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FULL PAPER

Multidetector CT imaging features of invasive renal parenchyma urothelial carcinoma

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Objective: To characterize the multidetector CT imaging features of invasive renal parenchyma urothelial carcinoma (IRPUC).

Methods: 29 patients with IRPUC were retrospectively evaluated. Tumour location, density, cystic or solid appearance, calcification, capsule sign, enhancement pattern and metastases were assessed.

Results: IRPUC involved the right kidney in 82.7% of patients. Medullary involvement was observed in 93.1% of patients. In 89.6% of patients, the reniform contour of the kidney was preserved. Tumours showed an infiltrative appearance (100%) with a poorly defined margin (100%), but an expansile component was also present (20.7%). Linear calcification was present (20.7%). Evidence of intra-abdominal metastatic disease (in 37.9% of cases)

and regional lymphadenopathy (in 27.5% of cases) was present. Tumour attenuation was less or equal compared with the renal cortex or medulla on unenhanced CT (p -value > 0.05), after i.v. contrast administration; 100% were of homogeneous low attenuation compared with the normal renal cortex and medulla (p -value < 0.05).

Conclusion: IRPUC tends to be more prevalent in the right kidney, poorly defined margin, medullary involvement, with homogeneous enhancement less than the cortex and medulla in all phases.

Advances in knowledge: IRPUC was more prevalent in the right kidney. IRPUC enhancement was less than that of the cortex and medulla on all phases. IRPUC showed poorly defined margin with medullary involvement and preserved reniform contour.

INTRODUCTION

Upper tract infiltrating urothelial carcinomas occur in $<10\%$ of patients with bladder tumours,¹ but invasive renal parenchyma urothelial carcinoma (IRPUC) is scanty. The distinctive feature of IRPUC is its infiltrative growth, whereas most renal cell carcinomas exhibit an expansile appearance.²

The type and severity of clinical signs and symptoms of IRPUC depend on the extent and location of the tumour. Most patients with IRPUCs present with at least microscopic haematuria. Hydronephrosis may result but may go clinically unnoticed if obstruction develops slowly;³ but, hydronephrosis or hydroureterosis is scanty in IRPUC.

Previously published reports^{3,4} on upper tract infiltrating urothelial carcinoma have documented the imaging, pathologic and clinical features of renal carcinoma.

There are relatively few previous reports focusing on IRPUC. Many scholars reported that IRPUC was similar to

renal inflammatory lesions or other renal carcinomas on clinical and CT features.⁴ However, patients with IRPUC have a differential therapeutic regimen from inflammatory lesions or other renal carcinomas for clinicians. The major therapies for patients with renal inflammatory lesions are anti-inflammatories. However, nephrectomy is indicated for renal parenchymal malignancies.⁵ So, an accurate diagnosis is important for the clinician. In this study, we retrospectively investigated multidetector CT (MDCT) findings of 29 cases of IRPUC. Our purpose was to characterize the imaging features of IRPUC.

METHODS AND MATERIALS

Patients

This study was approved by the institutional research ethics committee. A search of pathology records and the picture archiving and communication system identified 29 patients with IRPUC retrospectively, who were hospitalized at our hospital between 2003 and 2015. Age, sex, tumour size, right or left location, surgery or biopsy finding, metastasis location and clinical symptoms were recorded.

CT technique

CT examinations were performed by using 16-row (Light speed Ultra; GE Healthcare, Milwaukee, WI) ($n = 4$) or 64-row (Somatom Definition; Siemens Medical Solutions, Forchheim, Germany) ($n = 25$) detector scanners. Abdominal unenhanced CT ($n = 28$) and contrast-enhanced CT ($n = 29$) scans were performed. Parameters included: detector collimation of 16×0.6 mm and 64×0.6 mm, gantry rotation time of 0.5 s, pitch of 1.4, tube voltage of 120 kVp and abdominal reference tube current of 230 mAs. All images were reconstructed from the contrast-enhanced MDCT scan with 0.75-mm slice thickness and 0.5-mm reconstruction increment. Contrast-enhanced CT scan was started by continuously injecting a bolus of 80–100 ml of iopromide (Ultravist® 350; Bayer Schering Pharma AG, Berlin, Germany), followed by 40-ml saline solution into an antecubital vein *via* an 18-gauge catheter (injection rate 5 ml s^{-1}). The enhanced CT scans were performed at 20-s arterial phase (renal cortex phase, $n = 29$), 65-s corticomedullary phase (nephrographic phase, $n = 29$) and 240-s excretory phase (delayed phase, $n = 29$).

Imaging analysis

Two genitourinary radiologists analyzed the images together, a process that resulted in a consensus interpretation. The imaging parameters included the tumour position, size, cystic components or necrosis, calcification, tumour attenuation on unenhanced CT scan, the degree of enhancement (Hounsfield units) on different phases of the enhanced CT scan, lymphadenopathy, perinephric stranding, hydronephrosis, the presence or absence of a clear tumour boundary (capsule sign), vascular invasion and metastasis.

Table 1. Clinical data of 29 patients

Clinical data	Number of subjects
Age (years)	52 ± 12.8 (20–73)
Gender	
Male	18 (62.1%)
Female	11 (37.9%)
Side	
Left	5 (17.3%)
Right	24 (82.7%)
Flank pain	
Yes	8 (27.6%)
No	21 (72.4%)
Haematuria	
Yes	9 (31.0%)
No	20 (69.0%)
Fever	
Yes	7 (24.1%)
No	22 (75.9%)

Infiltrative growth was characterized by a lack of a clear boundary. The density of mass, normal renal cortex and medulla were measured on enhanced phases. However, intratumoral calcification and cystic components if present were avoided. 10-mm regions of interest were measured three times for each phase and the mean values were used.

Statistical analysis

Statistical analysis was undertaken using SPSS® v. 13.0 statistical software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Numeric data were expressed as means and standard deviations, and categorical data were expressed as percentages. The evaluated characteristics were compared using analysis of variance. p -values < 0.05 were considered statistically significant.

RESULTS

Clinical and multidetector CT appearances

The study included 29 patients (18 males and 11 females) with IRPUC (Table 1). The mean age at diagnosis was 52 ± 12.8 years (range 20–73 years) (Table 1). Presenting symptoms of IRPUC included flank pain ($n = 8$), haematuria ($n = 9$) and fever ($n = 7$). None of our cases were found to have ureteral cancer or bladder cancer. Abdominal MDCT scans were available for all patients. The maximal tumour diameter ranged from 3.9 to 6.3 cm (mean diameter, 5.1 ± 0.68 cm) (Table 2). IRPUC involved the right kidney in 24 (82.7%) of 29 cases (Table 2). Central or medullary involvement by tumour was present in 27 (93.1%) of 29 cases (Figures 1–3). Cortical

Table 2. CT imaging findings

Main CT finding	Value
Size (cm)	5.1 ± 0.68 (3.9–6.3)
Mass location	
Medullary involvement	27 (93.1%)
Cortical involvement	6 (20.7%)
Solid and cystic pattern	
Solid	25 (86.2%)
Solid and cystic	4 (13.8%)
Cystic	0 (0%)
Calcification	
Yes	6 (20.7%)
No	23 (79.3%)
Unenhanced CT density	
High attenuation	0 (0%)
Isoattenuation, hypoattenuation	29 (100%)
Capsule sign	
Yes	0 (0%)
No	29 (100%)
Lymph node metastasis	8 (27.5%)
Distant metastasis	11 (37.9%)
Renal or inferior caval vein invasion	0 (0%)

Figure 1. An invasive renal parenchyma urothelial carcinoma (IRPUC) of the right kidney in a 73-year-old male. (a) The axial unenhanced CT scan showing a poorly defined isodense mass (arrow) in the medulla. The attenuation of the mass is 35 HU. (b) The contrast-enhanced CT scan showing a mild enhancement less than that of the cortex and medulla on the cortical phase (67 HU), showing an infiltrative appearance and unclear boundary (arrow). (c) The axial attenuation of the tumour (83 HU) has increased (arrow) on the nephrographic phase. (d) The axial attenuation (62 HU) of the tumour has then decreased on the delayed phase (arrow). (e) Microscopic analysis of IRPUC tumour cells showing abundant amphophilic cytoplasm and large hyperchromatic nuclei. The nucleus is pleomorphic and has irregular contours (haematoxylin and eosin stain $\times 400$).

involvement was noted in 6 (20.7%) of 29 cases; an exophytic component beyond the expected renal contour was seen in 4 (13.8%) of 29 cases (Figure 4). The reniform contour of the

involved kidney was preserved in 26 (89.6%) of 29 cases (Table 2); an expansile component was also present in 6 (20.7%) of these cases. The mean tumour size among 26 cases with a

Figure 2. An invasive renal parenchyma urothelial carcinoma (IRPUC) of the right kidney in a 57-year-old male. (a) The axial unenhanced CT scan showing a poorly defined isodense mass (black arrow) in the renal medulla together with regional lymphadenopathy (white arrow). The attenuation of the mass is 40 HU. (b) The contrast-enhanced CT scan showing a mild enhancement less than that of the cortex and medulla on the cortical phase (arrow) (63 HU), showing an unclear boundary. (c) The axial attenuation of the tumour (81 HU) has increased (arrow) on the nephrographic phase. (d) The axial attenuation (64 HU) of the tumour has then decreased on the delayed phase, showing an infiltrative appearance (arrow). (e) Microscopic analysis of IRPUC tumour cells showing an abundant amphophilic cytoplasm and large hyperchromatic nuclei (haematoxylin and eosin stain $\times 400$).

Figure 3. An invasive renal parenchyma urothelial carcinoma (IRPUC) of the right kidney in a 70-year-old female. (a) The axial contrast-enhanced CT scan showing a mild enhancement (arrow) less than that of the cortex and medulla on the cortical phase (67 HU), showing an unclear boundary. (b) The axial attenuation of the tumour (80 HU) has increased (arrow) on the nephrographic phase together with cystic components. (c) The axial attenuation (62 HU) of the tumour has then decreased on the delayed phase, showing an infiltrative appearance (arrow). (d) The maximum intensity projection on the delayed phase showing calyceal destruction (arrows). (e) Microscopic analysis of IRPUC tumour cells showing abundant amphophilic cytoplasm with squamous differentiation (haematoxylin and eosin stain $\times 400$).

preserved reniform shape was 4.9 ± 0.5 cm vs 6.2 ± 0.1 cm among 4 tumours with an exophytic component.

The tumours appeared solid (29/29, 100%) on MDCT. 4 (13.8%) tumours had a small cystic component that represented

areas of necrosis at pathologic examination (Table 2). Of the 28 cases (28/29) with unenhanced images, all tumours showed less or equal attenuation of the soft-tissue component relative to the normal renal parenchyma (33.6 ± 3.1 vs 36.7 ± 2.8 vs 32.1 ± 3.3 ; p -value > 0.05 , $n = 28$) (Figures 1, 2 and 4). Linear calcification

Figure 4. An invasive renal parenchyma urothelial carcinoma (IRPUC) of the right kidney in a 20-year-old female. (a) The axial unenhanced CT scan showing an isodense mass, with an infiltrative and expansible appearance and distorted reniform contour together with calcifications (arrow). (b) The contrast-enhanced CT scan showing a mild enhancement less than that of the cortex and medulla on the cortical phase (68 HU), showing an infiltrative appearance and unclear boundary (arrow). (c) The axial attenuation of the tumour (84 HU) has increased on the nephrographic phase (arrow). (d) The axial attenuation (63 HU) of the tumour has then decreased on the delayed phase (arrow). (e) Microscopic analysis of IRPUC tumour cells showing abundant amphophilic cytoplasm and large hyperchromatic nuclei (haematoxylin and eosin stain $\times 400$).

was present in 6 (20.7%) cases (Figure 4). In 15 (51.7%) of the 29 cases, involvement of the renal sinus was present, but none of our cases had hydronephrosis or hydroureterosis. Evidence of intra-abdominal metastatic disease was present on CT in 11 (37.9%) of 29 cases. Regional lymphadenopathy was seen in 8 (27.5%) cases (Figure 2a). Direct tumour extension into the venous system was not seen in any of the cases.

After i.v. contrast administration, all tumours (29/29, 100%) were of homogeneous low attenuation compared with the normal renal cortex and medulla (Figures 1–4). On dynamic contrast-enhanced CT scan, the CT attenuation of IRPUC was less than that of the normal renal cortex and medulla (66.6 ± 5.3 vs 192.7 ± 7.2 vs 79.7 ± 4.6 ; p -value < 0.05 , $n = 29$) on the cortical phase, less than that of the cortex and medulla (79.8 ± 6.9 vs 209.7 ± 8.9 vs 111.6 ± 5.3 ; p -value < 0.05 , $n = 29$) on the nephrographic phase and less than that of the cortex and medulla (64.2 ± 4.3 vs 109.3 ± 7.9 vs 96.3 ± 5.1 ; p -value < 0.05 , $n = 29$) on the delayed phase. The enhancement was lower in IRPUCs than in the renal cortex and medulla in all enhanced phases (p -value < 0.05).

Therapy and follow-up

In this study, the number of patients with tumour stages Grades I–IV was 2, 4, 10 and 13 cases, respectively. All of the 29 patients with IRPUCs underwent radical nephrectomy radiotherapy or chemotherapy and were followed up from 12 to 76 months. 18 patients died within 3 years, 4 patients died within 5 years after the initial diagnosis and the remaining patients are still alive.

Microscopic findings

In this study, 9 patients were confirmed by biopsy and 20 patients were confirmed by surgery. Only 5 patients were confirmed by pre-operative diagnosis. Tumour cells had an infiltrating cohesive nest with an abundant amphophilic cytoplasm and a large hyperchromatic nucleus (Figures 1–4e). The tumour cells were polygonal with voluminous eosinophilic nucleoli and high mitotic figures (Figures 1–4e). Mitotic figures are common, with numerous abnormal forms. Immunohistochemistry staining demonstrated Uroplakin III, CK 20 and CK 7 were positive in 25, 23 and 26 cases, respectively.

DISCUSSION

Bladder cancer is the seventh most common cancer worldwide, with an estimated 260,000 cases each year in males and 76,000 in females. The most common type of bladder cancer in developed countries is urothelial carcinoma, derived from the uroepithelium, which constitutes more than 90% of bladder cancer cases in USA, France or Italy.⁶ Although upper tract infiltrating urothelial carcinomas have been relatively well described in pathology and imaging studies, IRPUC is scanty.^{7,8}

Some imaging features have been reported, such as infiltrative growth⁹ and cystic component. However, some imaging features remain uncertain or contradictory, such as tumour location, capsule sign, calcification and enhancement pattern.

Infiltrative growth patterns¹⁰ differ from clear cell renal cell carcinoma, which exhibits an expansible appearance with exophytic

growth. Infiltrative lesions could enlarge the renal contour; however, they usually maintain the reniform contour. Most of the IRPUCs exhibited an infiltrative growth but maintained the reniform contour. In our study, all patients (29/29, 100%) with IRPUCs had an infiltrative appearance (100%) and 26 cases (89.6%) maintained the reniform contour. This is consistent with the IRPUC boundary seen by surgery, as has been noted by others.¹¹ However, other tumours reported to have clear boundaries include the well-differentiated clear cell carcinoma,¹² chromophobe renal cell carcinoma and Wilms' tumour.¹³

In addition to IRPUC, there are also other renal lesions that are typically infiltrative in nature. For renal medullary carcinoma,¹⁴ in the clinical setting of a young person (mean age 22 years) with sickle cell trait, it is often possible to anticipate the correct diagnosis with imaging studies. Metastatic deposits such as cervical nodes or brain tumour may be the initial evidence of disease. Centrally located tumours with an infiltrative growth pattern, invading renal sinus, are typical. Caliectasis without pelviectasis and tumour encasing the pelvis are also described.^{15,16} It is interesting to note that 24 IRPUCs involved the right kidney in our study. The reason for this predilection is unknown. For uncomplicated pyelonephritis, CT scan without contrast injection shows an enlarged kidney with infiltration of the perirenal space fatty tissue. After contrast-enhanced CT scan, the renal parenchyma has a "spoked wheel" appearance.¹⁷

Our results show that IRPUCs are a homogeneous mass on unenhanced CT scan. Perlman et al¹⁸ reported that calcification within the tumours often suggested renal cell carcinoma subtypes. Renal cell carcinomas >3 cm often contain intratumoral necrosis, haemorrhage, calcifications and are usually of the clear cell variety.¹⁹ Although commonly homogeneous, when poorly differentiated, papillary renal cell carcinomas²⁰ can have necrosis and cystic change and, in such a situation, may appear heterogeneous. In our study, there was evidence of calcification in 6 (20.7%) patients, which is linear compared with the stippled calcification seen in cortical renal cell carcinomas.

In our study, after i.v. contrast administration, all tumours (29/29, 100%) were of homogeneous low attenuation compared with that of normal renal cortex and medulla. The degree of IRPUC enhancement was lower than that of the cortex and medulla in the arterial, nephrographic and delayed phases. This may be a distinguishing feature from tumours with a rich blood supply such as clear cell carcinoma,²¹ renal medullary carcinoma and renal angioma. Therefore, it may be easy to distinguish between IRPUC and tumours with a rich blood supply by the degree of enhancement.²²

In common with IRPUCs, collecting duct carcinomas, chromophobe renal cell carcinomas²³ and renal lymphomas are hypovascular compared with renal parenchyma on enhanced CT imaging. The majority of collecting duct carcinomas²⁴ show mild enhancement on all enhanced scan phases. However, the latter are reported to be more common in the medulla, which is dissimilar to IRPUC. The majority of papillary renal cell carcinomas show mild enhancement during all enhanced phases. Furthermore, papillary renal cell carcinomas may be multifocal and bilateral, 73% have a thick fibrous pseudocapsule.²⁵

Evidence of intra-abdominal metastatic disease was present on CT in 11 (37.9%) of 29 cases. Regional lymphadenopathy was seen in 8 (27.5%) cases. However, papillary renal cell carcinomas, lymphomas and chromophobe renal cell carcinomas are rarely associated with lymph node metastasis or renal vein infiltration.^{26,27} Hence, the differential biological behaviour of tumours may also provide useful diagnostic information.

Information regarding the clinical behaviour of IRPUC is limited owing to its rare incidence.²⁸ In our study, 20 patients with IRPUCs underwent radical nephrectomy, 9 patients underwent radiotherapy or chemotherapy, of which all patients were able to be followed up from 12 to 76 months. 18 patients expired within 3 years, 4 patients expired within 5 years after the initial diagnosis and the others are still alive.

The main limitation of our study is the small number of patients with IRPUC. Further studies with larger populations are recommended to validate the results of our study.

Second, even though we calculated the MDCT imaging features of IRPUC, the characteristics need further study. Finally, pathologic specimens were sectioned in a variety of planes. So, it was difficult to meticulously correlate the imaging findings with the histopathologic figures.

In conclusion, MDCT imaging findings that support the diagnosis of IRPUC include tumour in the right kidney, poorly defined margin, medullary involvement, with homogeneous enhancement less than that of the cortex and medulla in all phases. In addition, IRPUC usually has unclear boundaries with a high frequency of intra-abdominal metastatic disease and lymph node metastases. With such findings, IRPUC should be considered.

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