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Upper tract transitional cell carcinoma: An array of imaging conundrum

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Abstract

We report a 38-year-old gentleman who presented with painless haematuria for 6-months duration. Contrast-enhanced CT renal revealed a large, calcified intrapelvic mass with calyceal extension confined within the right kidney with moderate pelvicalyceal dilatation but no evidence of synchronous lesion elsewhere. Histopathological analysis showed high grade urothelial carcinoma of the renal pelvis with invasion of renal parenchyma. Upper tract urothelial carcinoma (UTUC) which was once thought similar to urothelial carcinoma of the bladder (UCB), is increasingly being recognized as a different entity. However, heterogenous array of imaging manifestations of UTUC is also increasingly being encountered and pose diagnostic challenges though UTUC is not as prevalent as UCB which is easier to diagnose. Despite distinctive features against renal cell carcinoma (RCC), UTUC may mimic numerous other renal pathologies especially the benign ones hence imaging plays a pivotal role in ascertaining the diagnosis. This disease is usually treated with radical nephroureterectomy with superadded neoadjuvant chemotherapy for high-risk cases. Less invasive endoscopic resection is also offered in certain cases but stringent surveillance of the whole urinary tract as well as post-operative follow-up are mandatory.

Keywords: *upper tract transitional cell carcinoma, upper tract urothelial carcinoma*

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Introduction

Urinary tract tumours show a wide range of pathological subgroups, which include urothelial carcinoma, adenocarcinoma, renal cell carcinoma, squamous cell carcinoma, and others (Lee, Dickstein & Kamat, 2011). All areas of the urinary tract lined with urothelium are susceptible to urothelial carcinoma, of which the majority of the cases (90-95%) arises from the lower tract (bladder, urethra). The remaining (5%) arises from the upper tract (renal pelvis, calyces and ureter). UTUC commonly arises from the extra-renal portion of the pelvis, followed by the infundibulocalyceal regions (Browne *et al.*, 2005). While UCB is prevalent, UTUC remains scanty. However, it is challenging to determine the precise incidence of UTUC since a lot of statistics combined this with renal cell carcinoma (Browne *et al.*, 2005). However, Prando, Prando & Prando (2010) suggested that urothelial carcinoma of renal pelvis and pelvicalyceal system constitutes about 10-15% of all renal tumours (Prando, Prando & Prando, 2010). Synchronous UCB constitutes 2-4%, while metachronous UCB occurs in 40% of patients with tumours affecting the upper urinary tract. These are the reasons for complete urothelial screening as well as

bladder monitoring when these patients attend follow-up.

Patient demographics include 6th-7th decades of life and male predominance with a ratio of 3:1. Risk factors for developing urothelial carcinoma include smoking, increasing age, male gender, exposure to cancer-causing chemicals (aniline, aromatic amines, azo dyes, benzidines), excessive caffeine intake and cyclophosphamide therapy. These substances are metabolized and excreted into the urine and act locally on the urothelium (Browne *et al.*, 2005). UTUC is also associated with structural abnormalities such as horse-shoe kidney, urine stasis, Balkan endemic nephropathy, analgesic abuse, human papilloma viral infection and hereditary non-polyposis colorectal cancer. Presentations include haematuria (either gross or microscopic), acute renal colic and dull flank pain caused by obstructive uropathy (Prando, Prando & Prando, 2010). Imaging plays an important role yet challenging to ascertain the diagnosis and guide subsequent management, unlike in UCB which is usually detected on cystoscopy (Lee, Dickstein & Kamat, 2011; *Browne et al.*, 2005). UTUCs that invade the muscle wall usually have a very poor prognosis with 5-year–specific survival is <50% for pT2/pT3 and <10% for pT4 UTUC (Rouprêt *et al.,* 2020).

Case Report

Our patient is a 38-year-old gentleman presented with painless haematuria for 6-months duration. This patient is a passive smoker with no other risk factor for urothelial carcinoma. Urine microscopy revealed numerous red and white blood cells. The patient is also mildly anemic with hemoglobin of 10.6 g/L while the renal profile was unremarkable. Contrast-enhanced computed tomography (CT) renal depicted enlargement of the right kidney with extensive hypodense renal pelvic mass infiltrating into the infundibulocalyceal system with hydronephrosis. No synchronous lesion is detected throughout the urinary system and the contralateral urinary tract is normal. The patient was later subjected to right radical nephroureterectomy.

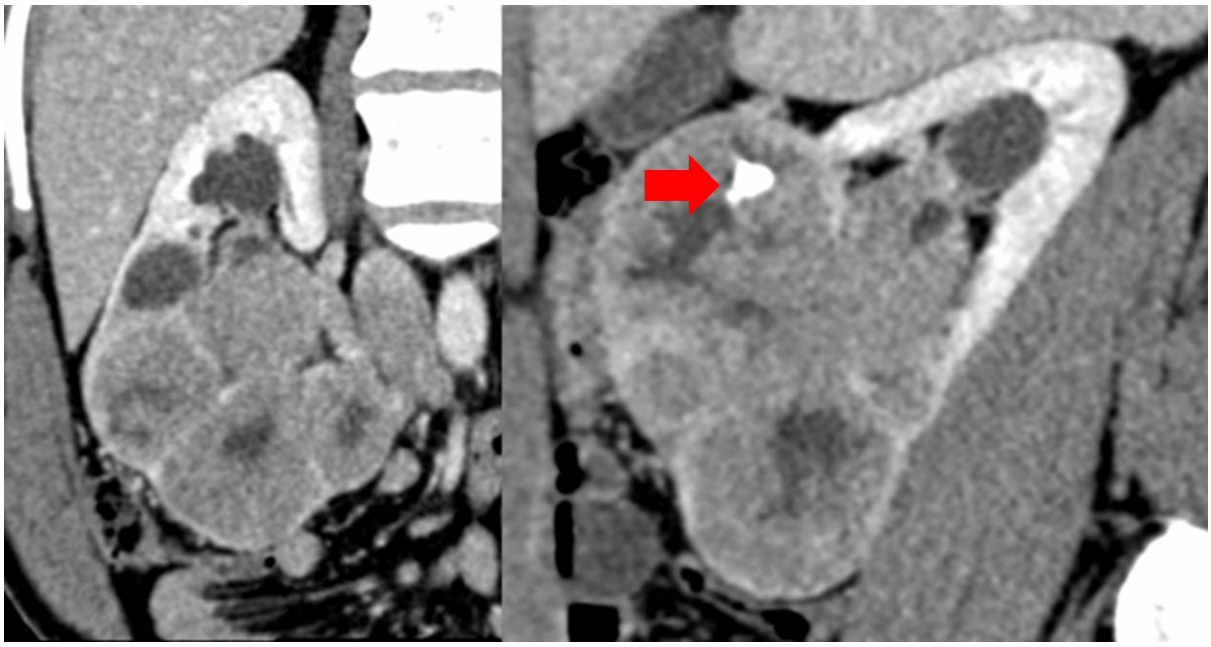

Figure 1. Coronal oblique and sagittal reformatted CT renal in nephrographic phase showing the right renal mass with preserved reniform contour, infiltrative appearance and homogenous low attenuation of the tumour, rendering the diagnosis of urothelial carcinoma. These are mainly seen

involving the interpolar region and the lower pole. Note the coarse calcification within the superior aspect of the mass (red arrow).

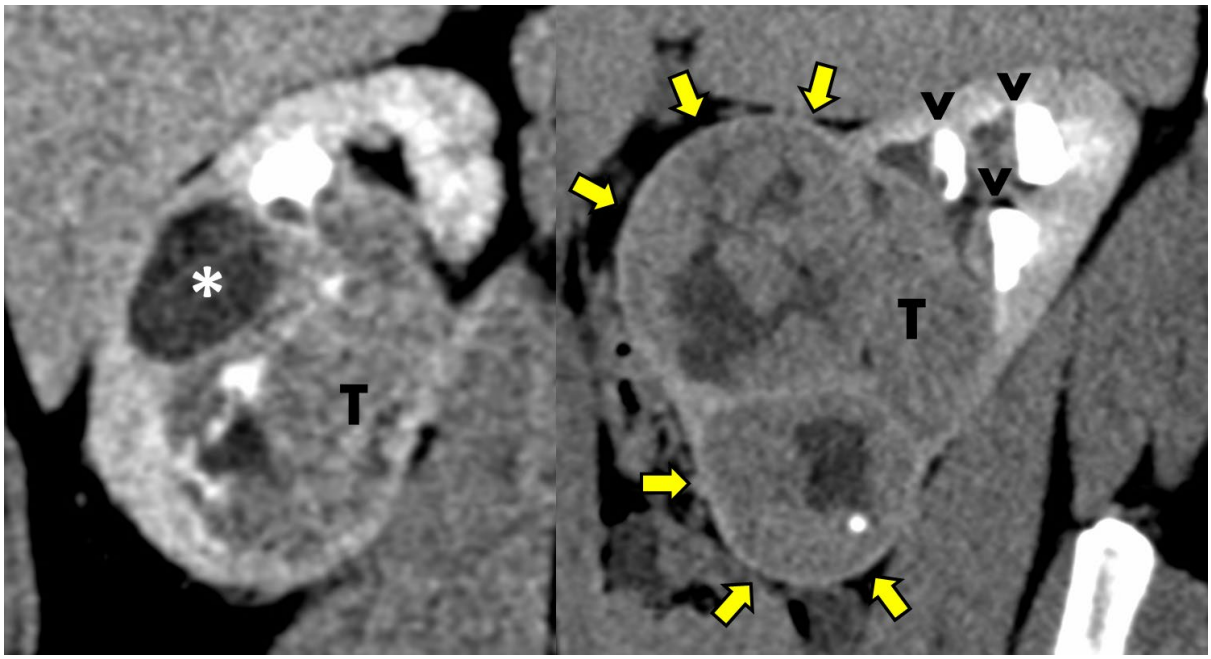

Figure 2. Coronal and sagittal reformatted CT renal in excretory phase demonstrating 'phantom calyces' (white asterisk) and 'oncocalyces' (yellow arrows). Note the urine-contrast level seen at the dilated upper pole calyces (black arrow heads). T = tumour.

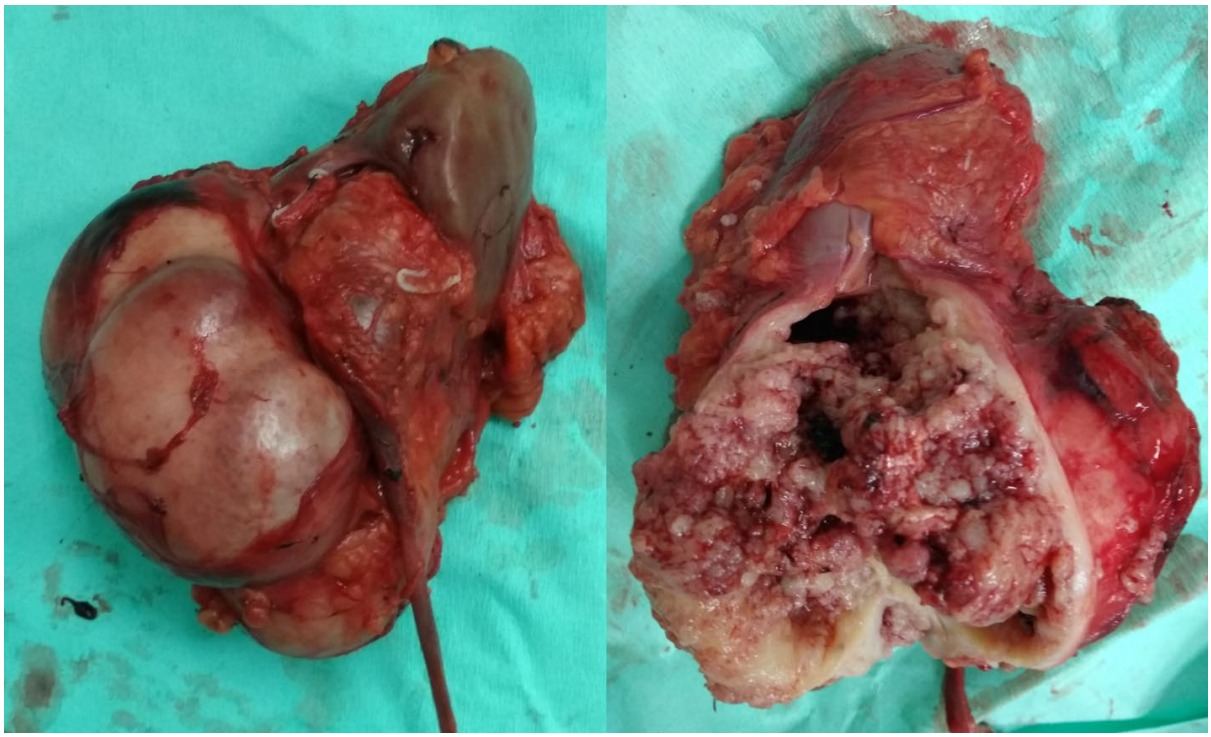

Figure 3. Cut section of the enlarged kidney revealed an irregular tumour with predominant involvement of the renal pelvis and infiltrating into the renal parenchymal tissue of the lower pole. The tumour showed papillary projections with extensive areas of necrosis.

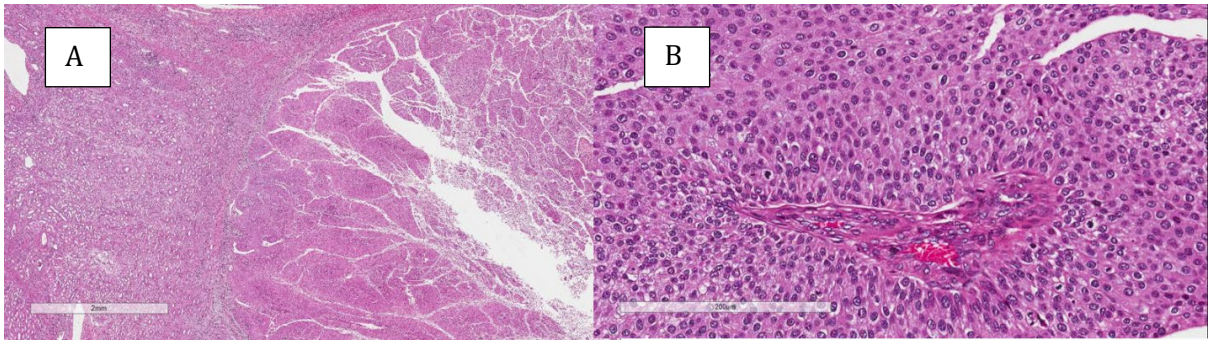

Figure 4. (A) Malignant urothelial cells arising from the renal pelvis arranged in papillary architecture, solid sheets and nesting patterns (H&E x20). (B) The malignant cells display moderate nuclear pleomorphism with irregular hyperchromasia, prominent nucleoli, and clear-pale to eosinophilic cytoplasm. Mitosis is brisk (H&E x 200)

Discussion

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques for radiological evaluation of UTUC (Raza et al., 2011; Rouprêt et al., 2020). Nonetheless, previous scholars reported that UTUC shares similar imaging characteristics with renal inflammatory lesions as well as other renal carcinomas like clear cell RCC. Pelvicalyceal carcinoma that is eccentric, localised and infiltrative inducing renal contour deformity may imitate RCC. Whereas if calcified, this pelvicalyceal carcinoma could mimic long-standing inflammatory kidney disease (Prando, Prando & Prando, 2010). Numerous benign lesions may mimic malignancies of the upper tract such as malakoplakia, infection, endometriosis, fibroepithelial polyps, hematoma, urolithiasis, ureteropelvic junction (UPJ) obstruction, tuberculosis and sloughed papilla (Lee, Dickstein & Kamat, 2011). Therefore, it is of utmost importance to differentiate these entities since they entail different treatment regimes. A thorough CT urography should be performed with attempts made to completely delineate the pelvicalyceal system and ureter as well as to enable the identification of renal vasculature, assess renal enhancement and excretion (Lee, Dickstein & Kamat, 2011). It is equally crucial to detect tumour in the contralateral kidney. In a nutshell, concerning the radiological imaging of the tumour, it is absolutely necessary to carry out a thorough assessment which include its enhancement pattern, lesion location, lesion multiplicity, urinary wall thickness and presence of periureteral fat stranding.

There are several imaging features which render UTUC distinct from RCC which include propensity of the right kidney, preserved reniform contour, infiltrative rather than expansible appearance and homogenous low attenuation of the tumour. These findings are depicted in this patient (Figure 1). Less remarkable features are linear calcification and intraabdominal metastases (Raza *et al.*, 2011; Zhu *et al.*, 2016). Zhu et al. proposed right kidney involvement in 83% (Zhu *et al.*, 2016), however Ronan *et al.* suggested no side predominance with equal distribution between right and left kidneys and about 2-4% cases occurring bilaterally (Browne *et al.*, 2005). Renal medullary involvement is also observed in 93% (Zhu *et al.*, 2016). Raza *et al.* and Zhu *et al.* also reported preservation of reniform contour in 90%, however there are other tumours which may demonstrate clear boundaries and these include clear cell RCC, chromophobe RCC and Wilm's tumour (Zhu *et al.*, 2016).

Zhu et al. proposed infiltrative appearances of the tumour with poorly defined margins in all cases of UTUC (Zhu *et al.*, 2016), which is portrayed in this case. Infiltrative appearance is defined as thickening or induration involving the pelvicalyceal wall with infiltration of the renal parenchyma due to obliteration of the renal sinus/

peripelvic fat which usually demarcates a non-infiltrative tumour from renal parenchyma (Prando, Prando & Prando, 2010; Browne *et al.*, 2005). Hence, UTUC is generally centred at the collecting system hence the filling defect appearance (Raza *et al.*, 2011). These masses usually result in distortion of the normal architecture of the kidney and pelvicalyceal amputation at varying degrees which does not alter the renal contour. This is different from clear cell RCC which usually resides within the renal cortex and exhibits expansible and exophytic morphology (Prando, Prando & Prando, 2010). Expansile component in UTUC is observed in only 21% (Zhu *et al.*, 2016). Even though the majority of infiltrative TCCs are located centrally, eccentric or peripheral tumours may occur and this may retain or distort the renal contour. If renal contour is compromised, this may simulate RCC. Other renal tumor that depicts infiltrative appearance includes renal medullary carcinoma commonly seen in young person with sickle cell trait. Uncomplicated pyelonephritis may also show similar appearance (Zhu *et al.*, 2016).

UTUC also depicts homogenous low tumoral attenuation compared to renal cortex/ medulla in all phases of post intravenous contrast in all cases (Raza *et al.* 2011; Zhu *et al.*, 2016). Bata *et al.* (2011) even discovered attenuation difference between UTUC and clear cell renal carcinoma in corticomedullary and nephrographic phases of CT renal protocol. Hence this feature is helpful in differentiating UTUC from tumours having abundant blood supply such as renal medullary carcinoma, clear cell RCC and renal angiomas. However, other hypovascular renal tumours need to be considered including renal lymphoma, chromophobe RCC and collecting duct carcinoma (Lee, Dickstein & Kamat, 2011). The presence of stipple sign which refers to contrast tracking into papillary lesion interstices may also be seen (Browne *et al.*, 2005). This is however also pertinent to blood clots or fungal balls (Browne *et al.*, 2005). On ultrasound (US), UTUC frequently appears mildly hyperechoic in comparison to the adjacent renal parenchyma. It also typically presents as a soft tissue mass located centrally within the echogenic renal sinus fat. On the other hand, high grade TCC may show mixed sonographic echogenicity (Browne *et al.*, 2005). Raza et al. (2011) also concluded that UTUC is the more likely diagnosis if cystic / necrotic change is absent and the tumour is seen extending towards the pelviureteric junction.

It is reported that UTUC also displays linear calcifications in 21%. In UTUC, peripheral or intratumoral calcifications occur in 2-7% and these may be in the form of punctate, linear or granular calcifications. Hence, these appearances may mimic cholesteatoma, leukoplakia, tuberculosis, tubular ectasia and small pelvicalyceal calculi (Prando, Prando & Prando, 2010; Browne *et al.*, 2005). On the other hand, cortical RCC often demonstrates stippled calcifications. Other renal neoplasms which demonstrate calcifications include the rare mucinous adenocarcinoma of renal pelvis in which the calcifications may occur at the periphery or centre of the mass (Prando, Prando & Prando, 2010). Differentiating renal tuberculosis from UTUC may pose a challenge particularly if multiple stricture-like pelvicalyceal lesions and calyceal amputations are present (Prando, Prando & Prando, 2010). UTUC also features intraabdominal metastases in 38% and regional lymphadenopathy in 28% (4). However, Browne *et al.* postulated that bones, liver and lungs are the commonest sites for metastases (Browne *et al.*, 2005). Papillary RCC, chromophobe RCC and renal lymphoma are rarely associated with renal vein infiltration or nodal metastasis (Zhu *et al.*, 2016).

Above all, there are unusual appearances of UTUC which are increasingly encountered and further diversify possible imaging features of UTUC (Prando, Prando & Prando, 2010). These include tumours in hydronephrotic kidney which are found incidentally due to obstruction of the pelviureteric junction. Hydronephrosis is an associated rather than incidental finding in this patient and it is detected predominantly involving the interpolar and lower pole calyces as an extension from the renal pelvic mass. No calyceal contrast opacification is

detected in the excretory images indicating 'phantom calyces'. Tumour-filled distended calices are called 'oncocalyces'. These are made worse by possible calyceal amputations by the mass. Even if the patient presents with hydronephrosis alone, meticulous evaluation is necessary particularly in elderly patients, those with horseshoe kidney or chronic UPJ obstruction in view of urine stasis. However, in diffuse disease, hydronephrosis may not be seen since the mass has entirely replaced the system (Prando, Prando & Prando, 2010). Pre-operative diagnosis of renal mass in non-functioning kidney due to long-standing staghorn calculus is difficult to ascertain whereby in such case, renal biopsy is mandatory. Stricture-like lesions if multiple may confuse UTUC with renal tuberculosis.

Due to its soft, frond-like growth, urothelial carcinoma completely fills the dilated collecting system by adapting to the geometry of the space it occupies. This is another unusual characteristic observed in this patient as extensive projections inside hydronephrotic sacs that resemble papillary fronds (Figure 2). Other uncommon imaging features of UTUC are transpelvic infiltrating solid masses which extend through the retroperitoneum, calcified and non-calcified focal infiltrative parenchymal mass and tumours predominantly invading the perirenal fat. Apart from these, other unusual characteristics include renal vein invasion of the tumour as the only finding, large multiloculated cystic masses with irregular and thick septa as well as paraaortic nodal metastases with undetectable primary tumour (Prando, Prando & Prando, 2010).

Reference standard treatment of UTUC is radical nephroureterectomy (Lee, Dickstein & Kamat, 2011). However, endoscopic local resection or otherwise known as fulguration is generally less radical and aims to spare nephrons hence minimizes patient morbidity. Patients with low-grade papillary lesions, poor performance status, shorter life expectancy, single kidney, and those who declined radical surgery are typically the ones who should employ this less intrusive procedure (Lee, Dickstein & Kamat, 2011). In accordance with surgical planning, urologists must ascertain the tumor's location (renal pelvis, mid ureter, or distal ureter), its extent (extraluminal or intraluminal), whether hydroureteronephrosis is present, and whether it has invaded any nearby organs. On the other hand, neo-adjuvant chemotherapy before definitive surgery is beneficial for certain patients with high-risk characteristics, such as our patient, who has a significant tumour burden, sessile architecture, and high-grade pathology. This leads to greater rates of both downstaging of the tumour bulk and complete remission (Lee, Dickstein & Kamat, 2011). Imaging is pertinent to identify suspicious lymph nodes and metastatic disease since these would indicate a need for immediate chemotherapy with adjunctive therapy depending on tumour response (Lee, Dickstein & Kamat, 2011). Stringent follow-up is mandatory to detect metachronous tumour, local recurrence of metastases; which are based on urinary cytology, imaging and cystoscopy finding (Taneja, 2011).

The following Table 1 summarizes several distinctive CT features of UTUC which helps in differentiating it from RCC.

Table 1. CT differentiating features of UTUC against RCC.

CT features	UTUC	RCC
Enhancement pattern	Homogenous low attenuation	High attenuation on corticomedullary phase (hypervascular)
Location	Arise from pelvicalyceal wall, favours right kidney	Arise from renal cortex
Reniform contour	Preserved	Not preserved due to the lesion being exophytic
Growth pattern	Infiltrative	Expansible
Cystic / necrotic change	Absent	Present
Additional features	• Pelvicalyceal amputation causing phantom calyces/ oncocalyces • Tumour extension towards pelviureteric junction	

Conclusion

UTUC displays heterogenous imaging manifestations affecting the kidney down to the bladder. Individual CT features most predictive of UTUC against centrally located RCC such as tumor found to be centered on the collecting system, a focal filling defect in the pelvicalyceal system, preservation of reniform contour, absence of cystic or necrotic change, homogeneous but modest tumor enhancement, and extension of the tumor toward the ureteropelvic junction subsequently guides patients' management. It is indispensable that radiologists provide the necessary information to the attending urologist with good understanding of the radiological features that have an impact on the treatment.

Conflict of Interest

None declared.

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