

CASE SERIES

The Place of Enucleation and Enucleo-Resection in the Treatment of Pancreatic Metastasis of Renal Cell Carcinoma

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ABSTRACT

Context Renal cell carcinoma has shown less response to systemic therapies including chemotherapy, radiotherapy and immunotherapy than other cancers. Metastasis of renal cell carcinoma to the pancreas occurs, even after long term radical nephrectomy, surgical resection remains the only potentially curative intervention. We performed surgery for pancreatic metastatic renal cell carcinoma and analyzed the results. **Methods** We retrospectively analyzed 11 patients who had undergone pancreatic resection or metastasectomy at our hospital from January 1994 to January 2010. Patient's demographics, clinical variables, types of pancreatic resections (standard or atypical resection), primary histopathology, surgical outcomes, survival and disease free interval were examined. We compared the standard pancreatic resection to atypical resection (enucleation or enucleo-resection). **Results** Eleven patients underwent 14 pancreatic resections or metastasectomy (3 pancreaticoduodenectomy, 4 distal pancreatectomy, 1 completion of pancreatectomy, 4 enucleations and two enucleo-resections) for pancreatic renal cell carcinoma metastasis. The median age was 73 years, the median time period between nephrectomy and finding of pancreatic metastasis was 11.4 years. One patient showed synchronous pancreatic metastatic lesions on radiology. One patient died from a splenic artery pseudoaneurysm rupture 35 days after the surgery. Major complications occurred in 4 patients with standard resection (one hemoperitoneum, three pancreatic fistulas), and in one patient with atypical resection (duodenal fistula); six patients with standard resection presented postoperative diabetes mellitus. Median survival age was 6.5 years (range 1-9 years). Two patients died of metastatic disease 5 to 6 years, while 7 patients are alive and well 1 to 9 years after surgery. **Conclusions** According to these results and regardless of the small number of cases, atypical resection of metastatic renal cell carcinoma has a high median survival rate even after pancreatic recurrence or distant metastasis. It seems reasonable to favor a good quality of life and less diabetes with a limited atypical resection.

INTRODUCTION

Renal cell carcinoma is the most common type of kidney cancer in adults, responsible for approximately 90% of cases [1]. It has shown less response to systemic therapies including chemotherapy, radiotherapy and immunotherapy (IL-2, INF- α) than other cancers [2]. Renal cell carcinoma can behave in a variable and unpredictable manner, up to 20% may have periods of slow tumor growth or stability lasting many years [3]. McNichols *et al.* found that among the 158 patients who survived more than 10 years, 11% had late recurrence in the form of metastasis [4]. Pancreatic metastasis from renal cell carcinoma is frequently the only metastatic site and metastases typically occur a long time after nephrectomy [5, 6, 7];

a period of 25 years [8] and 32.7 years [7, 9, 10, 11] after radical nephrectomy has been described. Management of metastatic renal cell carcinoma to the pancreas has become, by consensus, largely surgical [12]. Multiple case reports, case series and meta-analyses suggest that aggressive surgical resection confers a significant survival advantage in this situation [6, 13, 14, 15]. The five-year survival rate of patients with untreated metastatic renal cell carcinoma is less than 13% [16, 17] and up to 65% after surgical resection [18]. Multiple lesions throughout the pancreatic gland have been more frequently detected in patients with renal cell carcinoma than in those with other primary tumors. Other single-center series reported similar frequencies of multifocality with respect to pancreatic renal cell carcinoma metastases, ranging from 20 to 45% [6, 7, 9, 19].

A retrospective analysis of patients with pancreatic metastasis from renal cell carcinoma was performed and comparison was made between atypical pancreatic resection (enucleation or enucleoresection) and standard pancreatic resection (distal pancreatectomy and pancreaticoduodenectomy), to show the effects and the difference of those two strategies on postoperative morbidity, mortality and survival.

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MATERIALS AND METHODS

From January 1994 to January 2010, 11 patients underwent pancreatic resection of metastasized renal cell carcinoma to the pancreas at the Institute Mutualiste Montsouris (multidisciplinary, tertiary care medical center). Patient’s demographics, clinical variables, types of pancreatic resections, primary histopathology, surgical outcomes, survival and disease free interval (time between nephrectomy and pancreatic surgery in metachronous patients) were retrospectively reviewed. All patients who underwent resection of their pancreatic metastasis met the following criteria: i) pancreatic lesions were deemed resectable not only radiologically but also by the patient’s general condition; ii) metastatic disease was limited to the pancreas; iii) locoregional control of their primary renal lesions was obtained or obtainable; and iv) metastasectomy or standard pancreatic resection was performed for complete resection. Atypical Pancreatic resection was favored on the standard resection when complete resection was possible, especially with smaller metastatic lesions, distant from the pancreatic duct, and in multifocal lesions for pancreatic parenchymal sparing. The synchronous and metachronous pancreatic metastasis of renal cell carcinoma were included regarding the site of

metastasis, primary renal tumors involving the pancreas through direct extension were excluded. Overall survival was calculated from the date of pancreatic resection to the time of death or last follow-up. Pancreatic fistula classification was according to the international study group on pancreas fistula criteria [20].

All patients were investigated preoperatively and postoperatively for diabetes mellitus. Standard pancreatic resections were performed without the need for the preoperative ultrasound to locate the tumor or Wirsung canal.

ETHICS

Patients were managed according to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

STATISTICS

Median, range and frequencies were reported as descriptive statistics. Statistical analysis was performed using the Statistical Package for Social Sciences

Table 1. Table presenting the 11 cases of pancreatic surgical resection of metastatic renal cell carcinoma.

| Case | Age (years) | Surgical access | Surgical procedure | Nodal status | Margin status | Hospital stay (days) | Complications | Treatment of the complications | Recurrence | Survival (years) | Death (years) |
|------|-------------|-----------------|--|----------------|---------------|----------------------|--------------------------------|---|---|------------------|---------------|
| #1 | 75 | Open | Distal pancreatectomy | No | Yes | 57 | Pancreatic fistula Diabetes | Support | Local metastasis (1 yr) ^a | 6 | 6 |
| #2 | 80 | Open | Enucleoresection + Partial resection of DU3 | - ^d | No | 15 | - | - | - | 4 | 4 |
| #3 | 74 | Open | Distal pancreatectomy + Enucleation of the head ^c | No | No | 41 | Hemoperitoneum Diabetes | Splenectomy | - | 9 | - |
| #4 | 66 | Open | Distal pancreatectomy + Isthmectomy | Yes | No | 110 | Pancreatic fistula Diabetes | Radiographic drainage | Pancreatic ^b Distant metastasis (3 yrs) | 5 | 5 |
| #5a | 64 | Open | Pancreaticoduodenectomy | No | No | 14 | Diabetes | - | Pancreatic (9 yrs) ^b | 9 | - |
| #5b | 73 | Open | Total pancreatectomy | Yes | No | 14 | Diabetes | - | - | 8 | - |
| #6 | 53 | Open | Pancreaticoduodenectomy + Left nephrectomy | Yes | No | 14 | Diabetes | - | - | 9 | - |
| #7 | 73 | Laparoscopy | Enucleation of the head | - ^d | No | 19 | - | - | Pancreatic ^b Distant metastasis (1 yr) | 8 | - |
| #8 | 63 | Open | Pancreaticoduodenectomy | No | No | 36 | Pancreatic fistula Diabetes | Support | Distant metastasis (2 yrs) | 7 | - |
| #9 | 49 | Laparoscopy | Distal pancreatectomy | No | No | 11 | Hemoperitoneum at day 35 | Splenectomy for splenic artery pseudoaneurysm | - | - | 35 days |
| #10 | 70 | Open | Enucleoresection + Partial resection of DU2 | - ^d | No | 60 | Duodenal fistula | Surgical drainage Nutritional support | - | 5 | - |
| #11a | 73 | Laparoscopy | Enucleation of the head | - ^d | No | 7 | - | - | Pancreatic (2 yrs) ^b | 2 | - |
| #11b | 75 | Open | Enucleation of the tail + Transverse colectomy | - ^d | No | 26 | - | - | - | 1 | - |

DU2: second duodenum; DU3: third duodenum

^a Local pancreatic recurrence in the edge of the previous pancreatic resection

^b Pancreatic recurrence away from the previous pancreatic resection

^c Two pancreatic resection (distal pancreatectomy and enucleation of the head) in the same time

^d No lymph node found in the specimen

(SPSS, version 15.0; Chicago, IL, USA), comparison between standard pancreatic resection and atypical resection was made by means of the Mann-Whitney/Wilcoxon and the Fisher tests. Two-tailed P values less than 0.05 were considered significant.

RESULTS

A total of 11 patients (ten males, one female) underwent 14 pancreatic resections for pancreatic metastasis of renal cell carcinoma. The median age of the patients was 73 years (range: 49-80 years). Ten patients were asymptomatic at presentation, while one patient had an upper gastrointestinal bleeding. The median time period between nephrectomy and finding of pancreatic metastasis was 11.4 years (range: 1-20 years). There were 5 cases of stage 2 and 6 cases of stage 3 renal cell carcinoma, clear cell type. Two patients had a previous resection for metastatic location in the lung or the adrenal gland, 9 and 7 years earlier, respectively and two others were previously operated for a pancreatic metastasis of renal cell carcinoma. One patient had two simultaneous pancreatic resections (enucleation of the head and a distal pancreatectomy) for synchronous lesions.

All pancreatic metastases were hypervascular on arterial phase of CT imaging; the median tumor size was 23 mm (range: 14-50 mm). All patients had a solitary pancreatic metastasis, except one who showed two synchronous metastatic lesions on radiology. Fourteen operating procedures were done: 8 standard pancreatic resections (3 pancreaticoduodenectomies, 4 distal pancreatectomies with spleen sparing, and one completion of pancreatectomy 9 years after a previous pancreaticoduodenectomy) and 6 atypical resection (4 enucleations and two enucleoresections) (Table 1). One patient died in the postoperative period, he had a hemoperitoneum due to a splenic artery pseudoaneurysm rupture after a distal pancreatectomy with spleen preserving. Six patients had postoperative complications: 4 morbidity in the standard resection group (1 hemoperitoneum, 3 grade B pancreatic fistulas); one morbidity in the enucleoresection group (duodenal fistula in the case of enucleoresection with partial resection of the distal second part of the duodenum, the proximal resection margin was located just distal of the ampulla of Vater. The bowel continuity was reconstructed by a lateroterminal duodenojejunostomy located opposite to the ampulla of Vater in order not to induce a stricture of the papilla); and we had one case of synchronous head pancreatic metastasis from renal cell carcinoma, the two lesions were removed in the same operating time by a left nephrectomy and a pancreaticoduodenectomy. Six patients in the standard pancreatic resection group presented postoperative diabetes mellitus. In this series there was no difference in morbidity ($P=0.266$) and recurrence ($P=0.592$) between the standard resection group (4/7, 57.1% and 4/7, 57.1%, respectively) and the enucleation or enucleoresection group (1/6, 16.7% and 2/6, 33.3%, respectively); postoperative diabetes

mellitus was higher in the standard pancreatic resection (6/7, 85.7% vs. 0/6, 0%, $P=0.005$).

The median operating time was 290 min (range: 180-570 min); no one was transfused regarding a median blood loss of 332 mL (range 100-800 mL); the surgical procedures were open procedures except two enucleations and one distal pancreatectomy which were totally laparoscopic. Pathologic findings included negative surgical margins in 13 out of 14 cases and negative lymph nodes in 5 out of 8 cases and in the other 6 we did not found lymph nodes in the specimen. In the group of patients treated by enucleation or enucleoresection an ultrasound helped locate the metastasis and the distance from the resected edge to the pancreatic duct during the surgery.

The median hospital stay was 25 days in the standard resection group and 22.5 days in the enucleation or enucleoresection group. Overall median survival was 6.5 years (range: 1-9 years); it was 8 years in the standard resection group and 4.5 years in the enucleation or enucleoresection group. Two patients died from metastatic disease 5 and 6 years after operation, one patient died of natural cause 4 years later, while 7 patients are alive and well 1 to 9 years after surgery. Four of them are disease free at 5 years of follow-up, one has a shorter follow-up (1 year), and the other two have recurrence in the remaining pancreas or distant metastasis; these patients were treated by immunotherapy (IL-2) or a targeted therapy (sorafenib, sunitinib). Also no significant difference was found between the standard and the atypical resection concerning hospital stay (median: 40.9 vs. 28.0 days, respectively; $P=0.473$) and survival (median: 7.6 vs. 4.8 years, respectively; $P=0.069$).

DISCUSSION

The pancreas is an unusual site for metastasis, notably from renal cell carcinoma. For Konstantinidis *et al.* the pancreas was the first site of extrarenal recurrence in 85% and was synchronous with the primary renal cell carcinoma in 5% of the patients [21]. A meta-analysis places the incidence of synchronous disease at 12% [6]. According to the Johns Hopkins' experience [11] synchronous lesions should be resected with a survival expectancy close to that of metachronous ones. We had only one synchronous metastasis, he is still alive 9 years after surgical resection.

Some patients had an indolent natural history, with presentation of metastatic renal cell carcinoma many years after treatment. Yokonishi *et al.* reported a case of pancreatic metastasis 25 years after radical nephrectomy, and concluded on the existence of a subgroup of a slow growing tumor [8]. In this series a long time period between nephrectomy and pancreatic metastasis was observed, with a median of 11.4 years (range: 1-20 years).

The median age of this group was 73 years as previously described in the literature [12]. The early signs and symptoms of isolated pancreatic metastases are often non-specific and subtle. Isolated pancreatic

metastasis are often found with routine surveillance imaging for primary lesions or as an incidental finding on imaging done for an unrelated indication, 10 patients were asymptomatic and the diagnosis was an incidental finding during follow-up for renal cell carcinoma. As in the study of Kobayashi *et al.* [22], we reported a case of spontaneous rupture of pancreatic metastasis from renal cell carcinoma with upper gastrointestinal bleeding years after nephrectomy for renal cell carcinoma. In this study, the high rate of asymptomatic cases is related to the small size of the tumor, with a median size tumor of 23 mm (range: 14-50 mm), it is less than the 30 mm median size tumor of the series of Bassi *et al.* [5].

Surgical resection has been reported to improve the long-term survival of patients with isolated pancreatic metastasis and, thus to constitute the best therapeutic option [23]. In the series of Bassi *et al.* [5] four patients had a previous solitary relapse radically resected; in our series we had 4 patients with a previous solitary resected metastasis: one in the lung and one in the adrenal gland 9 and 7 years earlier respectively, and two in the pancreatic head 9 and 2 years earlier.

Three types of metastatic involvement of the pancreas have been described in the literature. The most common type of all metastases and in particular of renal cell carcinoma metastases, reported in 50-73% of cases, is that of a solitary, localized, well-defined mass. A second pattern of multiple pancreatic lesions has been reported in 5-10% of cases, and a third pattern of diffuse metastatic infiltration causing generalized enlargement of the organ in 15-44% of cases [24].

Surgical treatment for multiple pancreatic metastases remains controversial. In our series only one had a multifocal lesion seen preoperatively by CT scanner, that is lower than the series of Bassi *et al.* with their 30% [5], it was treated by distal pancreatectomy and enucleation of the head of the pancreas preventing a more aggressive total pancreatectomy and postoperative morbidity with the same survival.

In the 14 resections, 3 out of 8 invaded lymph nodes, in the 6 others no lymph nodes were found. The resection of the lesion was incomplete in one out of 14 cases, which is not different from the series of Konstantinidis *et al.* with 3 out of 12 positive lymph nodes and 4 out of 20 incomplete resections [21].

Bassi *et al.* recommended standard pancreatic resection in view of the high recurrence rate (50%) after atypical resection (enucleation or enucleoresection); atypical resection appeared to be responsible for the high overall morbidity rate: 3 out of 11 for standard and 5 out of 6 for atypical resection [5], while Konstantinidis *et al.* had no local failures with limited resections [21]. For Zerbi *et al.* since the frequency of multiple metastases is often more than 2, the occurrence of pancreatic recurrence is likely to be an expression of an undetected multilocality rather than the consequence of an inadequate surgical procedure [9], this is also observed in this series, since the pancreatic recurrence (4 out of 5) are not in the region of the pancreatic

resection and the only local recurrence occurred after positive resection margin. One of the arguments of standard resection is the ability to get pancreatic lymph nodes; however, an extensive review of the literature indicates the involvement of lymph nodes in metastatic pancreatic malignancy to be extremely unusual [6, 9], lymph node involvement was observed in about 30% of cases [25], 5 out of 8 in our series. With 14 pancreatic resections (six enucleations or enucleoresections and 8 distal pancreatectomy or pancreaticoduodenectomy), we had one postoperative mortality after a distal pancreatectomy, four postoperative morbidity in the standard resection group (one hemoperitoneum, 3 pancreatic fistulas) and one postoperative morbidity in the enucleoresection group (one duodenal fistula in the case of enucleoresection with partial second duodenum resection). Six patients in the standard pancreatic resection group presented postoperative diabetes mellitus. In this series there was no difference in morbidity ($P=0.266$) and recurrence ($P=0.592$) between the standard resection group and the enucleation or enucleoresection group, postoperative diabetes mellitus was higher in the standard pancreatic resection ($P=0.005$).

The 5-year survival rate of patients with untreated metastatic renal cell carcinoma is poor; usually less than 13% [16] as adjuvant irradiation and/or chemotherapy does not seem to prolong the survival of patients with pancreatic metastasis, including renal secondaries. Reviews of the world literature with aggressive surgery for isolated pancreatic metastasis of renal cell carcinoma have been shown to significantly improve survival [11, 23]. Five-year survival rate around 70% has been noted in some recent reports with a long term follow-up [11, 19]. Sweeney *et al.* in a recent meta-analysis concerning metastatic cancer to the pancreas in about 220 patients revealed that the primary tumor site was most commonly the kidney in 70.5%, with a median survival of 70 months (2- and 5-year survival rates were 78% and 65%, respectively) [18]. In a retrospective study (Akashi *et al.*) on 15 patients subjected to surgical resection of pancreatic metastasis, median survival was 31 months, 47% with metastases of renal cell carcinoma, and the median survival after pancreatectomy was 45 months in patients with renal cell carcinoma [26]. Law *et al.* found that 11 out of 14 patients who were operated of pancreatic renal cell carcinoma metastasis were alive at 32 months of follow-up although only 7 of them were disease free [13]. Bassi *et al.* found significant difference in 24- and 60-month survival comparing patients who had resection of metastasis to whom did not [5]. In our series, we had one postoperative mortality, one of natural cause, two of distant metastasis, 5 and 6 years later, and the 7 others are alive (1 to 9 years) after the operation with 4 out of 7 diseases free, the others had a metastatic pancreatic location or a distant metastasis. Also no statistical difference was found between the standard and the atypical resection concerning hospital stay ($P=0.525$)

and survival (P=0.069). The 6 recurrent local pancreatic and distal metastases were treated by IL-2 and targeted therapy. Recently targeted therapy was recommended as first line therapy for metastatic renal cell carcinoma but not as an adjuvant therapy [27].

First, we would encourage aggressive surgical resection of the clinically solitary metastasis, whether synchronous or metachronous. Continued follow-up of those patients may be necessary indefinitely because relapse is quite likely. Second, limited resection such as enucleation or enucleoresection is a good option to prevent diabetic disease occurrence in a disease known for its recurrence. Third, multiple metastasis must be managed with conservative surgery preventing total pancreatectomy which will cause a difficult and uncontrolled diabetes mellitus without a significant difference in survival from the conservative surgery.

Potential weaknesses of this study are related to its retrospective nature, and the limited number of patients with renal cell carcinoma. Regarding the progression of medical therapy especially immunotherapy, targeted therapy, surgery is still the first line therapy because the response rate is still low and very few patients show long-term clinical improvement [28]. Prospective studies must be done with a comparison between surgical resection and immunotherapy potential era for further study.

CONCLUSION

Renal cell carcinoma is an unpredictable tumor that may demonstrate delayed metastasis; we are more willing to do a standard radical pancreatic resection or a limited pancreatic resection such as enucleation or enucleoresection. Surgical resection of pancreatic metastasis from renal cell carcinoma is associated with a good median survival even with distal metastasis or local recurrence. Enucleation or enucleoresection should be favored because this approach has been proven to be associated with better quality of life without diabetes mellitus by preserving a maximum of pancreatic tissue. However, much is to be done in comparing the standard surgical resection to enucleation and immunotherapy in a prospective randomized clinical trial.

Conflict of interest The authors have no potential conflict of interest

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