LITERATURE REVIEW

Kidney Transitional Cell Carcinoma (Upper Tract Urothelial Cancer)

Akhada Maulana*[1], Shofi Suryalathifani[2], Moh. Suprayogi[3]

1 Division of Urology Medical Faculty of Mataram University
2 Risa Sentra Medika Hospital, Mataram
3 Dompu Public Hospital, Dompu

Corresponding authors:
* akhada_m@hotmail.com

ABSTRACT

Kidney transitional cell carcinoma or upper tract urothelial cancer (UTUC) is a rare malignant tumour that affects approximately 5% of all urothelial carcinoma cases. Various risk factors for this disease have been identified, including genetic and environmental such as smoking, aromatic amines exposure, aristolochic acid-induced nephropathy, analgesic abuse, chemotherapy regimens, and chronic urinary tract infections. Gross haematuria is the most common symptom of UTUC and only a small percentage of patients is asymptomatic. Radio-imaging has become main modalities for diagnosis of UTUC, mostly computer tomography urography (CTU) because of visualization ability of the lesion. Resection are the most treatment for low grade tumour and combine with immunotherapy for high grade tumour. Grade and stage of the disease have the most significant influence factors on survival rate.

Keyword: Kidney, Transitional cell carcinoma, UTUC

INTRODUCTION

Kidney malignancies are diverse and originate from different cell types with distinctive morphology and clinical behavior.1 Urothelial carcinoma (UC) or transitional cell carcinoma is the most common malignancy of the urinary tract.2,3 UC can be located in upper urinary tract (renal pelvic, ureter) or lower urinary tract (bladder, urethra).3,4,5 The majority of UC occurs in the urinary bladder (UBUC).2,6 Upper tract urothelial cancer (UTUC) is a rare malignant tumor that affects only about 5% of all UC cases.2,5 UTUC or kidney transitional cell carcinoma or renal urothelial carcinoma is a malignant tumor arising from transitional (urothelial) epithelial cells that line the upper urinary tract from the calyx to the orifice of the ureter.1,5 Pelvicalyceal tumors are anatomically three times more common than those located in the ureter. Gross hematuria is the most common symptom of kidney transitional cell carcinoma, only a small percentage of patients is asymptomatic. UTUCs are classified according to tumor, nodule, and metastasis (TNM). The outcome of UTUC is strongly associated with the stage of the tumor. Tumor grades of endoscopic biopsy can be used to predict stage and advise patients on treatment options.5 The aim of this literature review was to summarize current progress in UTUC research by focusing on epidemiology, etiology, staging and risk factors as well as on diagnosis and treatment.

EPIDEMIOLOGY

Urothelial carcinoma is the fourth most common tumor in developed countries and the most common malignancy of the urinary tract.2,3 It accounts for 10 to 15% of all primary renal malignancies and more than 90% of renal pelvic tumors.1,7 The incidence of disease in the ureter over the past 30 years has increased from 0.69 cases per 100,000 person/years to 0.91 cases per 100,000 person/years, the incidence of renal pelvic

disease has decreased slightly from 1.19 cases per 100,000 person/years to 1.15 cases per 100,000 person/years, and the overall incidence is tumors. The number of upper urinary tract cases increased from 1.88-2.06 per 100,000 person/years.8 The highest incidence is found in the Balkans, where urothelial carcinoma accounts for 40% of all renal cancers.1,7 Bladder tumors account for 90-95% of urothelial carcinoma and are the most common malignant neoplasms of the urinary tract.2,3,6 Transitional cell carcinomas in upper urinary tract occurs in about 5% of all urothelial carcinomas and 7% of all primary renal malignancies.1,3,5 Upper tract urothelial carcinoma (UTUC) is rare, with an estimated annual incidence of nearly 2 cases per 100,000 people in Western countries.2,3,4

ETIOLOGY AND RISK FACTOR

The exact cause of renal transitional cell carcinoma is not known. On the other hand, various risk factors for the disease have been determined.1 It divided into genetic and environmental factors.3,9

Genetic About 10-20% of all UTUCs have a genetic background.2,10 Familial UTUCs are linked to Lynch Syndrome or hereditary non-polyposis colorectal carcinoma (HNPCC), which have mutation in the DNA mismatch repair genes MLH1 (MutL homolog 1), MSH2 (MutS protein homolog 2), MSH6 (MutS protein homolog 6), and PMS2 (mismatch repair endonuclease PMS2). People with this syndrome have higher chance to develop gastric, pancreatic, colonic, urothelial, sebaceous, uterine and ovarian carcinoma.9 UTUCs ranks third (5%) after colon cancer (63%) and endometrial cancer (9%) within the group of Lynch syndrome-associated tumors.5,10 In Lynch syndrome-related UTUCs, immunohistochemistry analysis showed loss of protein expression consistent with disease-predisposing mismatch repair (MMR) gene mutations in 98% of samples (46% microsatellite instability, 54% is microsatellite stable). The majority of tumors occur in MSH2 mutation carriers. Patients should undergo DNA sequencing and family counseling if they are identified as a high risk for Lynch syndrome. Screening of all patients under the age of 65 with UTUC and those with a family history of UTUC is important to reduce the incidence of undiagnosed hereditary disorders in urological cancer (figure 1).3

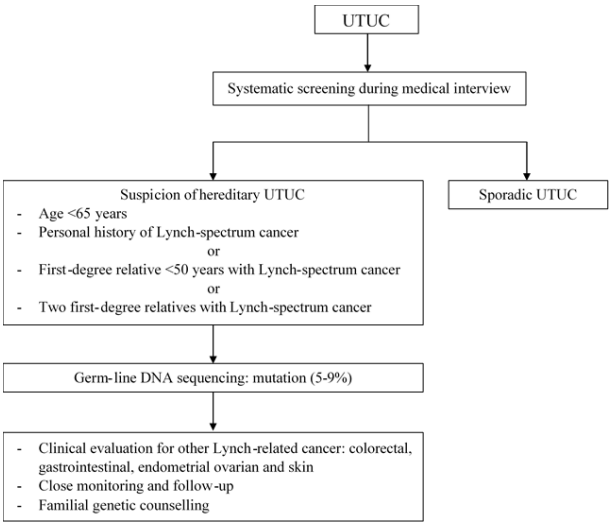

Figure 1. Selection of patients with UTUC (upper tract urothelial cancer) for hereditary screening during the first medical interview. (Adapted from European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma 2020).3

Environment

Various environmental risk factors contribute to the development of renal transitional cell carcinoma or UTUC. Cigarette smoking is a modifiable risk factor and probably the most important one.9 70% of men and 40% of women with UTUC are exposed to cigarettes.5 Tobacco exposure increases the relative risk from 2.5 to 7.0.3 The mechanism of carcinogenesis in cigarette exposure is complex. Toxic substances inhaled during smoking, including aromatic amines with

arylamine, benzopyrene, and dimethylbenzanthracene. This aromatic amine is metabolized by the body in the carcinogenic N-hydroxylamine. Enzyme systems such as cytochrome P450s with CYP1A1, glutathione S-transferases, and N-acetyl transferases detoxify these derivatives. Genetic polymorphisms in enzymes that neutralize N-hydroxylamine may reflect susceptibility to the carcinogenic effects of smoking. Patients with a 20 pack-year smoking history had an odds ratio (OR) of 2.0. For heavy smokers such as 60 or more pack-years, the respective ORs are 6.2. A 60% to 70% reduction in UTUC risk occurred with smoking cessation for more than 10 years (OR 2.3 for former smokers vs. 4.4 current smokers).9

Occupational exposure to carcinogenic aromatic amines associated with UTUC "Amino tumor". These fragrances are still used in products such as paints, textiles, rubber, chemicals, petrochemicals and coal. The aromatic amines benzidine and beta naphthylane are involved in carcinogenesis.9

Aristolochic acid-induced nephropathy increases the risk of urothelial carcinoma. About half of those affected develop urothelial carcinoma and 90% of these are UTUC. Exposure to aristolochic acid results from ingestion of herbal medicine (Aristolochic acid is included in Mu Fang Ji medicine) or contaminated wheat in Balkans (Aristolichia clematis contaminates the flour supply and causes Balkans endemic nephropathy). Characteristics of nephropathy are proximal tubular damage, renal interstitial fibrosis and slow progression to renal failure.5

Chronic use or high dose analgesic abuse of the phenacetin has been considered a risk factor for UTUC since the 1960s.5,11 It causes a characteristic nephropathy called capillosclerosis.11 Its use has been restricted or replaced, and the number of UTUC cases due to phenacetin is decreasing.5 The incidence of UTUC is high in Taiwan and is also associated with blackfoot disease.3,5,11 Blackfoot disease is recognized as an endemic peripheral vascular disease and is associated with arsenic-rich groundwater.11 Chemotherapy regimens such as cyclophosphamide and ifosfomide which are alkylating agents have been shown to induce UTUC through acrolein metabolites.5,9 Other risk factors for UTUC are chronic urinary tract infections and urolithiasis.5

MOLECULAR CHARACTERISTIC

UTUC is a rare part of urothelial carcinoma and has not improved in recent decades because its biological mechanism is still unknown. Due to its rarity, there are few comprehensive studies on the molecular basis of UTUC.6 A high incidence of potentially actionable genomic changes including repetitive activating mutations in receptor tyrosine kinase (FGFR3, ERBB2), HRAS, PIK3CA and TSC1 currently have been identified in UTUC. However, these molecular profiling studies have also identified numerous genomic variants of unknown significance and significant genetic diversity among UTUC patients.12 Lee et al. found that the most common amplifications in UC were NOTCH1 (17,7%) and FGFR3 (14,5%). The molecular basis of NOTCH1 amplification in UC needs to be further clarified. In the recent study, the landscape of alterations in UTUC and UBUC was similar. TP53 was the most frequently mutated gene (68.5% of all UC cases). On the other hand, FGFR3 mutations (13.0%) occurred less frequently. FGFR3 mutation is associated with low-stage, low-grade tumors, and TP53 mutation is associated with high-stage, high-grade tumors.6

STAGING

UTUCs are classified according to the tumor, node, metastasis (TNM) classification (Table 1). The outcome of UTUC is strongly associated with the stage of the tumor.3,5

Table 1. TNM (Tumour, Node, Metastasis) classification 2017 for upper tract urothelial cell carcinoma.3

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No Evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma *in situ*
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscularis
T3 (Renal Pelvis) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma
(Ureter) Tumour invades beyond muscularis into periureteric fat
T4 Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2 Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastatis
M0 No distant metastasis
M1 Distant metastasis

The American Joint Committee on Cancer (AJCC) further classified the staging of UTUC based on TNM classification.13 The staging classification is shown in table 2 below.

Table 2. The American Joint Committee on Cancer (AJCC) staging classification of UTUC.13

Stage	TNM
0a	Ta, N0, M0
0is	Tis, N0, M0
I	T1, N0, M0
II	T2, N0, M0
III	T3, N0, M0
IV	T4, N0, M0
	Any T, N1, M0
	Any T, N2, M0
	Any T, Any N,M1

DIAGNOSIS

Clinical Manifestation

Gross hematuria is the most common symptom of kidney transitional cell carcinoma, occurring in 75-95% of patients.1,3,11 Microscopic hematuria occurs in 3-11% of patients. Dull pain on flank is reported by about 14-37% of patients and is associated with gradual obstruction of the collecting system. Renal colic can also occur with the passage of a blood clot.1 Lateral abdominal pain occurs in about 20% of cases.3 Other symptoms that may occur include weight loss, lower extremity edema, fever, and fatigue.3,7 Only a small percentage (1-2%) of patients is asymptomatic. The patient's physical

examination is usually neither informative nor specific, especially in patients with early-stage disease. A palpable pelvic mass can be found in less than 20% of patients. The classic clinical triad of hematuria, pain, and mass is also rare (15%) and is usually an indicator of advanced disease.1

Imaging

Several studies had been conducted to improve the diagnosis of UTUC to be less invasive and easy to perform. The American Urological Association recommendation for standard work-up consists of urinalysis and cytologic analysis, cystoscopy, and excretory Urography. Recent studies shows that computer tomography urography (CTU) have been used as diagnostic tools with minimal invasive procedure, detection of urinary caliculi and renal parenchymal masses.14 However, a positive biopsy is required for a definitive diagnosis.2

Excretory Urography (EU)

Mostly used in investigation of hematuria. It is non-invasive method of imaging, offers detailed anatomy of pelvico-calyceal system and ureters.15,16 Transitional cell carcinoma (TCC) is characterized by a filling defect within contrast-enhanced, may be single or multiple and smooth, irregular, or stippled. Stipple sign refers to injection of contrast material into interstitial part of a papillary lesion (Figure 2).14

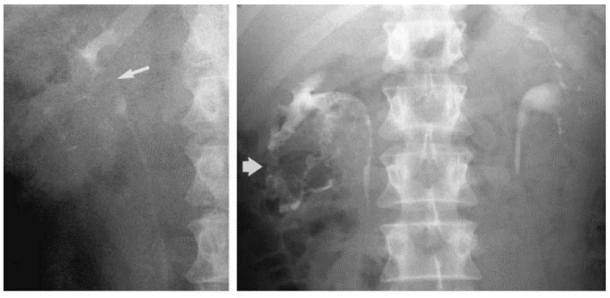

Figure 2. (small arrow) shows irregular filling defect in right pelvis and extending in to lower part of calices; (big arrow) shows a large stipple filling defect in collecting system of the right kidney.14

Retrograde Pyelography (RP)

RP is usually performed during cystoscopy to further analyze the abnormalities, in abnormal excreting ability of the kidney or in cases of allergy of contrast material. RP is an invasive procedure, yet it allows confirmation of diagnostic evaluation by providing biopsy or brushin and cytological examination of localized urine collections. In RP, renal TCC appears as intraluminal filling defect, may be smooth, irregular, or stippled. If TCC involves an infundibulum, there may be appearance of "amputated" calix with or without focal hydronephrosis and caliculi secondary to obstruction (Figure 3).14

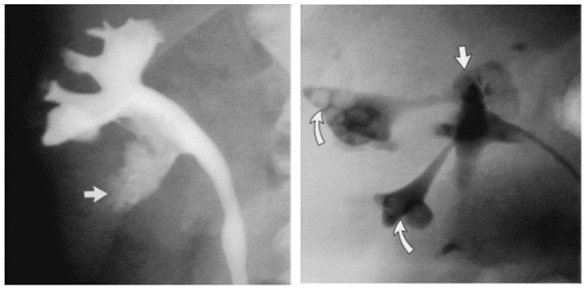

Figure 3. (Left) Diffuse infiltrating of TCC in right lower pole calix and irregular shape involves mucosa (arrow). (Right) Amputation of the upper pole of calix due to TCC (straight arrow) and multiple calliculi are seen in the lower pole and interpolar calices (Curved arrows).14

Computer tomography urography (CTU)

CTU has been shown to be more sensitive than EU in the detection of small renal mass lesions and urinary tract caliculi. The pre-enhanced scan is performed to exclude renal stone. CTU allows to evaluate mass, vascular abnormalities, and the extension of the masses

(Figure 4).14 CTU with at least one series of images during the excretory phase (10–15 min) after contrast injection is the standard imaging technique for detecting and staging UTUC.2

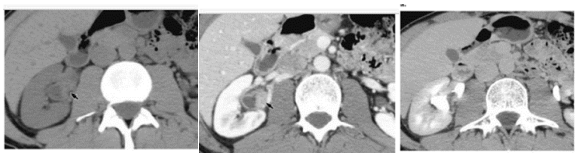

Figure 4. (left) axial non-enhanced CT-scan shows slightly hyperdense; (middle) axial nephrography shows an early enhancement of tumor and extension into situation of upper pole parenchym (arrow); (right) Axial excretory phase CT shows a mass within renal pelvis with surrounding excreted contrast medium.14

Magnetic resonance urography (MRU)

MRUs vary widely in the accuracy of UTUC classification. Therefore, it is recommended for patients who are not candidates for CTU, usually when radiation or iodinated contrast media are contraindicated.2,3 The sensitivity of MR urography is 75% after contrast injection for tumors < 2 cm.3

Ureteroscopy

Flexible ureteroscopy (URS) is used to visualize the ureter, renal pelvis, and collection system and to perform biopsy of suspicious lesions. The presence, appearance, and size of the tumor can be determined by URS. In addition, ureteroscopic biopsy can determine tumor grade in 90% of cases, regardless of sample size, and has a low false-negative rate.3

Cytologic

Primary upper urinary tract (UT) cytology and endoscopic biopsy play a central role in the UTUC treatment paradigm. UT urinary cytology is widely used and plays an essential role in the detection of UTUC. In the literature, the sensitivity of UT urine cytology in the detection of UTUC is widespread. Some studies have shown that high-grade UTUC is fairly reliably detected by UT cytology. On the other hand, the sensitivity of UT cytopathology to low-grade lesions is low. Some cytological features of low grade tumor (I and II) are nuclear hyperchromasia, lack nuclear pleomorphism. The characteristic of high grade (III and IV) tumor including nuclear hyperchromasia, nuclear enlargement, and irregular nuclear membrane.17

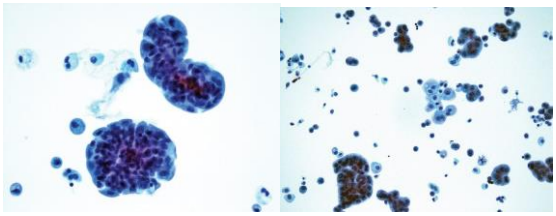

Figure 5. (left) Low-grade papillary urothelial carcinoma. Tight clusters of hyperchromatic urothelial cells show nuclear membrane irregularity. The cells lack nuclear pleomorphism. The concurrent histology revealed low-grade papillary urothelial carcinoma. (Right) Positive for high-grade urothelial carcinoma. Papillary clusters of malignant urothelial cells show nuclear hyperchromasia, nuclear enlargement, and irregular nuclear membrane.17

Histopathology

The spectrum of atypical morphology of UTUC resembles that of the bladder. Previous reports of resected specimens include UC with squamous cell differentiation, UC with glandular differentiation, microcystic UC, micropapillary UC, UC with reverse growth pattern, UC with choriocarcinoma or syncytiotrophoblastic giant cells (currently UC with trophoblastic differentiation), sarcomatoid UC (including cases with heterologous components present such as rhabdoid cells or chondrosarcoma), lymphoepithelioma-like UC, nested UC, plasmacytoid UC, signet ring cell (currently

included in plasmacytoid UC if no extracellular mucin component is present), , small cell carcinoma, clear cell UC, and lipid-rich UC, osteoclast-rich poorly undifferentiated carcinoma, and UC with pseudosarcomatous stromal changes.18

TREATMENT

The choice of treatment depends on clinical evaluation.19 Treatment for low-risk UTUC may include kidney-sparing surgery, flexible ureteroscopy or segmental resection or percutaneous approach. Meanwhile, for high-risk UTUC, RNU can be performed with or without peri-operative platinum-based combination chemotherapy and then a single post-operative dose of intravesical chemotherapy.3 The development of new therapeutical endourological intervention of kidney transitional cell carcinoma has provided new options for regional management of the cancer. Electrofulguration and resection or laser can be performed transuretrally or percutaneously and may reduce the primary cancer. The biopsy as treatment and diagnostic remain unclear.19

Nephroureterectomy (NU)

Nephroureterectomy (NU) is the gold standard approach for UTUC, but may be over-treatment for patients with distal or low-grade non muscle invasive ureteral tumors and may not be feasible in patients with a single upper urinary tract.5 Kidney-sparing surgery or partial nephrectomy for low-risk UTUC reduces the morbidity associated with radical surgery, without affecting cancer outcome. For low-risk cancers, this is the preferred approach because survival is similar to that after RNU.3 Radical nephroureterectomy (RNU) with excision of bladder cuff is the standard treatment for high-risk UTUC.5 Due to the high recurrence rate of ureteral stumps observed after simple nephroureterectomy, nephroureterectomy with bladder cuff resection was the main treatment.11 This can be done through several different open (ONU) approaches, such as a single midline incision, thoracoabdominal incision, or flank incision with Gibson or bladder incision to remove Gibson or bladder cuff, or laparoscopic (LNU) or robot-assisted laparoscopic technology.5 Electro-resection and fulguration or laser fulguration can be performed in superficial tumor. Segmental resection, ureterorenoscopic or percutaneous resection/ fulguration/ laser destruction can be performed if the renal unit is solitary or renal function is decreased.19 In low-grade non-invasive tumors that are too large for endoscopic treatment or in patients with high-grade tumors requiring nephron sparing, segmental ureterectomy can be performed.5

Ureteroscopy

Endoscopic ablation should be considered in low-risk clinical cancer patients.3 Some UTUCs such as low-grade noninvasive muscle tumors can be safely treated endoscopically, as long as it is accessible. Endoscopic management is recommended for patients with isolated upper airway (anatomy or function), those with bilateral UTUC, patients with poor baseline renal function, or patients with severe renal impairment, patients with a lot of comorbid to undergo RNU and for tumors that are low-grade non-muscle invasive lesions.5 Laser vaporization or coagulation can be done through endoscopy or percutaneous access. It depend on the accuracy of initial staging and the adequacy of visualization of the targeted lesion. The efficacy depend on staging at initial treatment and the monitoring after the procedure.19

Chemotherapy/immunotherapy and radiotherapy

The efficacy of thiotehpa, mitomycin, doxorubicin for superficial cancer therapy in the bladder may be used in UTUC. There may

be some consideration regarding the use of these therapies such as the extent of the disease in renal pelvis, the availability, patients' response to the treatment, and the accuracy and adequacy of initial tumor staging and monitoring.19 Topical immunotherapy or chemotherapy can be given retrogradely through a ureteral catheter or antegradely through a percutaneous nephrectomy. The agents used for adjuvant treatment of UTUC were mainly extrapolated from those used for bladder cancer. Several different agents have been described, including mitomycin C, thiotepa, bacille Calmette Guérin (BCG)/interferon, and BCG alone.5 Adjuvant radiation therapy has been suggested to control local disease after RNU. The data is still controversial and insufficient to draw conclusions.3

PROGNOSIS

UTUC is a rare subset of urothelial carcinoma which has a poor prognosis.6 Age was strongly correlated with overall survival. 5-year survival decreased from 75% of patients under 50 years to less than 20% of patients over 85 years. Race / ethnicity was associated with differences in overall survival, with Black non-Hispanic patients having a 30% higher mortality rate than Hispanic or White non-Hispanic patients. Genetic and biological differences, access to health care, and basic health, are hypothesized to be related to these differences.8 Tumor stage is the most important prognostic factor for urothelial carcinoma of the upper urinary tract. Survival is closely related to the stage of the tumor. Tumor size is prognostic and lies between the extremes of 3-12 cm in diameter, most in between. Tumor grade is another predictor of prognosis. Tumor malignancy usually follows the stage of the tumor, and patients with high-grade cancer have a more advanced stage. Stages and grades correlate up to 83% of the time, but stages are still a more accurate predictor of prognosis.1

CONCLUSION

Renal transitional cell carcinoma or upper tract urothelial carcinoma is a rare type of urothelial carcinoma. Various risk factors have been determined such as genetic and environmental factors. About 10-20% of all UTUCs have a genetic background. Cigarette smoking is a modifiable risk factor and probably the most important one. Due to its rarity, there are few comprehensive studies on the molecular basis of UTUC. TP53 was the most frequently mutated gene in urothelial carcinoma. Gross hematuria is the most common symptom (75-95%), and asymptomatic patients in only a small proportion (1-2%). CTU is the mainstay of diagnostic tools for UTUC because it's less invasive and convenient. However, a positive biopsy is required for a definitive diagnosis. The treatment mostly the resection of the mass and adjuvant with immunotherapy, but further studies need to be conducted for further evaluation of these treatments. The outcome of UTUC is strongly associated with the stage of the tumor.

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