

Surgical resection and survival of clear cell renal cancer metastases to the pancreas

Resección quirúrgica y sobrevida de metástasis de cáncer renal de células claras a páncreas

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Abstract

Introduction: Pancreas is considered one of the organs most frequently affected by recurrence after nephrectomy secondary to renal cell carcinoma reporting an incidence of 20%, 85% of these occur within the first 3 years. **Objective:** The objective of the study is to evaluate overall survival and disease-free survival in patients with renal cancer and pancreatic metastases who underwent surgical treatment. **Methods:** A retrospective cross-sectional study of patients with histological diagnosis of renal cancer associated with pancreatic metastasis was performed and included those treated by pancreatoduodenectomy or distal pancreatectomy during the period 1987-2020. **Results:** 14 patients with pancreatic metastasis were included. Two groups of patients were obtained: those who underwent pancreatic surgery for metastasis and those who did not undergo surgical procedure. According to the location of the metastasis, 71.4% corresponded to a single location and 28.6% to multiple locations. 57.1% underwent Whipple and 42.9% distal pancreatectomy. Survival after the surgical procedure was 1150 days versus 499 days in non-operated patients. **Conclusion:** Pancreatic metastases due to RCC can be curable, improve morbidity, and increase disease-free survival with surgical treatment.

Keywords: Renal cancer. Metastasis. Whipple. Pancreas. Survival. Distal pancreatectomy.

Resumen

Introducción: El páncreas es considerado de los órganos más frecuentemente afectados por recurrencia después de la nefrectomía secundaria a carcinoma de células renales notificándose una incidencia de 20%, 85% de estas ocurren dentro de los primeros 3 años. **Objetivo:** Evaluar la sobrevida general y sobrevida libre de enfermedad en pacientes con cáncer renal y metástasis pancreáticas sometidos a tratamiento quirúrgico. **Métodos:** Se realizó un estudio retrospectivo transversal de pacientes con diagnóstico histológico de cáncer renal asociado a metástasis pancreática y se incluyeron aquellos tratados mediante cirugía de tipo pancreatoduodenectomía o pancreatectomía distal durante el periodo de tiempo 1987-2020. **Resultados:** Se incluyeron 14 pacientes con metástasis a páncreas. Se obtuvieron dos grupos de pacientes: sometidos a cirugía pancreática por metástasis y aquellos que no se les realizó procedimiento quirúrgico. De acuerdo a la localización de la metástasis 71.4% correspondía a ubicación única y 28.6% a ubicación múltiple. Al 57.1% se les realizó Whipple y 42.9% pancreatectomía distal. La sobrevida tras el procedimiento quirúrgico, fue de 1150 días vs. 499 días en no operados. **Conclusión:** Las metástasis a páncreas por CCR pueden ser curables, mejorar la morbilidad y aumentar la sobrevida libre de enfermedad con tratamiento quirúrgico.

Palabras clave: Cáncer renal, metástasis. Whipple. Páncreas. Sobrevida. Pancreatectomía distal.

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Introduction

Metastases that commonly affect the pancreas correspond to renal cell carcinoma (RCC), melanoma, colorectal carcinomas, mammary carcinomas, and sarcomas¹.

RCC accounts for 90% of the different types of cancers that originate in the kidney, encompassing 10 different subtypes, of which clear cell renal cell carcinoma (CCRCC) is the most common and is associated with the highest mortality².

Metastasis of RCC is common, it is present in approximately 25% of patients³, it can extend directly to the ipsilateral adrenal gland or to the adjacent musculature and, not often, to the liver, spleen, colon, and pancreas⁴. Focusing attention on the latter, clinically, secondary neoplasms affecting the pancreas are uncommon, representing 2-5%^{1,5}. It is considered the seventh most common cancer in men and the ninth most common cancer in women worldwide, usually presenting at an average age of 65 years. It is important to diagnose RCC metastasis because it can manifest itself more than a decade after its initial presentation and diagnosis^{1,5}. The pancreas is considered one of the organs most frequently affected by recurrence after nephrectomy secondary to RCC, with an incidence of 20-30%, 85% of which occur within the first 3 years after nephrectomy¹.

As for the clinical presentation, if the lesion is smaller than 2 cm and is well localized in the pancreas, it does not show clinical features that could be suspicious of metastasis to the pancreas. If the lesion is larger, the clinical manifestations are jaundice, weight loss, and pain⁶. Pancreatic lesions are localized after ultrasound, computed tomography (the most important method for making the pre-operative decision, usually a hyperdense lesion), routine magnetic resonance imaging, or positron emission tomography⁷.

The diagnosis of certainty for CCRCC will be by nephrectomy or cytology, for which a fine needle aspiration biopsy guided by endoscopic ultrasound should be performed; often it is not necessary before surgery since the diagnosis is made with imaging studies and clinical history^{7,8}. Histopathologically, CCRCC cells appear as large polygonal cells in clusters or single cells with abundant vacuolated or granular cytoplasm (glycogen and lipids in vacuoles) giving the appearance of "empty" or "clear," nucleus with mild to moderate pleomorphism, prominent nucleolus

and a thin capillary network. Immunohistochemically, it is positive for EMA, PAX-8 CD10, RCC, CD12, CD15, and MUC-1⁹.

The current approaches for the treatment of metastatic CCRCC include immunotherapy with interferon- α , targeted therapy, or one of these therapies combined with metastasectomy¹⁰, within the techniques used are pancreatoduodenectomy, distal pancreatectomy, total pancreatectomy, etc. The surgical strategy for metastatic pancreatic tumor has not been established¹¹, a decision must be made to achieve clear resection margins depending on the location of the tumor within the pancreas. Regardless of the site of recurrence, several reports have shown that complete metastatic clearance is the key to prolonged survival¹².

A median survival of 72 months has been reported for surgically treated patients, whereas those who did not undergo pancreatic resection had a median survival of only 10 months¹³.

According to the literature, renal cancer occurs in very low proportion in the population, and even more so metastases to the pancreas from renal cancer. There are few case reports, as well as a series of studies at international level of metastasis of renal carcinoma to pancreas as well as the surgical treatment given to them. In the Mexican population, the evidence is null, which is why the study of our population is relevant. The aim of the present study is to evaluate overall survival and disease-free survival in patients with renal cancer and pancreatic metastases undergoing surgical treatment.

Methods

A retrospective cross-sectional study of patients with histological diagnosis of clear cell renal cancer associated with pancreatic metastasis was performed and included those who were treated by pancreatoduodenectomy or distal pancreatectomy type surgery during the time period 1987-2020 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

Electronic and physical records were reviewed, as well as the clinical evolution registry (overall survival and disease-free survival) in all patients who underwent surgery for pancreatic metastasis due to clear cell renal cancer. Descriptive statistics were used including mean and ranges for quantitative variables as well as frequency and percentage for qualitative variables.

Table 1. Characteristics of the patients with renal cell carcinoma and pancreatic metastasis

Case	Age/Sex	Primary tumor	Treatment for the primary tumor	Interval (days)	Location of pancreatic metastases	Operative procedure	Outcome
1	69-F	Clear cell RCC	Nephrectomy	7270	Head	Whipple	Die
2	34-F	Clear cell RCC	Nephrectomy	5878	Periampullary	Whipple	Alive
3	84-F	Clear cell RCC	Nephrectomy	3649	Periampullary	Whipple	Alive
4	50-M	Clear cell RCC	Nephrectomy	1244	Head and body	Whipple	Alive
5	45-F	Clear cell RCC	Nephrectomy	4630	Head and body	Whipple	Alive
6	65-F	Clear cell RCC	Nephrectomy	5492	Head	Whipple	Alive
7	64-F	Clear cell RCC	Nephrectomy	2418	Head	Whipple	Alive
8	43-M	Clear cell RCC	Surveillance	0	Head	Whipple	Alive
9	77-M	Clear cell RCC	Nephrectomy	1986	Body	DP	Alive
10	65-M	Clear cell RCC	Nephrectomy	121	Head and tail	DP	Alive
11	40-F	Clear cell RCC	Nephrectomy	5	Head and tail	DP	Alive
12	53-M	Clear cell RCC	Nephrectomy	366	Peripancreatic	DP	Alive
13	45-M	Clear cell RCC	Nephrectomy	4468	Tail	DP	Alive
14	60-F	Clear cell RCC	Nephrectomy	4063	Body	DP	Alive

Interval days from diagnosis of primary tumor to diagnosis of pancreatic metastases. M: male; F: female; RCC: renal cell carcinoma; DP: distal pancreatectomy.

Results

According to the analysis, 302 patients with CCRCC were analyzed, of which only 14 patients had pancreatic metastasis (4.2%). Two groups of patients were obtained: those who underwent pancreatic surgery for metastasis (n = 14) and those who did not undergo pancreatic surgery (n = 6) table 1.

Of the group of operated patients, there is a slight difference in relation to sex, 57.1% corresponds to the female sex (n = 8) and 42.9% to the male sex (n = 6). In relation to the clinical stage of CCRCC, clinical stage 4 (A and B) was found most frequently in 42.8% (n = 6), although in 42.8% (n = 6) the clinical stage at diagnosis could not be obtained as it was not reported in the file. 78.6% (n = 11) had no metastases at diagnosis, 21.4% (n = 3) were diagnosed with metastases to pancreas along with CCRCC. Only 14.3% (n = 2) received radiotherapy prior to pancreatic surgery. According to the location of the metastasis 71.4% corresponded to single location, being in order of frequency head, body, tail, periampullary and peripancreatic fat (21.4%, 14.3% 14.3%, 14.3% 7.1%, respectively) and 28.6% to multiple location corresponding to head-body, head-tail, body-tail (14.3%, 7.1% 7.1%, respectively). Regarding the

surgical procedure, 57.1% (n = 8) underwent Whipple and 42.9% (n = 6) distal pancreatectomy.

The average size of the metastatic lesion to the pancreas was 2.9 cm (0.9-6 cm range) (Table 2) Only one of the operated patients presented extrapancreatic metastasis, located in the stomach. Two of the non-operated patients had extrapancreatic lesions in the liver and lung.

Regarding survival after the diagnosis of metastasis, after the surgical procedure, it was 1150 days on average. In contrast to those who did not undergo surgery, survival after diagnosis of metastasis was 499 days.

Post-operative complications presented by the patients were mainly: 42.8% abdominal sepsis (n = 6), 14.28% (n = 2) pancreatic fistula, and 7.14% (n = 1) delayed emptying. There were no in-hospital deaths.

Of the patients who did not undergo surgery, 50% (n = 3) received management with ERCP and stent placement, 33.3% (n = 2) underwent biliodigestive bypass and one was a candidate for cycles of Soratenib.

Discussion

Secondary neoplasms affecting the pancreas are rare, accounting for 2-5% of all malignant neoplasms

Table 2. Surgical characteristics of pancreatic metastases

Case	Size (cm)	Operative time (min)	Operative bleeding (ml)	Post-operative complication	Clavien-Dindo
1	3.5 × 2.5	-	-	Sepsis DGE	IIIa II
2	5	350	400	None	-
3	4.9 × 4	300	450	None	-
4	2.1 × 1.3 (head) and 0.9 × 0.9 (body)	300	200	None	-
5	2.1 × 1.3 (head) and 0.9 × 0.9 (body)	300	200	Sepsis	IIIa
6	2.1 × 1.5	350	550	Sepsis POPF	IIIa II
7	1.9 × 1.4	210	200	None	-
8	6 × 4.5 × 3.5	600	5000	Sepsis	IIIa
9	1.4 × 1.4	240	300	Intra-abdominal collections	II
10	5.5 × 4.5 × 4	315	450	None	-
11	1.3 × 0.5 × 0.4	445	3000	Pneumothorax Sepsis Dehiscence of anastomosis	I II IIIb
12	6 × 4	300	500	None	-
13	2 × 1.4	230	350	Intestinal occlusion POPF Sepsis	IIIb II III
14	4 × 2.7	180	600	Atelectasis	I

cm: centimeters; mL: milliliters; min: minutes; DGE: delayed gastric emptying; POPF: post-operative pancreatic fistula.

of the pancreas^{1,14} which agrees with the analysis of this study since it was recorded at 4.2%. Our hospital, being a referral center for patients diagnosed with renal and pancreatic cancer considered as a high level in specialized hepatopancreaticobiliary surgery, confirms the rarity of this type of metastasis for clear cell renal cancer. In this study, they only found 14 patients with clear cell renal cancer metastasis in pancreas.

It is suggested that metastases to the pancreas due to CCRCC occur within the 1st year, from 5 to 10 years according to the literature^{3,10}, in this study, it was found that the average time between nephrectomy and the diagnosis of recurrence to the pancreas was 8.3 years (3033 days), being 19.9 years (7270 days) the longest time in which the metastasis was detected.

Survival from CCRCC diagnosis obtained in our case series within our tertiary care center averaged 4167 days to last follow-up (range 803-8327 days) in patients who had pancreatic surgery while in patients

who it was decided not to operate for metastasis, it was 4063 days (range 71-8751 days).

According to the results of this study, surgery is probably the best treatment option for pancreatic metastasis^{3,15}, since the survival from the diagnosis of metastasis to the last follow-up in patients who underwent surgery was 1150 days (range 104-3068 days), while those who did not undergo surgery had a survival of 499 days (range 3-1201 days).

Survival at 1, 3, and 5 years of patients with pancreatic metastasis due to CCRCC who underwent surgery was 92.85%, 50%, and 35.71%, respectively, compared with the survival after diagnosis of pancreatic recurrence of those who did not undergo surgery, which was 28.57% at 1 year, 14.28% at 3 years and no survival at 5 years, which coincides in its majority with international literature^{9,11,13} and favors the surgical management of metastasis. Only one of the operated patients died in the 1st year after pancreatic surgery, with a follow-up of less than 6 months (163 days), due to age and post-surgical complications.

Conclusion

Pancreatic metastases due to CCRCC can be curable, improve morbidity, and increase disease-free survival with surgical treatment. The fact is that they can be diagnosed in time, since their growth is slow, the appearance of symptoms is not frequent and they take years to recur after nephrectomy for the primary tumor. Despite the poor data that exist in Latin American centers about this condition, the patients in this study saw a greater survival at 1, 3, and 5 years after pancreatic surgery. Despite this finding, a larger case series with longer follow-up is needed to further clarify the role of pancreatic metastases and also to know which patients benefit most from surgical management.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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