Review Article on Upper-Tract Urothelial Carcinoma: Current State and Future Directions

Epidemiology, clinical presentation, and evaluation of upper-tract urothelial carcinoma

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Abstract: An overview of epidemiological pattern of upper tract urothelial carcinoma (UTUC), including outcome of UTUC over past decades as well as factors responsible for observed epidemiological changes was performed. Gender and racial disparities influencing incidence of UTUC were reviewed. The incidence of multifocal urothelial carcinoma and relation of UTUC to urothelial carcinoma of bladder were examined.

Keywords: Upper tract urothelial carcinoma (UTUC); epidemiology; incidence; clinical presentation; ureteral cancer; renal pelvic cancer

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Epidemiology and incidence of upper tract urothelial carcinoma (UTUC)

Epidemiology

UTUC is defined as malignant changes to the urothelial cells lining the urinary tract anywhere from renal calyces, renal pelvis, or ureter down to ureteral orifice. Although 61,700 estimated new cases of bladder cancer are diagnosed in 2019 in the United States (1), UTUC is still relatively an uncommon type of genitourinary malignancy representing 5% of urothelial cancers and less than 10% of renal tumors (2). It is difficult to determine the exact incidence of UTUC because often renal pelvis and ureteral malignancies are reported combined with renal cell carcinoma in a single category as renal tumors (1).

The estimated annual incidence of UTUC in the Western countries is up to 2 new cases per 100,000 person-years (3,4). Urothelial pelvicalyceal tumors are diagnosed as twice as urothelial carcinoma of the ureter (5). The epidemiological patterns of UTUC over a period of 30 years was analyzed using a large population-based cohort from Surveillance, Epidemiology, and End Results (SEER) in the United States (2). Raman *et al.* showed a minimal decrease in incidence of renal pelvicalyceal tumors from 1.19 to 1.15 cases per 100,000 person-years compared to an increase in incidence of ureteral tumors from 0.69 to 0.91 cases per 100,000 person-years accounting for an increase in overall incidence of UTUC from 1.88 to 2.06 cases per 100,000 person-years (2). UTUC have a peak incidence between ages 70–90 years (3,6). The mean age at diagnosis has increased over the past 30 years with an overall increase of 5 years from 68 to 73 years (2).

The outcome of UTUC is closely associated with the stage of disease at presentation (5). At time of diagnosis, approximately 40–50% of patients have non-muscle invasive UTUC (pTa/T1), 50–60% of patients present with muscle-invasive or non-organ confined disease (P≥T2), and up to 25% of patients presents with metastasis at diagnosis (5,7,8). Over a 30-year period, the incidence of *in situ* tumors have increased from 7.2% to 31%, compared to significant reduction in incidence of local tumors over the same period (50.4% to 23.4%, P<0.001). Remarkably, regional UTUC was noted to significantly increase by 2.6% (P=0.003), whereas the incidence of distant UTUC did not differ over time (P=0.12) (2).

There have been multiple factors influenced the incidence of UTUC and observed changes in epidemiological patterns of the disease over the past decades. Earlier detection of smaller tumors using advanced cross-sectional imaging technologies such as computed

tomography or magnetic resonance imaging significantly outperformed intravenous pyelography used in the past (9). The pivotal and revolutionary advancement in endoscopic technology with introduction of small-diameter flexible and digital ureteroscopes with improved functional deflection, and innovation of various types of biopsy forceps and baskets allowed for a better-quality biopsy and thus improved histologic detection of early-stage tumors (10). Ultimately, advancement in bladder cancer diagnosis and treatment led to boosted cancer-specific survival and thus an increase in incidence of upper-tract disease shedding the light on the natural history of UTUC.

Gender

Studies have shown that UTUC develops 2–3 times more commonly in men than women (6-8). Conclusive evidence of gender influence on outcome of patients with UTUC is currently lacking, despite men seems to have a higher incidence of disease, whereas survival outcomes might be independent of gender. Over the past decades, Raman *et al.* found that male gender was associated with worse overall survival (P<0.005), with 7% (64% *vs.* 57%) and 5% (52 *vs.* 47%) at 3 and 5 years, respectively compared to female gender (2). However, multi-institutional retrospective studies found no association between pathologic features, disease recurrence, or cancer-specific mortality and gender of patients with UTUC treated with radical nephroureterectomy (RNU) (6,11). On the contrary, one SEER-based study, found female patients having higher cancer-specific mortality rate, but this finding lost significance in their multivariable competing-risks regression model (12). Another study from Austria described women having worst survival outcomes in advanced stages (13). However, a recent large hospital-based cancer registry study from an endemic area in Taiwan reported female patients had significantly improved survival outcomes compared to their male counterparts, which were mostly driven by the non-muscle-invasive disease (14). Taken altogether, although differences in survival based on gender are noticeable, it is difficult to pinpoint exact etiology as to whether this is because of biology of disease or the presence of associated comorbid conditions in male patients.

Race

Similar to other urologic malignancies, racial disparities have been noticed in UTUC with the vast majority patients affected by UTUC are Caucasians (80–90%) (2,15,16). However, over the past decades, the incidence of UTUC has deceased among white patients (92.6% to 88.3%, P<0.001), while incidence has increased among black patients (3.4% to 4.3%, P=0.09) and other ethnicities (4.0% to 7.5%, P<0.001) (2). Race-associated survival outcome differences were also observed in population-based study with black non-Hispanic patients having 30% higher mortality compared to other radical groups (2). In contrast, an international multi-institutional study found no effect of race or ethnicity on recurrence or cancer-related death (16). As such, different ethnicities have different clinico-pathologic features of their UTUC, yet race has not been shown to be an independent predictor for survival (3).

Relation of UTUC to urothelial carcinoma of bladder

Urothelial carcinoma is inherently multifocal disease with a tendency for recurrence after initial treatment. These disease characteristics make urothelial carcinoma one of the most perplexing cancer to treat including synchronous and/or metachronous tumors as well as multifocality within the urothelium, whether involving upper tract, bladder or urethra. There are 2 proposed theories for development of multifocal synchronous and/or metachronous tumors. The monoclonality hypothesis describes occurrence of multifocal tumor as a consequence of a single genetically abnormal cell spreading throughout the urothelium. Whereas, field cancerization effect causes an independent development of synchronous or metachronous nonrelated tumors at different location within urothelial tract (17,18). Spread of malignant cells has been described via either intraluminal seeding and/or intraepithelial migration. Therefore, often it is difficult to establish origin of these lesions whether represent seeding sites from same primary tumor or represent true second primary "*de novo*" lesions.

Synchronous urothelial carcinoma of bladder and UTUC

The incidence of concomitant bladder and upper urothelial tract tumors is 8–17% (3,19). However, contralateral recurrence of UTUC has been report to be up to 6%, with multifocal UTUC in one third of cases (3,20). Synchronous bilateral UTUC are also rare at presentation and 80% of patients in one population-based study had urothelial carcinoma of bladder diagnosed either before or following diagnosis of UTUC (21).

Primary urothelial carcinoma of bladder followed by metachronous UTUC

The incidence of UTUC ranges from 0.7% to 1.7% with a median of 4.1 years following diagnosis of urothelial carcinoma of bladder (22,23). The incidence of UTUC after radical cystectomy ranged from 0.75% to 6.4% in a large meta-analysis involving 27 studies as early as 2.4 to 164 months following cystectomy (24,25). Prior history of muscle-invasive urothelial carcinoma of bladder was shown to be significantly associated with an increased risk of UTUC recurrence and cancer-specific death (26). In another multi-institutional study primary carcinoma *in situ* of bladder was found to be an independent predictor of UTUC recurrence and death after RNU (27). At time of diagnosis or treatment with RNU, approximately 25% of UTUC patients previously had non-muscle invasive urothelial carcinoma of bladder (7,8).

Primary UTUC followed by metachronous urothelial carcinoma of bladder

The incidence of urothelial carcinoma of bladder following treatment of UTUC is approximately 15% to 50% (19,28) with intravesical recurrence represents the most common site of recurrence. Metachronous bladder tumors usually occur within an average of 1–2 years after treatment of primary UTUC (28-31). Approach to RNU did not appear to influence risk of bladder recurrence (32) or overall survival (33,34).

Diagnosis: clinical presentation and evaluation

Clinical presentation

The most common presenting symptom in two third of patients with UTUC is either gross or microscopic hematuria (35) whereas 25% of patients present with flank pain secondary to obstruction of either the kidney and/or the ureter by upper tract tumor (3). Findings of hydronephrosis on preoperative imaging can be seen in 37% to 80% of patients. Studies have suggested the presence of preoperative hydronephrosis is prognostic indicator for advanced disease and this information may impact decision for neoadjuvant chemotherapy as well as extent of radical resection (36,37). Less commonly, patients may present with a flank mass (3) and rarely, UTUC found incidentally on imaging and these patients are asymptomatic at diagnosis. The presence of constitutional symptoms of weight loss, anorexia, fatigue, malaise, fever, night sweats and cough associating UTUC should trigger a thorough metastatic workup since these symptoms predict worse outcome (3).

Clinical evaluation

The clinical assessment of patients thought to have UTUC should start with history evaluating risk factors and physical examination including abdominal exam. Workup including microscopic urinalysis to detect microscopic hematuria ruling out concomitant urinary tract infection, urine cytology, laboratory tests including hemoglobin level and renal function, and upper tract axial imaging with CT or MR urography, or renal ultrasound, CT/MR without contrast and retrograde pyelography if iodinated or gadolinium-based contrast are contraindicated. Nuclear renogram might also be obtained if indicated. Ultimately, cystoscopy, ureteroscopy with biopsy can be pursued.

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Footnote

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