % [30].

The prognosis of patients undergoing repeated resection of pancreatic metastases of renal origin in our series was excellent, with a median overall survival of 85 months (95 % CI 64–105.9) months. Rates of OS at 1, 3, 5, and 7 years were 100 %, 100 %, 100 % and 75 % respectively. These figures are somewhat lower than the rates obtained after resection of the SPS group in which the median survival was 102.4 months (95 % CI: 82–122.9), although the differences were not statistically significant. However, these rates are similar or even somewhat higher than those published by other authors for pancreatic resection due to renal cancer metastasis in general. In their systematic review of this entity, Jaen-Torrejimeno et al. found that the 3 and 5-year OS rates were 69.3 % and 53.9 % respectively [19]. In another recent systematic review that studied the results obtained after the enucleation of pancreatic metastases of renal origin, the authors reported overall survival figures of 91

% at 3 and 5 years; they did not assess the issue longer than 5 years due to the low number at risk and the high disease-free survival rates of 78 % and 64 % at 3 and 5 years respectively, excluding patients with repeated resection [25]. In our series, the median DFS after pancreatic resection was 33 months (IQR: 10.86–55.13) in the SPS group compared with 84 months (IQR: 0–176.14, p = 0.195) in the IPS group (after the last pancreatic resection). This indicates that relapse in the pancreas alone may occur later than in other organs and could be patients with a more favorable tumor biology.

Our study has some limitations, above all the small sample size and the retrospective design. This may mean that some information during follow-up may be missing. The participation of a large number of institutions may also mean that the criteria used for indicating repeated resection of the pancreas were not homogeneous. Additionally, since our study looks at an extended period of time, we were unable to assess the effect of more recent drugs on patient survival and so we did not take into account the role of systemic treatment. However, given the small number of reported cases of repeated resection, we consider that our series contributes useful information on this topic.

5. Conclusions

Repeated pancreatic resection in case of relapse of pancreatic metastasis of renal origin in the pancreatic remnant is justified, since. It achieves overall survival results similar to those obtained after the first resection.

Conflicts of interest

None.

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Data statement

The data that support the findings of this study are available on request from the corresponding author.

Ethical approval

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

CRediT authorship contribution statement

Adela Rojas-Holguín: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Constantino Fondevila-Campo:** Data curation, Writing – review & editing. **Alfonso Sanjuanbenito:** Data curation, Writing – review & editing. **Joan Fabregat-Prous:** Data curation, Writing – review & editing. **Luís Secanella-Medayo:** Data curation, Writing – review & editing. **Fernando Rotellar-Sastre:** Data curation, Writing – review & editing. **Fernando Pardo-Sánchez:** Data curation, Writing – review & editing. **Mikel Prieto-Calvo:** Data curation, Writing – review & editing. **Héctor Marín-Ortega:** Data curation, Writing – review & editing. **Santiago Sánchez-Cabús:** Data curation, Writing – review & editing. **Luis Diez-Valladares:** Data curation, Writing – review & editing. **Óscar Alonso-Casado:** Data curation, Writing – review & editing. **Carmen González-Serrano:** Data curation, Writing – review & editing. **Juan Carlos Rodríguez-Sanjuan:** Data curation, Writing – review & editing. **Gabriel García-Plaza:** Data curation, Writing – review & editing. **Isabel Jaén-Torrejimeno:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Miguel Ángel Suárez-Muñoz:** Data curation, Writing – review & editing. **Antonio Becerra-Massare:** Data curation, Writing – review & editing. **Paula Senra-del Rio:** Data curation, Writing – review & editing. **Elizabeth Pando:** Data curation, Writing – review & editing. **Rafael López-Andújar:** Data curation, Writing – review & editing. **Elena Muñoz-Forner:** Data curation, Writing – review & editing. **Mario Rodriguez-López:** Data curation, Writing – review & editing. **Fernando Pereira:** Data curation, Writing – review & editing. **Alejandro Serrablo-Requejo:** Data curation, Writing – review & editing. **Víctor Sánchez Turrión:** Data curation, Writing – review & editing. **Manuel Jiménez Garrido:** Data curation, Writing – review & editing. **Fernando Burdío:** Data curation, Writing – review & editing. **Elena Martín-Pérez:** Data curation, Writing – review & editing. **Rafael Estevan-Estevan:** Data curation, Writing – review & editing. **Diego López-Guerra:** Data curation, Writing – review & editing. **José Castell-Gómez:** Data curation, Writing – review & editing. **Javier Salinas-Gómez:** Data curation, Writing – review & editing. **José Ángel López-Baena:** Data curation, Writing – review & editing. **Santiago López-Ben:** Data curation, Writing – review & editing. **Lorena Solar-García:** Data curation, Writing – review & editing. **Alejandro J. Pérez-Alonso:** Data curation, Writing – review & editing. **Luis Alberto Martínez-Insfran:** Data curation, Writing – review & editing. **Juan Luis Blas:** Data curation, Writing – review & editing. **Marian Cornejo:** Data curation, Writing – review & editing. **Alberto Gutierrez-Calvo:** Data curation, Writing – review & editing. **Carlos Domingo-del Pozo:** Data curation, Writing – review & editing. **Federico Ochando-Cerdan:** Data curation, Writing – review & editing. **Luis Muñoz-Bellvís:** Data curation, Writing – review & editing. **José Rebollar-Saenz:** Data curation, Writing – review & editing. **Belinda Sánchez:** Data curation, Writing – review & editing. **José María Jover:** Data curation, Writing – review & editing. **Miguel Ángel Gómez-Bravo:** Data curation, Writing – review & editing. **José M. Ramia:** Data curation, Writing – review & editing. **Gerardo Blanco-Fernández:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Guerra, J. Castell-Gómez, J. Salinas-Gómez, J.Á. López-Baena, S. López-Ben, L. Solar-García, A.J. Pérez-Alonso, L.A. Martínez-Insfran, J.L. Blas, M. Cornejo, A. Gutierrez-Calvo, C.D.-D. Pozo, F. Ochando-Cerdan, L. Muñoz-Bellvís, J. Rebollar-Saenz, B. Sánchez, J.M. Jover, M.Á. Gómez-Bravo, J.M. Ramia, A. Rojas-Holguín, Pancreatic metastases from renal cell carcinoma. Postoperative outcome after surgical treatment in a Spanish multicenter study (PANMEKID), Eur. J. Surg. Oncol. 48 (2022) 133–141, https://doi.org/10.1016/j.ejso.2021.08.011.

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