

CT diagnosis for metastasis of clear cell renal cell carcinoma to the pancreas

Three case reports

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Abstract

Rationale: Clear cell renal cell carcinoma (CCRCC) metastasis to pancreas is clinically rare. Misdiagnosis for these cases is frequently due to the low incidence, lack of specific clinical symptoms, and laboratory results.

Patient concerns: Three female patients aged 47 years, 69 years, and 76 years, respectively, were admitted to hospital for routine examination after resection of clear cell carcinoma of kidney for 69 months, 57 months, and 123 months, respectively. All 3 cases had no specific clinical symptoms. Routine laboratory tests and common tumor markers including CEA, AFP, CA19-9, and CA125 showed no obvious abnormality.

Diagnosis: All 3 cases were finally diagnosed with CCRCC metastasis to pancreas on the basis of CT and pathological findings. On unenhanced CT, foci of the pancreas showed single or multiple nodules or masses with mildly low or equal density and obscure boundary. On enhanced CT, the enhanced mode of foci was similar to CCRCC and showed “fast in fast out.” The main body was confined in the pancreas. The peripheral structure was clear relatively. Obstruction of common bile duct, main pancreatic duct, and local infringement of foci cannot be seen. Additional metastases of right adrenal gland can be seen in one case.

Interventions: All 3 cases underwent CT examination and surgical treatment, with complete removal of metastatic tumors.

Outcomes: All 3 cases underwent surgical treatment successfully, and recovered successfully after operation.

Lessons: The manifestations of pancreatic metastases from CCRCC on CT show certain characteristics, which may be useful to assess the histological features of pancreatic metastases from CCRCC and facilitate the preoperative diagnosis.

Abbreviations: AFP = alpha fetoprotein, CA = carbohydrate antigen, CCRCC = clear cell renal cell carcinoma, CD = cluster of differentiation, CEA = carcino-embryonic antigen, CK = cell keratin, CT = computed tomography, RCC = renal cell carcinoma.

Keywords: clear cell renal cell carcinoma, clinic, computed tomography, diagnosis, metastases, pancreas

1. Introduction

The pancreas is an unusual site for tumor metastasis and only 2% to 5% of malignancies affect the pancreas.^[1] Malignancies that can metastasize to pancreas include renal cell carcinomas (RCC), melanomas, colorectal carcinomas, breast carcinomas, and

sarcomas.^[1,2] RCC metastasizing to pancreas occurs in 1% to 2% of all RCC cases.^[2] Clear cell renal cell carcinoma (CCRCC) accounts for the vast majority of all RCC, and metastasis from CCRCC accounts for nearly 1.3% in all pancreas-related malignancies.^[1,3] CCRCC is known for its late metastasis to unusual sites after resection of the primary tumor.^[2-4] Due to the low incidence and the lack of specific clinical symptoms and laboratory results, metastasis of CCRCC to pancreas is frequently misdiagnosed in practice.^[1,4,5] However, if accurate diagnosis and treatment were made timely and properly, most of patients can have satisfactory prognosis.^[1,4] To improve the understanding of such disease, we retrospectively described the computed tomography (CT) manifestations and clinical presentations of 3 patients with metastatic CCRCC to the pancreas. A literature review was also performed.

Informed consent was obtained from every patient and the study was approved by the ethics review board of the People's Hospital of Cixi City.

2. Case report

2.1. Case 1

A 47-year-old woman was examined routinely for 69 months after resection of clear cell carcinoma of left kidney. The patient presented no obvious clinical symptoms prior to admission. The

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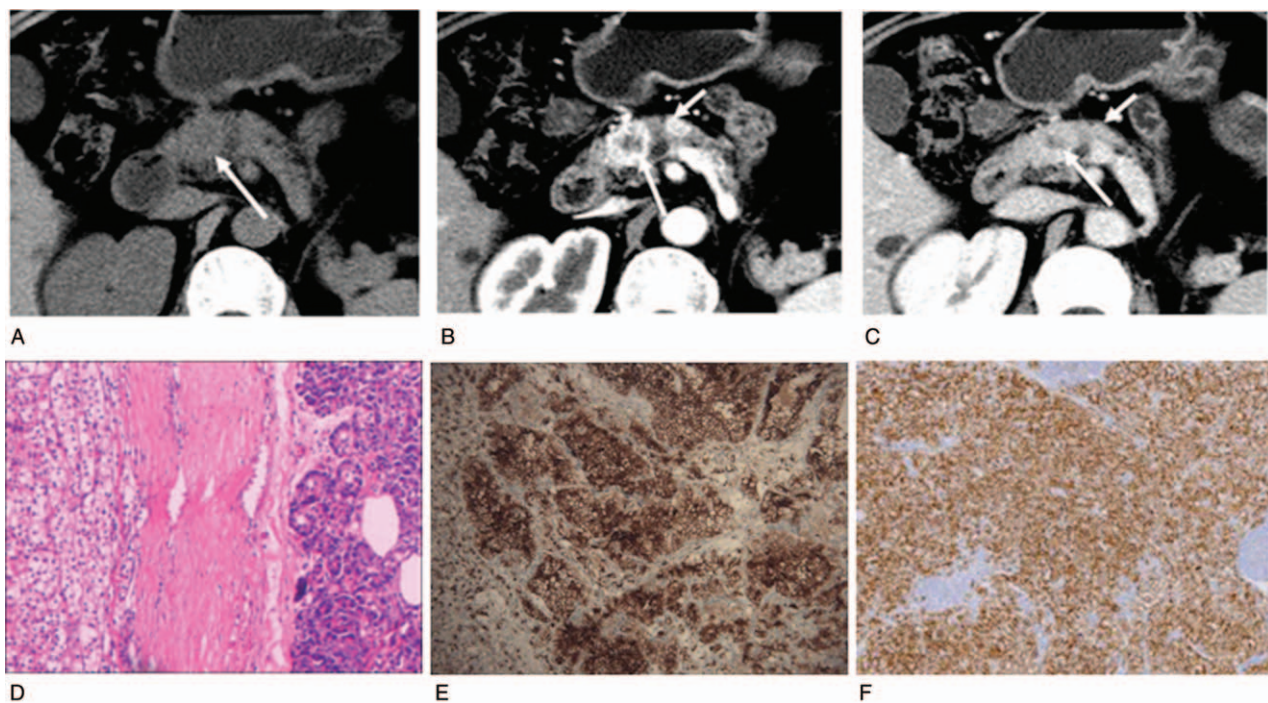


Figure 1. CT and histopathological examination of Case 1. (A) Unenhanced CT only showed one oval nodule in pancreatic head with dim boundary and heterogeneous mild low density (arrow). (B) Enhanced CT of arterial phase showed the nodule of pancreatic head with significantly heterogeneous annular enhancement (long arrow), and another small nodule of pancreatic neck with homogeneous significantly enhancement (short arrow). (C) Enhanced CT of venous phase showed the enhancement of nodule of pancreatic head (long arrow) and neck (short arrow) declined obviously and the enhanced mode was “fast in fast out.” (D) H&E staining; Scale bar: 120 μm. Immunohistochemical examination demonstrated positive (E) renal cell carcinoma and (F) cluster of CD10. Scale bar: 60 μm. CT = computed tomography.

results of laboratory tests on blood, urine, stool, hepatic function, and renal function were normal. The tests for tumor markers including carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), carbohydrate antigen (CA) 19-9, and CA125 were also normal. Color duplex ultrasound showed mixed echo of multiple nodules with rich blood supply in pancreatic head and neck. The patient was also scanned on a 64-row multidetector CT scanner (GE Light Speed VCT, GE Healthcare, Piscataway, NJ) with the following parameters. Scanning scope: from the diaphragm to the lower edge of the right kidney. Number of scanning slices: 84 slices in nonenhanced CT and each phase of enhanced CT. Slice thickness was 3 mm. Contrast agent of enhanced CT was Ultravist (300mg I/mL; Bayer Schering Pharma, Berlin, Germany). Axial CT of abdomen showed one oval nodule at

pancreatic head with dim boundary and heterogeneous mild low density compared with the normal tissue of pancreas, and there was no obvious abnormality in the rest part of the pancreas (Fig. 1A) (Table 1). Enhanced CT in artery phase showed the nodule of pancreatic head had obviously heterogeneous annular enhancement, and obviously high density at the peripheral area of nodule compared with the normal tissue of pancreas. Another small nodule was obviously enhanced in pancreatic neck with homogeneous high density (Fig. 1B). Enhanced CT in venous phase (Fig. 1C) and delayed phase showed the enhancement of 2 nodules decreased, with mild low and equal density compared with the normal tissue of pancreas. The 2 foci showed “fast in fast out” mode. Small patchy and punctiform areas without enhancement could be seen in the middle of nodule in pancreatic

Table 1

The CT characteristics of 3 cases of pancreatic metastasis from CCRCC.

Item	Number	Location	Diameter, mm	Shape	Unenhanced CT	Enhanced CT		
						Arterial phase	Venous phase	Delayed phase
Case 1	2	Pancreatic head	23	Oval	Heterogeneous mild low density	Obvious annular enhancement	Moderate annular enhancement	Mild annular enhancement
		Pancreatic neck	11	Oval	Equal density	Obvious homogeneous enhancement	Moderate homogeneous enhancement	Mild homogeneous enhancement
Case 2	1	Pancreatic body and tail	41	Hemispherical	Equal density	Obvious annular enhancement	Moderate annular enhancement	Mild annular enhancement
Case 3	1	Pancreatic head	18	Oval	Mild low density	Obvious homogeneous enhancement	Moderate homogeneous enhancement	Mild homogeneous enhancement

CT = computed tomography.



Figure 2. CT examination of Case 2. (A) Unenhanced CT showed the well-stacked body and tail of pancreas. A blurry mass with equal density and dim boundary was seen (long arrow). A small round nodule with mildly low density was observed in the right adrenal gland (short arrow). (B) Enhanced CT of arterial phase showed the foci of pancreas (long arrow) and the right adrenal gland (short arrow) with obviously heterogeneous annular enhancement. (C) Enhanced CT of venous phase showed the enhancement of pancreatic mass and right adrenal nodule declined obviously (long arrow and short arrow). CT = computed tomography.

head with persistent low density. The 2 foci were confined in the pancreases, with clear boundary on enhanced CT. The maximum diameters were 23 mm and 11 mm, respectively. Main pancreatic duct was broadened with obvious infringement at adjacent tissues. The seroperitoneum and swollen lymph nodes of posterior peritoneum were not observed (Fig. 1A–C).

The patient underwent resection of pancreas head and neck and 2 nodules. The texture of 2 separated nodules was soft with red and yellow color. Cystic lesions with necrosis were observed in central area of pancreatic head. Histopathological examination of 2 nodules showed tumor cells with obvious atypia pleomorphism in the shape of acinus and glandular tube. The cells had deeply stained cell nucleolus, abundant and transparent cytoplasm, and slim reticular interval of vessel in the mesenchyme (Fig. 1D). Immunohistochemical analysis showed positive expressions on renal cell carcinoma (RCC) (Fig. 1E), cluster of differentiation (CD) 10 (Fig. 1F), CD56 and Vimentin, while the negative expressions on broad-spectrum cytokeratin, chromaffin granules protein, synaptophysin, E-cadherin, CD117 and cell keratin (CK). The final pathological diagnosis was pancreatic metastasis from CCRCC (2 foci).

2.2. Case 2

A 69-year-old woman was admitted to hospital after resection of clear cell carcinoma on right kidney 57 months ago. She had left upper abdominal pain and waist back pain for nine months, with weight loss and fatigue for 6 months. She had diabetes mellitus for 7 years. Medications included metformin, repaglinide, atorvastatin, and aspirin. The results of laboratory tests on blood, urine, stool, hepatic, and renal function were normal. Fasting blood-glucose was 8.2 mmol/L (reference range, 3.9–6.1). CEA was 5.4 ng/mL (reference range, 0–5.0). AFP, CA19-9, and CA125 were normal. Color duplex ultrasound showed mixed echo with rich blood supply in pancreatic body and tail. CT scanning was performed on a 64-row multidetector CT scanner (GE Light Speed VCT, GE Healthcare, Piscataway, NJ) with the following parameters. Scanning scope: from the diaphragm to the lower edge of the right kidney. Number of scanning slices: 72 slices in nonenhanced CT and each phase of enhanced CT. Slice thickness was 3 mm. Contrast agent of enhanced CT was Ultravist (300 mg I/mL; Bayer Schering Pharma, Berlin, Germany). Axial CT of abdomen showed the pancreatic body and tail was plump, in which an equal density mass with

hemispherical shape and dim boundary could be observed (Fig. 2A) (Table 1). In arterial phase of enhanced CT showed the periphery of the mass with obvious enhancement, and the central area with faint enhancement, together with small spotted area of cystic lesions without enhancement (Fig. 2B). Enhanced CT in venous phase showed weakened enhancement of the mass periphery, but the enhancement was still evident than the normal tissue of pancreas (Fig. 2C). The enhanced mode was in a “fast in fast out” mode on radiology. The mass had clear boundary and smooth outline on enhanced CT. Its maximum diameter was 41 mm. The anterior area of the mass extruded the pancreatic slightly, but the main body was located in the pancreas. The main pancreatic duct behind the mass was pressed slightly, but not obstructed. The upstream pancreatic duct showed no obvious broadening, and the infringement of adjacent tissue out of pancreas was not observed. Additionally, a small round nodule with mildly low density was observed in the right adrenal gland and its diameter was 9 mm approximately (Fig. 2A). Enhanced CT in arterial phase showed obvious annular enhancement, and the enhancement declined in venous and delayed phase (Fig. 2B and C). The enhanced mode was also “fast in fast out.” Small spotted cystic area inside the nodule of right adrenal was not enhanced, and ascites or swollen lymph nodes of enterocolica and posterior peritoneum were not observed.

The patient underwent resection of the mass of pancreatic body, tail, and the nodule of right adrenal. The pathological examination showed the mass of pancreas and nodule of right adrenal with wrapped pseudocapsule were tenacious in texture and light yellow mixed with other colors on the surface. Histopathological examination revealed irregularly arranged tumor cells with different size, deeply stained big nuclei, the pathological mitotic figure in nuclear, and abundant transparent cytoplasm. Immunohistochemical analysis showed positive expressions on CD56, vimentin, and epithelial membrane antigen, and the negative expressions of chromaffin granules protein, synaptophysin, E-cadherin, CD117, CA19-9, and CK. The final pathological diagnosis was metastasis of pancreatic body and tail and right adrenal from CCRCC.

2.3. Case 3

A 76-year-old woman was admitted because resection of clear cell carcinoma on right kidney for 123 months with pain at right upper abdomen, abdominal distention and loss of appetites for 6

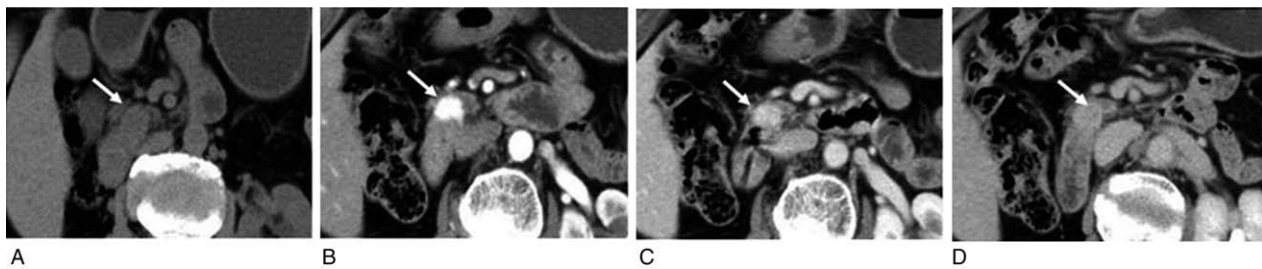


Figure 3. CT examination of Case 3. (A) Unenhanced CT showed a blurry round nodule with mild low density and dim boundary in pancreatic head (arrow). (B) Enhanced CT of arterial phase showed the foci of pancreatic head with obviously homogeneous enhancement and high density near aorta (arrow). Enhanced CT of venous phase (C) and delayed phase (D) showed the enhancement of focus in pancreatic head declined obviously (arrow), and the enhanced mode was “fast in fast out.” CT = computed tomography.

months. She had hypertension for 20 years. The laboratory tests for blood, urine, stool, and hepatic renal function were normal. Tumor markers including CEA, AFP, CA19-9, and CA125 were also normal. Color duplex ultrasound showed a solid echo with rich blood supply in pancreatic head. This patient was scanned on a 64-row multidetector CT scanner (GE Light Speed VCT, GE Healthcare, Piscataway, NJ) with the following parameters. Scanning scope: from the diaphragm to the lower edge of the right kidney. Number of scanning slices: 66 slices in nonenhanced CT and each phase of enhanced CT. Slice thickness was 3 mm. Contrast agent of enhanced CT was Ultravist (300 mg I/mL; Bayer Schering Pharma, Berlin, Germany). Axial CT of abdomen showed a blurry round nodule with mild low density and dim boundary in pancreatic head (Fig. 3A). Enhanced CT in arterial phase showed obvious homogeneous enhancement, with obvious high density near to aorta of the nodule (Fig. 3B) (Table 1). In venous phase of enhanced CT, the enhancement declined and was mildly evident than the normal tissue of pancreas (Fig. 3C). In delayed phase, the enhancement declined further, and showed low density compared with the normal tissue of pancreas (Fig. 3D). The enhanced mode was “fast in fast out.” The nodule confined in pancreatic outline had clear boundary on enhanced CT and its maximum diameter was 18 mm approximately. The common bile duct and main pancreatic duct were pressed slightly without obvious infringement or expansion. The descending part of duodenum was pressed slightly, while the rest tissues were normal. In addition, the retroperitoneal structure was clear (Fig. 3A–D).

The patient underwent a sectional resection of pancreatic head with the nodule. The pathological examination of the nodule showed that wrapped pseudocapsules were tenacious in texture and yellow on the surface. Histopathological examination showed that tumor cells with different size arranged in bubble nests or atypia pleomorphism, with abundant cytoplasm and eosinophilic, big and deeply stained nuclei. The nucleoli were in different sizes. Immunohistochemistry showed positive expressions of CD10, CD56, Vimentin, epithelial membrane antigen, and chromaffin granules protein, and negative expressions of synaptophysin, CD117, CA19-9. The final pathological diagnosis was CCRCC metastasis to the pancreatic head.

3. Discussion

The most common sites of RCC metastasis are the lung, bone, liver, brain, and adrenal tissue.^[6,7] Another less common site of RCC metastasis is the pancreas.^[4] As we know, CCRCC accounts for the vast majority of all RCCs, and metastasis of

CCRCC to the pancreas is rare. Therefore, surgical resection is feasible and it will be beneficial for long-term survival.^[1,4] As such, it is important to accurately diagnose pancreatic involvement by CCRCC, especially given that CCRCC metastasis may manifest more than a decade after its initial presentation and diagnosis.

Pancreatic metastasis from CCRCC usually is shown years after the diagnosis of primary tumor.^[2,4,8,9] As far as we know, the longest length of time was 32.7 years.^[3] Metastasis of CCRCC to pancreas may occur via the hematogenous route (involving the draining collateral veins from the primary CCRCC lesion) and the lymphatic route (involving the retrograde lymph flow through the retroperitoneal nodes), or may rarely direct spread to the pancreas.^[7,10,11] In our study, all 3 cases were postoperative transfer from CCRCC and the intervals were 69 months, 57 months, and 123 months, respectively.

Most cases of pancreatic metastases from CCRCC do not present specific clinical symptoms or specific laboratory results.^[1,4,7] Clinical manifestations in some cases present as ache and unwell of upper abdomen and lower back, distension, fatigue, loss of appetite, weight loss, and other nonspecific symptoms. Occasionally, gastrointestinal bleeding and jaundice may occur due to the involvement of duodenal and common bile duct.^[2] Pancreatitis may rarely occur due to the obstruction of pancreatic duct.^[12] In addition, there were no obvious symptoms in some cases.^[4] In our study, one case (Case 1) presented no obvious symptoms, while 2 cases (Case 2 and 3) presented slight symptoms such as abdominal pain, distension, and loss of appetite. Tumor markers such as CEA, CA125, and CA19-9 may rise slightly in few cases, but there is no specificity.^[13] Among 3 cases in our study, only one case (Case 2) showed slightly increased CEA, while the rest tumor markers were all normal in all 3 cases. Therefore, quite a lot of pancreatic metastases from CCRCC are detected during check-ups or routine physical examination. And, they are easily misdiagnosed.^[4]

Pancreatic metastases from CCRCC could locate in any part of pancreas, such as head, neck, body or tail indistinguishably.^[1–5,14] Most of cases showed single focus or multiple foci in oval or cloddy shape and different sizes.^[2,6,7] In addition, diffuse lesion is rare.^[4] In our cases, 4 foci were detected altogether with 2 foci in the pancreatic head, one focus in the neck and one focus in the body and tail.

Diagnosis of pancreatic metastases from CCRCC typically relies on findings from CT and ultrasonography examinations.^[5,7,15] On unenhanced CT, most foci showed nodules or masses with low or mildly low density, while a few foci could be equal density and not detected.^[16] Small tumors are usually

confined in pancreas, while large tumors are more likely to stick out of pancreas. Thus, the maximum diameter of most small focus is inside the pancreas.^[5,7] Most foci usually present blurry boundary and heterogeneous density on unenhanced CT. The cystic and necrotic tissue inside the focus shows lower density than peripheral area.^[5,15] The enhanced level and mode of most foci are similar to primary CCRCC usually, and show significant enhancement in artery phase, while decreased enhancement in venous phase.^[5,15,16] However, the enhancement may be still apparent relatively in venous phase in some cases.^[16] Finally, they usually showed obviously declined enhancement in delayed phase. In brief, enhanced CT of most foci shows that the enhanced mode is in “fast in fast out” mode.^[5,14] In our cases, 2 cases (Case 1 and 2) showed heterogeneous enhancement. The peripheral area showed “fast in fast out,” but cystic and necrotic area with low density inside the tumors showed no enhancement. The other case (Case 3) showed uniform enhancement. Its enhanced mode was also “fast in fast out” but there was no necrosis inside the focus. On enhanced CT, the boundary of all 4 foci was clear, and their outlines were relatively smooth.

Infringement or obstruction of common bile duct or main pancreatic duct is infrequent in pancreatic metastases.^[15,16] In our study, one focus located in the pancreatic head (Case 3) showed mild oppression of common bile duct and main pancreatic duct without obvious infringement. Another focus located in the pancreatic body and tail (Case 2) showed mild oppression of main pancreatic duct, without obvious infringement either. Moreover, the upriver pancreatic tissue of the 4 foci had no obvious atrophy, and their adjacent retroperitoneal structure was relatively clear and without local infringement or package. These features are different from those of pancreatic adenocarcinoma in differential diagnosis.^[17]

Differential diagnosis: (1) Pancreatic neuroendocrine neoplasms. Pancreatic neuroendocrine neoplasms can be classified into functional and nonfunctional types. Most foci show lower density and with clear boundary relatively on unenhanced CT, and show obviously continuous enhancement on enhanced CT, especially in arterial and venous phase. Functional tumors are small in size, and usually show obvious hormone-related symptoms. Nonfunctional tumors don't show hormone-related symptoms. However, the size is large or even enormous, and hepatic metastases are common relatively.^[18] (2) Solid pseudopapillary tumor. Most solid pseudopapillary tumors show cystic-solid mass of pancreatic head or tail, with clear boundary and low density on unenhanced CT. On enhanced CT, the solid components of tumors show mild-to-moderate enhancement unevenly, cystic degeneration, and hemorrhage are commonly inside the tumor. The malignancy of tumor is low, and local infringement of adjacent structural or metastasis is extremely rare.^[19] (3) Pancreatic adenocarcinoma: Pancreatic adenocarcinoma is the most common malignant tumor of pancreas. On unenhanced CT, most foci show low-density nodule or mass of pancreatic head with mild enhancement in arterial phase but delayed enhancement in venous and delayed phase on enhanced CT. Internal necrosis can be seen occasionally. The obstructions of common bile duct and main pancreatic duct are common and accompanied with atrophy of upstream pancreatic tissue. At the same time, local infringement of adjacent structure and metastasis of lymph node and liver are common^[20].

Due to the long duration between the detection of pancreatic metastases and the resection of primary CCRCC, additional metastases from CCRCC outside pancreas could be found in some cases, such as metastases of liver, lungs, spleen, adrenal,

peritoneum, abdominal cavity, spine, or abdominal and retroperitoneal lymph nodes.^[2,5,7] These metastases usually show similar enhanced mode of “fast in fast out” on enhanced CT as primary CCRCC. In our study, only Case 2 was accompanied with single additional metastasis of the right adrenal gland. Other than this, there was no additional metastasis in any other sites in the reported 3 cases.

This study has some limitations. First, the sample size was relatively small. There were only 3 cases of metastases of CCRCC to pancreas and 4 foci in pancreas altogether. The CT findings of these 4 foci may not be able to fully summarize the CT features of these tumors. Second, we only described the CT manifestations and clinical presentations of 3 cases of metastatic CCRCC to pancreas before surgical treatment. However, the follow-up and prognosis after surgical treatment were not included. Therefore, the effect of surgical treatment for this kind of tumor may not be deduced according to the 3 cases in this study.

In conclusion, the manifestations of pancreatic metastases from CCRCC on CT show certain characteristics in general. On unenhanced CT, most foci show single or multiple nodules or masses with mildly low or equal density and obscure boundary. Cystic and necrotic area inside the foci shows lower density in some cases. On enhanced CT, the enhanced mode is similar to CCRCC and shows “fast in fast out” mode. In addition, the boundary became clear, and the outline is relatively smooth on enhanced CT. The main body is usually confined in the pancreas. The peripheral structure is clear. Obstruction of common bile duct, main pancreatic duct and local infringement of foci is infrequent. Additional metastases outside of pancreas can be seen in some cases. If the history of CCRCC and metastatic foci outside pancreas are determined, pancreatic metastases from CCRCC should be considered primarily.

Author contributions

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