Pancreatology

Surgical Therapy of Intrapancreatic Metastasis from Renal Cell Carcinoma

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Abstract
Background: Pancreatic metastases from renal cell carcinoma (RCC) are clinically rare but highly resectable. The aim of this article is to identify patients who profit from pancreatic resection of RCC despite the invasiveness of the surgery. **Methods:** Between January 1996 and December 2007, data from 744 patients were collected in a prospective pancreatic surgery database, and patients with metastasis into the pancreas from RCC were identified. **Results:** Resective surgery was performed in 14 patients with metastasis to the pancreas from RCC. Most patients were clinically asymptomatic. The median interval between primary treatment of RCC and occurrence of pancreatic metastasis was 94 months (range 32–158). The morbidity rate was 42.8%. Patients with a metastasis size <2.5 cm had a much better survival after resection (100 months) than those with a metastasis size >2.5 cm (44 months). Moreover, the number of metastases predicts the survival after resection. **Conclusions:** In patients with pancreatic metastases from RCC who have only limited disease, complete resection of all lesions can be successfully performed with a low rate of complications. Thus, patients with a history of RCC should be monitored for more than 10 years after nephrectomy to detect recurrence.

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Introduction

Primary pancreatic carcinoma constitutes the vast majority of pancreatic malignancies: between 85 and 90% of all pancreatic tumors are included in this category [1]. Metastatic carcinoma of the pancreas from another primary site is uncommon and represents a small group comprising between 2 and 5% of all pancreatic cancers [2]. Metastatic tumors to the pancreas are clinically rare and are exceedingly difficult to differentiate from a primary pancreatic neoplasm; the reported incidence of these metastatic lesions in autopsy studies is in the range of 1–11% of widespread metastatic disease [3]. There are a variety of cancers which have been shown to metastasize into the pancreas as mass lesions, such as colon cancer, non-small cell lung cancer and melanoma [4]. In particular, primary kidney tumors have an increased disposition for metastasis to rare sites such as the pancreas [5]. The difficulty of distinguishing between clear cell primary pancreatic tumors and solitary pancreatic metastases may lead to clinical misdiagnosis. In some cases the metastatic deposit in the pancreas is the primary manifestation of an unknown primary tumor. Therefore, an accurately defined elaboration of the medical history is critical for the diagnostic workup for tumors in the pancreas. Pancreatic resections were for many years associated with high rates of morbidity and mortality, but recent data have clearly shown that pancreatic surgery in high-volume clinical centers is increasingly safe. For ex-

Table 1. Characteristics and operative procedure for metastatic RCC

Case	Age/gender	Symptoms	Primary tumor stage of RCC	Time since primary, months	Localization of metastasis	Follow-up months	Operative procedure	Status
1	66/f	Asymptomatic	pT3a N0 M0 G2	158	Head	14	Excision	Alive
2	58/f	Back pain	pT3a N0 M0 G3	36	Body	111	PPPD	Alive
3	63/f	Asymptomatic	pT2 N0 M0 G2	96	Tail	54	DPS	Alive
4	54/m	Jaundice	pT2 N0 M0 G2	32	Head	75	Whipple	Dead
5	66/m	Asymptomatic	pT2 N0 M0 G3	52	Head	49	Whipple	Dead
6	58/f	Jaundice	pT3b N0 M0 G2	76	Head	15	Whipple	Dead
7	74/m	Jaundice	pT2 N0 M0 G1	60	Head	116	Excision	Dead
8	68/m	Asymptomatic	pT2 N1 M0 G3	120	Tail	0	DP	Dead
9	64/f	Asymptomatic	pT3b N0 M0 G2	156	Head	14	PPPD	Dead
10	58/f	Asymptomatic	pT2 N0 M0 G2	132	Tail	81	DPS	Alive
11	70/f	Asymptomatic	pT3a N0 M0 G3	157	Head	19	PPPD	Alive
12	70/m	Asymptomatic	pT2 N0 M0 G2	108	Tail	72	DP	Dead
13	61/f	Asymptomatic	pT3b N1 M0 G3	46	Head	102	PPPD	Dead
14	71/m	Asymptomatic	pT2 N0 M0 G2	84	Tail	12	DP	Alive

PPPD = Pylorus-preserving pancreatoduodenectomy; DPS = distal pancreatectomy with splenectomy; DP = distal pancreatectomy.

ample, recent studies have shown that mortality after pancreatectomy has decreased to <5% when performed by experienced surgeons [6]. Today the indications for these operations have been extended even for patients with metastatic disease to the pancreas [7]. The potential benefit of metastasectomy in renal cancer is well documented in the literature. So far, approximately 250 cases of pancreatic resections for metastatic renal cell carcinoma (RCC) have been reported in the literature [8, 9]. In all studies, pancreatic resection was recommended in the presence of isolated pancreatic localization and when technically feasible. Especially for patients with the history of kidney primary tumors, resection of metastasis can improve quality of life as well as prognosis [10].

The purpose of this article is to identify subgroups of patients who profit from pancreatic resection of RCC metastases despite the invasiveness of the surgery. The benefits of this procedure can be shown with improved safety and a relatively good prognosis with low morbidity and mortality rates after pancreatic resection of RCC metastases.

Materials and Methods

Between January 1996 and December 2007, 14 patients (8 women and 6 men) with a median age of 64 years (range 54–74) were checked on a prospective database of all pancreatic resections (n = 744). All patients were admitted and treated at our department and diagnosed with a renal cell metastasis into the pancreas. A thorough follow-up was performed for every patient including clinical examination, complete laboratory workup, yearly abdominal ultrasonography (US) and computed tomography (CT) scan on pathological findings in any of the other examinations.

Standard pancreatic resections were pylorus-preserving pancreatoduodenectomy (PPPD) or Whipple pancreatoduodenectomy for tumors in the head or uncinate process. Distal pancreatectomy was performed for tumors in the pancreatic body or tail. Two patients were treated by local tumor excision (table 1).

An accurate preoperative staging was performed to exclude the presence of extrapancreatic metastases. All patients underwent a CT scan and abdominal US. MRCP or MR angiography was additionally used for metastases in the pancreatic head. Primary tumor location, location of metastases, size of metastases and the interval between primary treatment and metastases (disease-free interval) were evaluated. Moreover, presenting symptoms, surgical treatment, perioperative morbidity and long-term mortality were evaluated.

Continuous data are presented as means. Survival distributions were analyzed by the methods of Kaplan and Meier. Patients dying from other than cancer-related causes were censored for the Kaplan-Meier estimation. Differences were evaluated by the log-rank test. A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS Version 15.0 (SPSS, Chicago, Ill., USA).

Results

Among the 14 observed patients, 8 were women and 6 were men; mean age was 64 years (range 54–74) (table 1). The median interval from nephrectomy was 94 months (range 32–158). Primary RCC originated from the right kidney in 7 patients and from the left kidney in 7 patients. Most patients (10/14) were clinically asymptomatic, and the diagnosis of pancreatic metastasis was incidental dur-
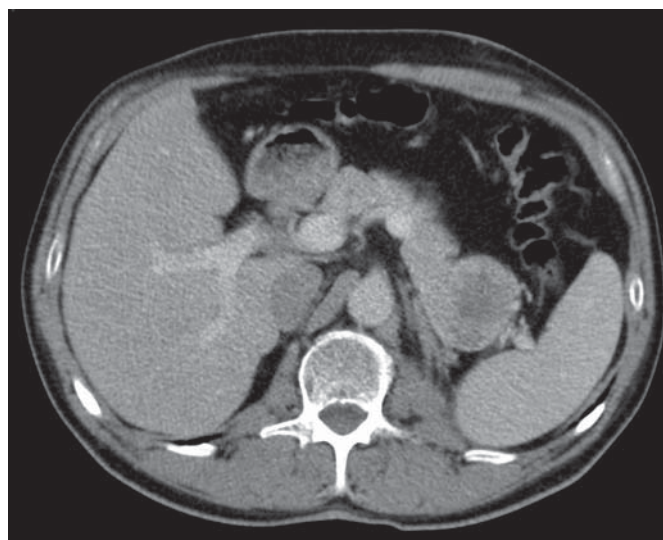
Table 2. Surgical procedure and early postoperative outcome

Procedure	n	Complications	n
Pylorus-preserving pancreatoduodenectomy	4	Postoperative bleeding	1
		Lymph fistula	1
Whipple procedure	3	Postoperative bleeding	1
Distal pancreatectomy	2	Myocardial infarction	1
		Mortality	1
Distal pancreatectomy with splenectomy	3	None	
Excision	2	Pancreatitis	1
		Pancreatic fistula	1

Table 3. Analysis of factors predicting survival

	Time since primary mean value months		Survival after resection mean value months
RCC location			
Right	107.0	n.s.	90.2
Left	80.6		67.8
Metastasis location			
Head	92	n.s.	66.3
Other	96		98.0
Metastasis size			
<2.5 cm	92.1	n.s.	100.9
>2.5 cm	96.0		44.0
Time since primary			
<60 months			84.2
>60 months			77.8
Gender			
Female	107	n.s.	81.6
Male	76		78.0
Number of metastases			
Solitary	104.7	n.s.	111.3
Multiple	74.0		49.4
Symptoms			
Asymptomatic	98.9	n.s.	89.7
Jaundice	81.0		55.0
Operative procedure			
Whipple/PPPD	79.3	n.s.	64.3
Distal resection enucleation	108.3		101.3

Fig. 1. CT scan of a patient with renal cell metastasis in the pancreatic tail.

ing follow-up, mainly detected by US and CT. Four patients had the following symptoms: jaundice in 3 patients and back pain in 1 patient. Pancreatic metastases were located in the pancreatic head in 8 patients and in the tail in 5 patients. One patient had pancreatic metastases in the body. Solitary metastases were identified in 10 patients, and 4 patients had two or more metastases in the head, body and tail.

All patients underwent radical resection. Resection margins were histologically negative for tumor infiltration in all patients (R0). The following surgical procedures were performed: 4 pylorus-preserving pancreatoduodenectomies, 5 distal pancreatectomies, 3 Whipple procedures and 2 excisions. In 3 cases we combined a distal resection with a splenectomy. Of the 14 patients, 6 patients were still alive at the end of the observation period (June 2008), whereas 8 patients had died. We observed one postoperative mortality 17 days after surgery because of an extended myocardial infarction. The morbidity rate was 42.8% (table 2).

One patient needed reoperation for intraperitoneal bleeding that occurred the first day after the Whipple procedure. The bleeding source was found in the right liver lobe after removal of extensive adhesions due to previous operations. Another patient developed a bleeding episode at the pancreatojejunostomy that was treated successfully by endoscopic intervention. Other complications included one pancreatic fistula (grade B according to Bassi et al. [11]), one lymphatic fistula and one postoperative pancreatitis. One patient had a major myocardial infarction as mentioned above. In this group of patients, all undergoing pancreatic resection, 6 patients are alive and free of disease. Median survival after pancreatic re-
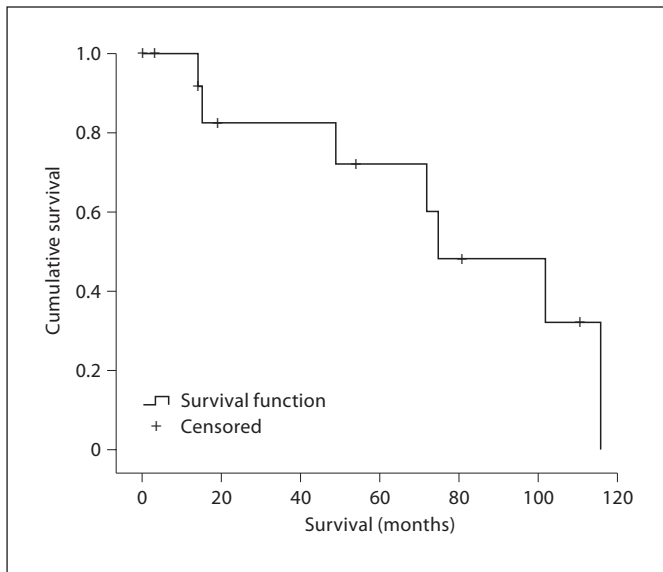
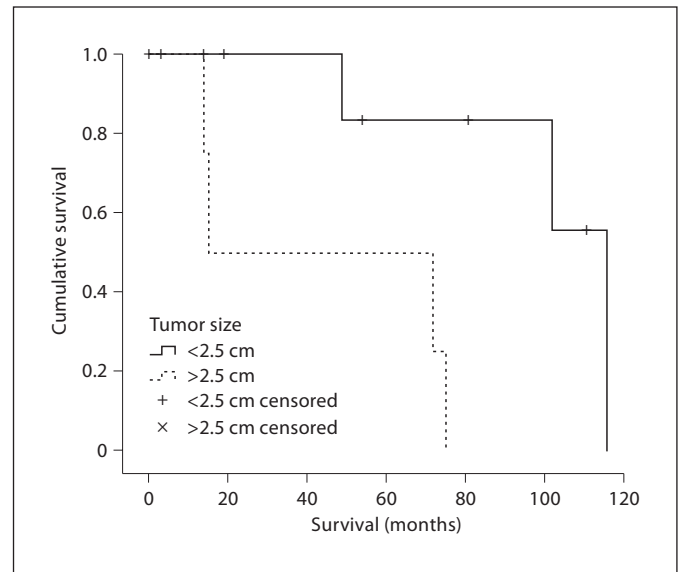**Fig. 2.** Kaplan-Meier curve of 14 patients undergoing pancreatic resection for metastases from RCC.

Fig. 3. Kaplan-Meier curve of survival depending on metastasis size.

section was 75 months (95% confidence interval, 40.1–109.9) (fig. 1). Moreover, we analyzed factors predicting survival after pancreatic resections (table 3). Survival was not predicted by the location of the RCC, location of the metastasis, time since resection of the primary tumor, gender, symptoms, operative procedure, blood loss or age of the patients.

Patients with a metastasis size <2.5 cm had a much better survival after resection (100.9 months) than those with a metastasis size >2.5 cm (44.0 months) (fig. 2, 3). The difference between the two groups was statistically significant (p = 0.01). Furthermore, we could show that the number of metastases predicts the survival after resection. The difference between patients with solitary metastasis and patients with multiple metastasis (111 vs. 49 months) was statistically significant (p = 0.04).

Discussion

Isolated metastatic disease to the pancreas is uncommon relative to metastases to sites such as the liver, lungs and brain. Only about 250 cases have been published in the scientific literature so far. This is the first study that shows the results of pancreatic resections in patients with a RCC and limited disease.

Metastatic RCC with pancreatic localization seems to represent a special clinical situation: pancreatic metasta-

sis typically occurs a long period after the initial nephrectomy, but nevertheless it seems related to a good prognosis [12, 13]. The largest single-center series of pancreatic resection for renal cell metastasis included 22 patients, and surgical resection was performed in 17 of these 22 patients [13]. In a review, Hirota et al. [14] gathered 66 cases of RCC metastatic to the pancreas of which 49 were surgically resected. The median time between nephrectomy and the diagnosis of pancreatic metastasis was 8 years, which is similar to our series of patients, with a median of 8 years. Similar results have been previously reported, with a median interval after nephrectomy ranging from 6 to 12 years [15, 16], the longest interval being 32 years [12].

Therefore, patients with a history of RCC should be monitored for more than 10 years after nephrectomy to detect recurrence. It has been shown that complete surgical resection even for multiple pancreatic metastases from RCC is the most effective treatment option, leading to 5-year survival rates of up to 75%. Moreover, in patients with good general condition and limited disease, complete resection of all lesions, if surgically possible, can successfully be performed with low morbidity and mortality. Recent studies additionally have shown that partial resection can be performed laparoscopically with almost comparable results [17, 18]. However, the operation should be performed in high-volume centers. Birkmeyer et al. [19–23] showed that the 3-year survival after pancreatoduodenectomy was higher at high-volume cen-

ters (37%) than at medium- (29%), low- (26%), and very low-volume hospitals (25%).

Schwarz et al. [24] have studied the impact of splenectomy on hospital stay and survival after resection of pancreatic adenocarcinoma. In this analysis, splenectomy has no significant measurable impact on postoperative recovery, but has a negative influence on long-term survival independent of disease-related factors. The authors concluded that splenectomy should be avoided in the operative treatment of exocrine pancreatic cancer at any localization. Even though in our study we just had 3 patients that were treated by distal pancreatectomy with splenectomy (DPS), these 2 patients had a better long-term survival. Other authors showed that splenectomy has been linked to decreased long-term survival, e.g. for gastric cancer [25].

Moreover, Choueiri et al. [26] showed in a retrospectively reviewed metastatic RCC database that right-sided kidney tumors had a better long-term prognosis than left-sided ones. We can also confirm that patients with right-sided kidney tumors had a better prognosis than those with RCC on the left side. Although there is not a good explanation so far, it is an interesting finding and should be looked at in further prognostication studies in RCC.

The tumors in the present analysis involved the pancreatic head in 8 patients, while the other 6 patients had lesions in the pancreatic body or tail. Although data are still limited, renal metastases appear to be rather more frequent in the pancreatic head than in the body or tail.

Solitary and small metastases in the pancreas are more common than multifocal involvement and seem to be related to a better prognosis [12]. Our data show a significant difference in survival after resection between patients with a metastasis size <2.5 cm and patients that have pancreatic lesions >2.5 cm. These results differ from other studies of pancreatic resections; Carter et al. [27] showed for ampullary tumors that the size of tumor did not predict survival.

Similar results have just been shown in a recent study concerning renal cell metastases in the lungs. Assouad et al. [28] showed that the size of RCC lung metastases is an important prognostic factor. The report includes 65 patients presenting with lung metastasis of RCCs; when the size of the metastasis was >2 cm, patients had significantly shorter survival rates than those with smaller metastases.

Unlike liver or lung, the pancreas is a rather unusual site for metastasis. Other uncommon locations of RCC metastases include the ipsi- or contralateral adrenal glands and the contralateral kidney. Various attempts have been made to explain this type of metastasis. Some authors advocate venous spread along the collateral veins of the hypervascular tumor with renal venous thrombosis [29–31]. However, renal lymphatic drainage might be the predominant way of metastasis, as retroperitoneal lymph node involvement may lead to a retrograde lymphatic backflow in the thoracic duct and the common para-aortic lymph node territories [32–34]. This also explains the occurrence of iterative involvement of the pancreas and metastasis to the contralateral kidney and adrenal glands which are not uncommon features of RCCs [13].

Conclusion

Pancreatic metastases of RCCs can be treated by radical resection with low morbidity and mortality. Patients with small and singular lesions benefit most from the resection as they display good long-term survival. Therefore, as metastases can occur several years after resection of the primary tumor, long-term cancer surveillance should be performed to ensure early diagnosis and treatment.

References

1 Adsay NV, Andea A, Basturk O, Kilinc N, Nassar H, Cheng JD: Secondary tumors of the pancreas: an analysis of a surgical and autopsy database and review of the literature. Virchows Arch 2004;444:527–535.
2 Barras JP, Baer H, Stenzl A, Czerniak A: Isolated late metastasis of a renal cell cancer treated by radical distal pancreatectomy. HPB Surg 1996;10:51–53; discussion 53–54.
3 Peters K, Kloppel G: Undifferentiated pancreatic carcinomas. Leap into chaos (in German). Pathologe 2005;26:18–21.
4 Roland CF, van Heerden JA: Nonpancreatic primary tumors with metastasis to the pancreas. Surg Gynecol Obstet 1989;168:345–347.
5 Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF: Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. Cancer 1971;28:1165–1177.

6 Tsiotos GG, Barry MK, Johnson CD, Sarr MG: Pancreas regeneration after resection: does it occur in humans? Pancreas 1999;19: 310–313.

7 Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA: Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248–260.

8 Sellner F, Tykalsky N, De Santis M, Pont J, Klimpfinger M: Solitary and multiple isolated metastases of clear cell renal carcinoma to the pancreas: an indication for pancreatic surgery. Ann Surg Oncol 2006;13:75–85.

9 Wente MN, Kleeff J, Esposito I, Hartel M, Muller MW, Fröhlich BE, Büchler MW, Friess H: Renal cancer cell metastasis into the pancreas: a single-center experience and overview of the literature. Pancreas 2005;30: 218–222.

10 Sohn TA, Yeo CJ, Cameron JL, Nakeeb A, Lillemoe KD: Renal cell carcinoma metastatic to the pancreas: results of surgical management. J Gastrointest Surg 2001;5: 346–351.

11 Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Büchler MW: Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138: 8–13.

12 Thompson LD, Heffess CS: Renal cell carcinoma to the pancreas in surgical pathology material. Cancer 2000;89:1076–1088.

13 Bassi C, Butturini G, Falconi M, Sargenti M, Mantovani W, Pederzoli P: High recurrence rate after atypical resection for pancreatic metastases from renal cell carcinoma. Br J Surg 2003;90:555–559.

14 Hirota T, Tomida T, Iwasa M, Takahashi K, Kaneda M, Tamaki H: Solitary pancreatic metastasis occurring eight years after nephrectomy for renal cell carcinoma. A case report and surgical review. Int J Pancreatol 1996;19:145–153.

15 Z'Graggen K, Fernandez-del Castillo C, Rattner DW, Sigala H, Warshaw AL: Metastases to the pancreas and their surgical extirpation. Arch Surg 1998;133:413–419.

16 Law CH, Wei AC, Hanna SS, Al-Zahrani M, Taylor BR, Greig PD, Langer B, Gallinger S: Pancreatic resection for metastatic renal cell carcinoma: presentation, treatment, and outcome. Ann Surg Oncol 2003;10:922–926.

17 Pierce RA, Spitler JA, Hawkins WG, Strasberg SM, Linehan DC, Halpin VJ, Eagon JC, Brunt LM, Frisella MM, Matthews BD: Outcomes analysis of laparoscopic resection of pancreatic neoplasms. Surg Endosc 2007;21: 579–586.

18 Mabrut JY, Fernandez-Cruz L, Azagra JS, Bassi C, Delvaux G, Weerts J, Fabre JM, Boulez J, Baulieux J, Peix JL, Gigot JF: Laparoscopic pancreatic resection: results of a multicenter European study of 127 patients. Surgery 2005;137:597–605.

19 Büchler MW, Wagner M, Schmied BM, Uhl W, Friess H, Z'Graggen K: Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg 2003;138:1310–1315.

20 Hashimoto M, Miura Y, Matsuda M, Watanabe G: Concomitant duodenal and pancreatic metastases from renal cell carcinoma: report of a case. Surg Today 2001;31:180–183.

21 Logue AJ, Behrman SW: Recurrent metachronous metastatic multifocal renal cell carcinoma to the pancreas. Am Surg 2007; 73:407–409.

22 Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE: Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–1137.

23 Birkmeyer JD, Warshaw AL, Finlayson SR, Grove MR, Tosteson AN: Relationship between hospital volume and late survival after pancreaticoduodenectomy. Surgery 1999; 126:178–183.

24 Schwarz RE, Harrison LE, Conlon KC, Klimstra DS, Brennan MF: The impact of splenectomy on outcomes after resection of pancreatic adenocarcinoma. J Am Coll Surg 1999;188:516–521.

25 Wanebo HJ, Kennedy BJ, Winchester DP, Stewart AK, Fremgen AM: Role of splenectomy in gastric cancer surgery: adverse effect of elective splenectomy on long-term survival. J Am Coll Surg 1997;185:177–184.

26 Choueiri TK, Rini B, Garcia JA, Baz RC, Abou-Jawde RM, Thakkar SG, Elson P, Mekhail TM, Zhou M, Bukowski RM: Prognostic factors associated with long-term survival in previously untreated metastatic renal cell carcinoma. Ann Oncol 2007;18: 249–255.

27 Carter JT, Grenert JP, Rubenstein L, Stewart L, Way LW: Tumors of the ampulla of Vater: histopathologic classification and predictors of survival. J Am Coll Surg 2008;207:210–218.

28 Assouad J, Riquet M, Berna P, Danel C: Intrapulmonary lymph node metastasis and renal cell carcinoma. Eur J Cardiothorac Surg 2007;31:132–134.

29 Tongio J, Peruta O, Wenger JJ, Warter P: Duodenal and pancreatic metastases of nephroepithelioma (in French). Ann Radiol (Paris) 1977;20:641–647.

30 Kassabian A, Stein J, Jabbour N, Parsa K, Skinner D, Parekh D, Cosenza C, Selby R: Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. Urology 2000;56:211–215.

31 Uemura T, Kurita A, Nishimura R, Ishizaki M, Takashima S: Solitary pancreatic metastasis from renal cell carcinoma concomitant with early gastric cancer 17 years after nephrectomy: report of a case. Surg Today 2003;33:395–398.

32 Bonsib SM: Renal lymphatics, and lymphatic involvement in sinus vein invasive (pt3b) clear cell renal cell carcinoma: a study of 40 cases. Mod Pathol 2006;19:746–753.

33 Assouad J, Riquet M, Foucault C, Hidden G, Delmas V: Renal lymphatic drainage and thoracic duct connections: implications for cancer spread. Lymphology 2006;39:26–32.

34 Hirai I, Murakami G, Kimura W, Tanuma K, Ito H: Origin of the thoracic duct and pancreaticoduodenal lymphatic pathways to the para-aortic lymph nodes. J Hepatobiliary Pancreat Surg 2001;8:441–448.