



Upper Tract Urothelial Carcinoma: Clinical Features and Management

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Abstract

Only approximately 5% of urothelial tumors arise in the upper urinary tract, > 90% of which are urothelial (formerly called transitional cell) carcinomas. Upper tract urothelial carcinoma (UTUC) arise from the renal pelvis and the ureter. Genetic and environmental risk factors may contribute to the development of UTUC. Exposure to or consumption of tobacco, phenacetin, aristolochic acid, aromatic amines, and arsenic contaminated drinking water are known risk factors for urothelial carcinogenesis. Clinical features include hematuria, flank pain, hydronephrosis, palpable flank mass, renal insufficiency, hypertension and a high propensity for distant metastasis. Paraneoplastic syndrome may include hypercalcemia, thrombocytopenia and leukemoid reaction. Because estimated 60% of UTUCs are invasive at diagnosis, appropriate diagnosis and management is most important. The predominant sites of distant metastasis at diagnosis of UTUC were the lungs, lymph nodes, bone and liver. Cutaneous metastasis is extremely rare and indicates the late manifestation of a systemic spread. Combinations of urine cytology, cystoscopy, ureteroscopic biopsy, and computed tomography are currently diagnostic tools. Surgery with radical nephroureterectomy and excision of a bladder cuff is the gold standard for locally invasive tumors. Neoadjuvant or adjuvant chemotherapy with cisplatin- or platinum-based regimens may improve survival in patients with metastatic disease. Checkpoint inhibitors immunotherapy targeting programmed cell death 1 receptor and its ligand have provided a new treatment option, particularly for patients with progressive UTUC disease following platinum-based chemotherapy. Tumor grade and stage are major prognostic factors for oncological outcomes. As potential tumor recurrence, repeated surveillance by urine cytology, cystoscopy, upper tract imaging and ureteroscopy following treatment are required.

INTRODUCTION

The term “urothelium” is used to delineate the lining surface epithelium of the urinary tract. The exposure of the urothelium to potential carcinogens that are either excreted or activated in the urine is thought to be associated with cancer formation [1]. Urothelial (formerly named transitional cell) carcinoma (UC) is derived from the urothelium of the urinary tract, including cancers of the renal pelvis, ureter, bladder, and down the urethra. Upper tract urothelial carcinoma (UTUC) comprises any UC arising from the level between the renal pelvis and the distal ureter [2]. UTUC comprises only a small fraction of cases as compared to UC of the bladder. Roughly 92-95% of all UCs arise in the bladder, but only 5-7 % occurs in the lining of the kidney (mainly renal pelvis) and the ureter. Nonetheless, UTUC comprises 266 (36%) of 736 UC cases in Taiwan [2].

As UTUC is relatively rare, the data of clinical features are generally not enough to guide the management of the disease.

A recent genomic assessment of UTUC demonstrates novel mutations, frequencies and distributions of mutations different to those of bladder cancer [3]. Approximately 17 percent of patients will have a concurrent bladder cancer at presentation [4]. In addition, UTUC may occur in approximately 2 to 4% of patients with bladder cancer. This may reflect the “drop metastases” of cancer cells to flow down from the renal pelvis or reflux from the bladder to the ureter. Among patients with UTUC, recurrence in the bladder is relatively common and the risk is lifelong. Recurrent bladder tumors often locate around the ureteral orifice of an affected ureter, supporting metastasis from the original UTUC. Intraluminal tumor cell seeding is associated with multifocality and recurrence of UC [5]. Thus, routine surveillance based on urinary cytology and on cystoscopy is recommended for patients following treatment for UTUC for at least 5 years.

Epidemiology

UTUCs are almost twice as common in men compared with women (closer to 2:1), with a mean age at diagnosis of 73 years [6]. The incidence of these cancers peak in individuals in their 8th and 9th decades of life. There is significant geographic variation in the incidence of UTUCs, likely due to differences in the prevalence of underlying risk factors. In Balkan nations, UTUC may represent up to 40% of all kidney-related cancers. In Western nations, the estimated annual incidence of UTUC is approximately 2 per 100,000 population [6,7]. Interestingly, the incidence of UTUC appears to be increasing, accompanied with an increasing proportion of earlier stage cancers [8]. The proportion of in situ tumors of UTUC increased significantly from 7.2% to 31.0% [6].

Data is mixed on the association between patient gender and outcomes in UTUC. While some authors have reported

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that women are more likely to have advanced stage of disease and worse outcomes following nephroureterectomy [9], other analyses have demonstrated no difference [10]. Southern Taiwan is an endemic area for UTUC cases. A total of 506 patients with localized UTUC were enrolled from a large registry-based surgical database. There were more female patients (57.9%). A subgroup analysis suggested that better survival outcomes for females only existed in the non-muscle-invasive stage, but not in the advanced stage [11].

Etiology

Genetic and environmental risk factors may contribute to the development of UTUC. Hereditary UTUC is associated with hereditary nonpolyposis colorectal carcinoma syndrome and endometrial tumors (Lynch syndrome) [12-14]. These patients with MSH2 (a mismatch repair gene) mutations are at an increased risk for UTUC and bladder cancer [14]. Hereditary UTUC should be suspected among younger patients or those with a personal or family history of colon or endometrial cancers.

A number of environmental risk factors are known for UTUC. Aristolochic acid nephropathy shares common pathway of Balkan endemic nephropathy and Chinese herb nephropathy, which are associated with UTUC by consumption of Aristolochia fangchi [15]. In the Balkan region (Bulgaria, Greece, Romania, former Yugoslavia), an indolent inflammatory process of the renal interstitium (so called Balkan endemic nephropathy) is associated with the development of urothelial tumors of the renal pelvis and ureter [15]. In that geographic region, these urothelial tumors account for almost 50 percent of all renal cancers. Chinese herb nephropathy can cause a progressive renal fibrosis that is frequently associated with UC of the renal pelvis [16,17]

In Western countries, smoking is a much more common risk factor. This is associated with the production of N-hydroxylamine from aromatic amines. Smoking seems to confer a higher risk of ureteral tumors than renal pelvic lesions [18]. Arsenic exposure, typically through contaminated underground water, has also demonstrated an association with the development of UTUC with a female preponderance [19-21]. Exposures to aromatic hydrocarbons, analgesic phenacetin, alkylating chemotherapy and chemic laxatives have been associated with a significantly increased risk of UTUC [22-24].

Pathology

The vast majority of upper tract tumors are urothelial in origin (>90%). Squamous cell cancers and adenocarcinomas make up a small proportion of upper tract malignancies. Squamous cell carcinomas account for approximately 8 percent of tumors of the renal pelvis [25]. These tumors are associated with a poorer prognosis than urothelial tumors because they tend to be large, sessile and deeply invasive at presentation. Squamous cell carcinomas have been associated with antecedent calculi or chronic infection [26]. Micropapillary UC is a rare variant and often presents at an advanced stage with lymphovascular invasion, distant metastasis and a poor clinical course [27].

Grading

UTUCs can develop as low- or high-grade tumors. In general,

low-grade tumors are not invasive and very rarely spread from the kidney or ureter. These tumors are more likely to intraluminal recurrence than distant spread. High-grade tumors have an aggressive appearance under a microscope and are assumed invasive in the kidney or ureter. High-grade UTUC can be aggressive to spread from the kidney or ureter and systemic chemotherapy before or after surgery may be recommended to reduce the risk of recurrence elsewhere in the body. There are significant differences in the prognosis for high-grade and high-stage tumors [28]. The survival was high in patients with low grade tumors, tumors without invasion and tumors without coexisting atypia in the adjacent urothelium but it was poor in those with high grade tumors, tumors with invasion and tumors with atypia of the adjacent urothelium [29].

The majority of renal pelvis UCs are of high histologic grade and present in advanced stages. Renal pelvis UCs show a tendency to frequently display unusual morphologic features, especially micropapillary areas, squamous differentiation and squamous cell carcinoma. Of 42 cases of high-grade renal pelvis UC, 26 (62%) died of tumor with a median survival of 31 months [30]. The patients who did not die of their UCs showed only minimal or focal infiltration of the renal parenchyma, whereas those who died of their UCs showed massive infiltration of the kidney.

CLINICAL FEATURES

The majority of patients with UTUC present with gross or microscopic hematuria. Up to 98% of all patients with UTUC will have hematuria and 70 to 80 percent of patients present with hematuria at diagnosis. However, UTUC remains uncommon among patients presenting with hematuria. Patients with UTUC may also experience discomfort or severe flank pain in 20 to 40 percent of cases [31,32]. This can occur because the tumor or bleeding that may obstruct or block the ureter or kidney, causing hydronephrosis and infections, and they can result in renal insufficiency. In rare cases, a flank mass, caused either by the tumor or associated hydronephrosis, may be palpated. Bladder irritation occurs in less than 10 percent of cases. UTUC may also present entirely without symptoms as an incidental finding. Hypertension is a common symptom of renal pelvis UC [28]. Vascular invasion was present in only high-grade tumors [32].

Metastasis

Of those patients diagnosed with UTUC, 50-56% of patients are diagnosed with non-muscle-invasive carcinoma, and the remaining UTUC patients are diagnosed with invasive, advanced, or metastatic diseases. These tumors disseminate via lymphatic and hematogenous spread as well as direct extension [33, 34]. Metastatic diseases usually appear late in the course of disease. The predominant sites of distant metastasis at diagnosis of UTUC were the lungs (55%), distant lymph nodes (37%), bone (32%) and liver (20%) [35]. Overall, from a study consisting of 52 UC patients (renal pelvis, 73%; ureter, 27%), lymph nodes (75%), lung (65%), liver (54%), bone (39%), and peritoneum (19%) were the most common metastatic sites [36]. In a Taiwanese study [28], distant metastasis of UC was detected in 37 of 141 (26%) patients. The most common sites were bone (46%), lung (22%), liver (14%) and colon (8%). Thus, preoperative staging

comprises CXR, chest CT, abdominal sonography or computed tomography (CT), liver function testing, and bone scan. In addition, for patients for whom nephroureterectomy is being considered, assessment of the contralateral renal function is necessary. Figures (1-5) demonstrate the common sites of distant metastasis of UTUC.

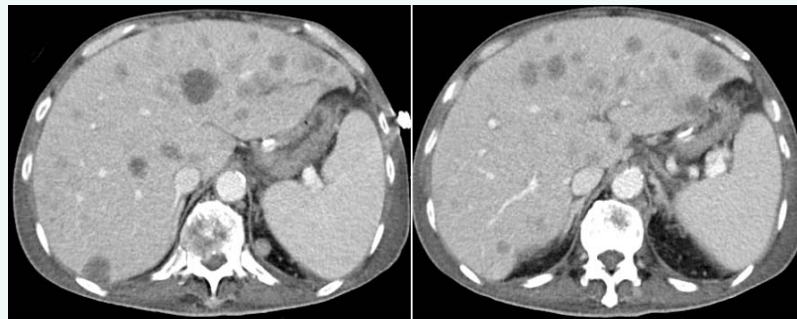
Skin metastasis occurred in (2.3%) of 44 patients with distant metastatic UC in a German report [37]. Cutaneous penile metastasis of UTUC is extremely rare and generally accepted as the late manifestation of a systemic spread [38]. Thus, it is important to physical examinations of the skin of patients with UC, including those apparently without organ-specific metastatic disease, even years after radical cystectomy or nephroureterectomy [39-41]. The first manifestation of cutaneous metastases from UC is an

inflammatory pattern of nodular erythematous skin rash, which may be diagnosed as carcinoma erysipelatodes [42]. Cutaneous metastases do not have distinctive gross appearance and are often misdiagnosed as common dermatologic disorders (Figure 6). It is imperative that urologists have high index of suspicion for metastasis in patients with persistent skin rash in the setting of advanced genitourinary carcinomas [41].

Brain metastasis is uncommon in patients with urothelial carcinoma [43].

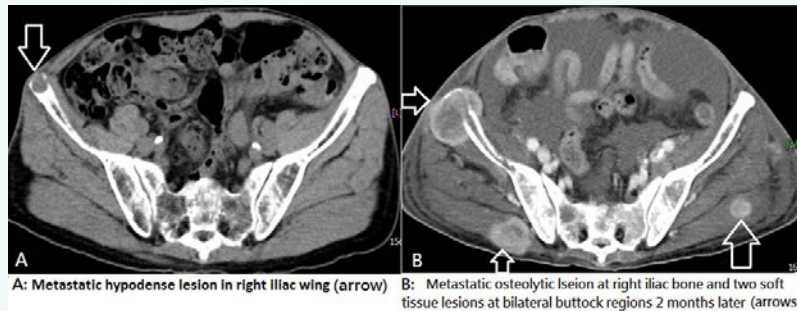
Paraneoplastic syndrome

Hypercalcemia: Hypercalcemia was found to in a patient with renal pelvis UC (Figure 7). On removal of the tumors, calcium



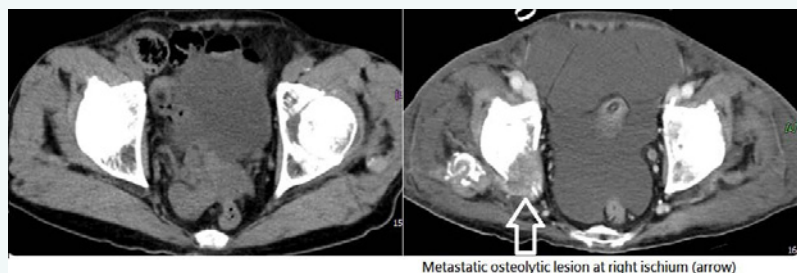
Multiple metastatic hypovascular tumors in both hepatic lobes

Figure 1 The computed tomography (CT) scans of the abdomen (left and right) are showing multiple metastatic hypovascular tumors in both hepatic lobes..



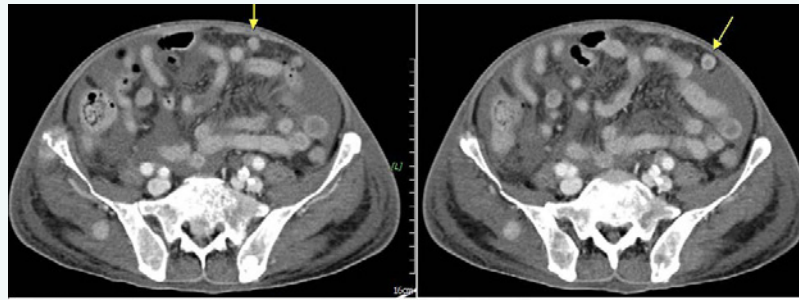
A: Metastatic hypodense lesion in right iliac wing (arrow) B: Metastatic osteolytic lesion at right iliac bone and two soft tissue lesions at bilateral buttock regions 2 months later (arrows)

Figure 2 (A): The CT scan of the pelvis is showing a metastatic hypodense lesion in right iliac wing (arrow). (B): The CT scan is showing an enlarging metastatic osteolytic lesion at right iliac bone and two new soft tissue lesions at bilateral buttock regions (arrows).



Metastatic osteolytic lesion at right ischium (arrow)

Figure 3 (Left): Normal appearance of CT scan at right ischium. (Right): A metastatic osteolytic lesion at right ischium (arrow).



Multiple metastatic tumors are seen at the peritoneum and bilateral retroperitoneum.

Figure 4 The CT scans of the abdomen (left and right) are showing multiple metastatic tumors at the peritoneum (arrows) and bilateral retroperitoneum.

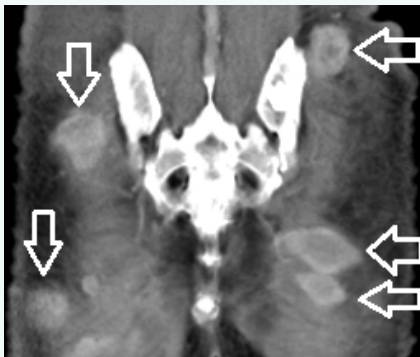


Figure 5 Multiple metastatic tumors at bilateral upper thigh (arrows).

levels fell to normal, indicating that a humoral factor produced by the tumor caused the hypercalcemia [44]. Hypercalcemia is an uncommon manifestation in UCs, especially those of the renal pelvis [45,46].

Leukemoid reaction: A case of hypercalcemia associated with a renal pelvis squamous neoplasm presented with severe hyperleukocytosis, resembling a leukemoid reaction (Figure 8). After failure of standard therapy, a trial of low dose epirubicin in this patient, obtaining a short-term clinical remission [47].

Thrombocytopenia: Isolated thrombocytopenia, hypercalcemia and acute kidney injury were found in a patient with UC and diffuse infiltration of the bone marrow by urothelial cancer [48].

Hormone-related peptide: In addition to leukemoid reaction, bone marrow metastasis, hypercalcemia may be associated with a rare occurrence of parathyroid hormone-related peptide (PTHrp), which would show response to bisphosphonate therapy. Intact PTH will be suppressed in cases of humoral hypercalcemia of malignancy, which is mediated by PTHrP. In general, PTHrp-induced hypercalcemia is associated with a grave prognosis, with a mean survival of 65 days from presentation [49].

DIAGNOSIS

Combinations of urine cytology, cystoscopy, and computed

tomography are currently used for diagnosis and monitoring modalities of UC.

Today, triphasic computed tomography, so called CT urography (CTU), is the imaging modality of choice for the diagnosis of UTUCs [50,51]. The sensitivity of CTU, as well as the negative predictive value, is reported to near 100% [52]. CTU offers better visualization of the urinary collecting system as well as evaluating for direct extension or nodal involvement [53]. Most UTUCs present with a filling defect or a mass in the renal pelvis (Figure 9). CT or magnetic resonance imaging (MRI) of the abdomen and pelvis may also detect extension of the tumor outside the collecting system, the presence of adjacent organ involvement, and/or the presence of distant metastases.

In equivocal cases, retrograde pyelography, selective ureteric washings for cytology, or ureteroscopy may be necessary. Due to the association between UTUC and bladder cancer, cystoscopy is necessary to rule-out concomitant bladder cancer [54]. Further, in the workup of a patient with hematuria, bladder cancer is a much more common underlying etiology than UTUC.

Flexible fiberoptic ureteroscopy can allow direct visualization of the entire collecting system for histologic diagnosis with biopsy or brushings [55,56]. However, these biopsies are limited in the amount of tissue and may underestimate the risk of more severe disease, so that tumor grading is more reliable than disease staging based on these samples. The tumorous grade concordance between biopsy and resection was high (89%), but 30% of cases showed invasion only on resection [57].

Urine cytology examination may be employed in the work-up of UTUC but could be of no help in the diagnosis [29]. While cytology is highly specific, it lacks sensitivity with poor diagnostic accuracy [58]. Cytologic examination of urine is less reliable for UTUC than for bladder cancers. As in one series, there was agreement between cytology and histology in 70 percent of patients with UTCC [59].

Diagnostic biomarkers

Urine- and blood-based biomarkers for detection of UC represent a considerable research area, including urine, blood tumor DNA, RNAs, proteins, and extracellular vesicles. For instance, NMP-22, bladder tumor antigen, and Xpert Bladder



Figure 6 (A to D):

Cutaneous metastasis of upper tract urothelial carcinoma: a firm and round nodule progressively enlarged into an erythematous nodule with vesicle and small bullae on anterior mid-upper abdominal wall

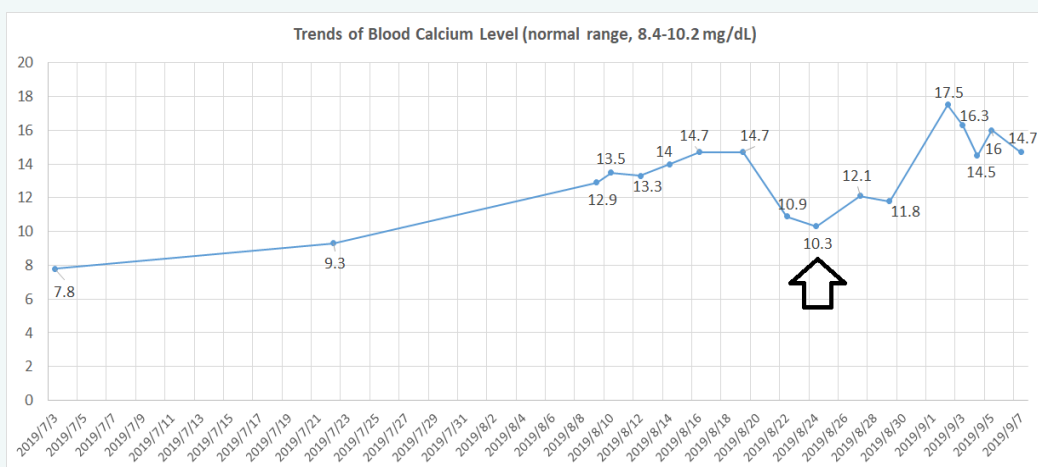


Figure 7 Trends of hypercalcemia in a patient with upper tract urothelial carcinoma. Therapy with forced diuresis achieved transient response (arrow).

Cancer are currently available in clinical practice. However, few biomarkers achieve high sensitivity and specificity [60]. Emerging biomarkers are continuously developed for clinical applications in bladder cancer and UTUC. For examples, CK 20 is a suitable marker for the detection of disseminated UC cells in peripheral venous blood samples and may be helpful in the molecular staging of UC patients [61]. Dysregulated androgen receptor (AR) signaling is implicated in several types of tumor, including carcinomas of the prostate, breast, liver, bladder and UTUC. AR-enhanced migration and invasion of UTUC cells may play a critical role in the establishment of the invasive phenotype of UTUC. Thus, the AR may also serve as a novel biomarker and

potential therapeutic target for UCs [62].

The Ki-67 expression in ureteroscopic biopsies was significantly correlated with high tumor grade, concomitant carcinoma in situ, and stromal invasion in surgical resection specimens. Thus, Ki-67 may aid diagnosis of UTUC in ureteroscopic biopsy specimens. Determination of Ki-67 expression in ureteroscopic biopsy specimens is potentially helpful in clinical decision making for patients with suspected UTUC [63].

Stage

Staging requires integration of imaging studies as tumor

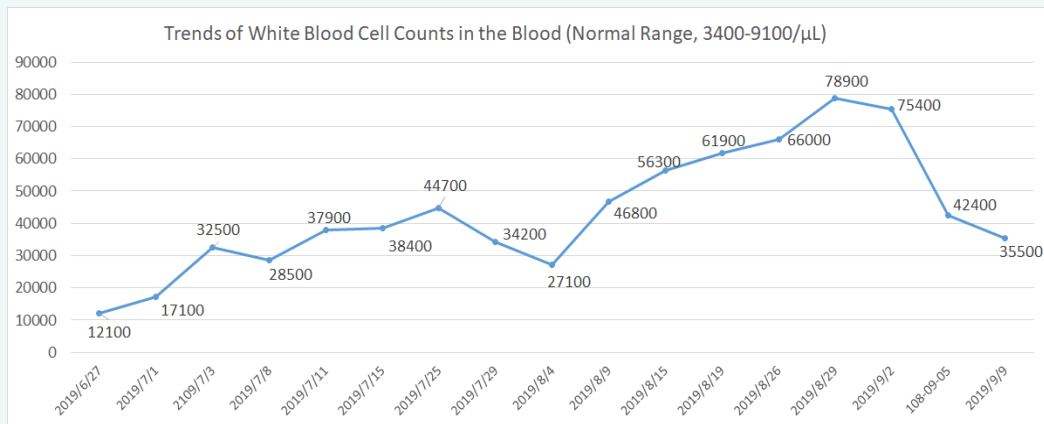
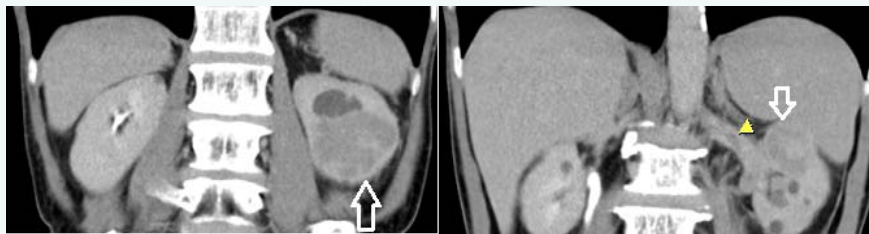


Figure 8 Trends of leukemoid reaction in a patient with upper tract urothelial carcinoma.



An ill-defined enhanced soft tissue lesion is seen involving the collecting system of the left kidney (arrow), with tumor invasion into the perirenal fat (arrow) and thrombosis of the left renal vein (arrow head).

Figure 9 (Left) An ill-defined hypodensity soft tissue mass is seen involving the collecting system with hydronephrosis of the left kidney (arrow). (Right) The tumor local invasion into the perirenal fat (arrow) and thrombosis of the left renal vein (arrow head) are seen.

grade. Routine staging procedures should include cystoscopy to exclude associated bladder cancer, a chest radiograph or CT, radionuclide bone scan if there are symptoms suggesting bone involvement or an elevated bone-derived alkaline phosphatase, and an evaluation of hepatic, renal, and hematologic function. CT or magnetic resonance imaging (MRI) of the abdomen may be performed to assess for the presence of retroperitoneal lymphadenopathy, disease extension and distant metastasis. The eighth edition (2017) of the tumor, node, metastasis (TNM) system is widely used to stage tumors of both the renal pelvis and ureters [64]. Any nodal involvement or distant metastasis constitutes stage IV disease in the TNM system. The TNM stage is correlated with outcome following definitive treatment.

Prognostic Factors: Pre-therapeutic evaluation

The prognosis following definitive treatment for UTUC is related to pathological tumor stage and the presence or absence of regional lymph node involvement, as well as tumor grade [65-68].

The 5-year recurrence-free and cancer-specific survival estimates for patients who underwent radical nephroureterectomy with ipsilateral bladder cuff resection were 75% and 78%, respectively [65]. Survival of the patients with low-grade tumors was significantly longer than those with

high-grade tumors (77 versus 31 months, $p = 0.01$). Age and gender had no consistent impact on survival. Stage, according to the TNM classification, is the most important predictor [69]. Unfortunately, it is sometimes difficult to ascertain stage preoperatively. Certainly, nodal involvement is independently associated with worse survival outcomes.

The UTUC patients had higher proportions of advanced clinical stage (T2-4) and poor cell differentiation [2]. UTUC patients with the advanced T4 stage had a significantly greater risk of poorer overall survival (HR = 8.7). Tumor location, whether in the renal pelvis or ureter, however, was not significantly associated with oncologic outcomes [65,70,71], whereas improved survival among patients with renal pelvic tumors has been found [72]. Both grade and stage are excellent predictors of survival [71].

The presence of hydronephrosis has been shown to be associated with worse survival [73]. Hydronephrosis at the time of diagnosis of UTUC is associated with advanced disease and is a predictor of poorer outcomes. On preoperative multivariable analysis controlling for age, gender, tumor location, ureteroscopic biopsy grade, and urinary cytology, hydronephrosis was independently associated with cancer metastasis (HR 8.2, $P = 0.02$) and cancer-specific death (HR 12.1, $P = 0.03$). Hydronephrosis can be a valuable prognostic tool for preoperative planning and counseling regarding disease outcomes [73].



Larger tumors (typically defined as greater than 3 or 4 cm) are also associated with worse outcomes. Other factors including tumor multifocality, tumor necrosis, and lymphovascular invasion have also been associated with worse outcomes though the data are somewhat inconclusive. A novel prognostic model of renal function, performance status, liver metastasis, number of metastatic sites could be useful for providing prognostic information to predict survival in patients with metastatic UTUC [74]. Furthermore, the 5-factor clinical prognostic model in patients receiving salvage systemic therapy for advanced UC include performance status, liver metastasis, hemoglobin, albumin and time from prior chemotherapy [75]. Elevated plasma fibrinogen was an independent unfavorable prognostic factor for oncological outcomes (advance tumor stage, high tumor grade and tumor size) in patients with UTUC [76].

A number of molecular markers have been evaluated for prognostication in patients with UTUC [77]. These include cytogenetic abnormalities, oncogenes (c-MET, RON and AIB1), markers of apoptosis (surviving and Bcl-2), markers of cell migration and invasion (E-cadherin and MMPs), tumor suppressor genes (p53 and CDKN1A), mitosis (Aurora-A), angiogenesis, cell proliferation (Ki-67 and EGFR), and cell differentiation (uroplakin III) [78]. FGF7 is the most significant gene up-regulated during UC progression. FGF7 over expression predicted advanced clinical features in patients with upper tract and bladder UC, justifying its potential prognostic value for UC [79]. Positive programmed death-ligand 1 (PD-L1) expression negatively regulates T cell activation. PD-L1 in approximately one-third of primary invasive UTUC was associated with high histologic grade, high pathologic stage, and angiolymphatic invasion [80, 81].

MANAGEMENT

Surgery

Surgery is the only potentially curative treatment modality for UTUC. Treatment is directed toward the primary tumor and relief of bilateral renal or ureteral obstruction. Surgery may include radical nephroureterectomy (whether open or laparoscopic), segmental ureterectomy, and endoscopic/percutaneous tumor ablations.

Radical nephroureterectomy remains the gold standard for large, high-grade and suspected invasive tumors of the renal pelvis and proximal ureter. Formal excision of a bladder cuff is the gold standard approach for management of the distal ureter. Total laparoscopic and laparoscopic-assisted nephroureterectomy are acceptable alternatives as effective minimally invasive treatments to open surgery in the treatment of UTUC [82, 83]. After a median follow-up time of 25 months for 116 patients who underwent laparoscopic radical nephroureterectomy, 23 patients (20%) died and distant metastases occurred in 11 patients (9%) [82].

Lymph node dissection may provide a survival benefit in patients undergoing nephroureterectomy for UTCC, particularly in those patients with muscle-invasive disease. The 5-year recurrence-free survival and cancer-specific survival rates were 27-65% and 32-95%, respectively [84]. An extended

lymphadenectomy during surgery for UTUC improves staging with a highly probable therapeutic benefit [85].

For selected patients with non-metastatic UTUC, robotic radical nephroureterectomy and segmental ureterectomy are technically feasible and achieved promising peri-operative and oncologic outcomes [86]. To reserve renal function for those patients with a solitary kidney, chronic renal insufficiency, or bilateral synchronous tumors, selected lesions of renal pelvis UC may be considered for nephron-sparing approaches or partial nephrectomy, provided they are not high-grade urothelial cancers [87]. For patients with early stage disease of low-grade and non-invasive tumors, retrograde endoscopic or percutaneous ablation offer the potential for nephron-sparing treatment [88, 89].

Surgical resection of metastases can be considered as a treatment choice in advanced/metastatic urologic malignancies to improve survival rates. Metastasectomy can be suggested in conjunction with effective chemotherapy if complete resection is possible [90].

Chemotherapy

Cisplatin-based chemotherapy seems to improve survival in patients with metastatic UTUC disease [71]. Pre-surgical neoadjuvant platinum (cisplatin, carboplatin, oxaliplatin or nedaplatin)-based induction chemotherapy followed by consolidative surgery was very encouraging in patients with clinical lymph node metastatic UC [91].

Adjuvant gemcitabine-cisplatin (GC) chemotherapy following nephroureterectomy demonstrated a significant improvement in disease-free survival and progression-free survival of patients with locally advanced UTUC [92]. Cisplatin-based regimen is the most common first-line chemotherapy consisting of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or GC. After failure of gemcitabine and paclitaxel as a second-line chemotherapy, gemcitabine and nedaplatin chemotherapy is a favorable third-line chemotherapeutic option for patients with progressive metastatic urothelial carcinoma. Then the disease-control rate was 40%, the median overall survival was 8.8 months and the median progression-free survival was 5.0 months [93].

Of 102 patients with metastatic UTUC in Japan, 70 patients (69%) died during the median follow-up period of 6 months, and the 2-year overall survival rate was estimated at 22%. The median survival time to all-cause mortality was 8.5 months [35]. Patients who received chemotherapy and surgery showed significantly better prognosis (median survival time 25.8 months) compared with patients treated with chemotherapy alone (median survival time 7.3 months) [35]. Within the National Cancer Data Base (2004-2012) in USA, radical nephroureterectomy in addition to systemic chemotherapy for widely metastatic UTUC may be associated with an overall survival benefit compared to chemotherapy alone [94].

Checkpoint inhibitors immunotherapy with antibodies targeting programmed cell death 1 receptor (PD-1) and its ligand (PD-L1) have provided a new second-line treatment option for patients with UTUC, who have progressive disease following



platinum-based chemotherapy or have chronic kidney disease unable to tolerate cisplatin-based chemotherapy. Immune PD-1 inhibitors (pembrolizumab, nivolumab) or PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab) have been approved by the United States Food and Drug Administration for first- or second-line use in metastatic UC [95].

Post-treatment recurrence

UC represents a clinical challenge because of its post-treatment recurrence rate and prognosis. Following treatment, repeated surveillance by urine cytology, cystoscopy, upper tract imaging and ureteroscopy are required. Thoracic imaging, biochemical studies including liver function testing, and bone scan may be indicated to survey distant metastases. For all patients who undergo a renal-sparing procedure, frequent surveillance is required because of the high risk of recurrent disease. When nephrectomy alone or incomplete nephroureterectomy was performed, subsequent UC developed in 30% of the ureteral stumps [96].

The incidence of tumor recurrence after nephroureterectomy with bladder cuff excision was significantly higher in those with ureter UC (13%) than renal pelvis UC (3.6%) [28]. The mean time from radical nephroureterectomy to first disease recurrence was 15.0 months and around 90% of patients experienced disease recurrence within the first 3 years after surgery. Most patients died from UTUC within 3 years, even though systemic chemotherapies were administered after relapsing. The presence of liver metastasis and the number of recurrence sites were independently related to poor survival after systemic chemotherapy [97].

Of 733 patients with UTUC in Japan, a total of 218 (30%) patients experienced disease recurrence. Of these patients, 39 % developed distant recurrence; and 17 % experienced both local and distant recurrences. Renal pelvic tumors had a higher prevalence of distant relapse in the lungs [98].

The expression of PD-L1 was significantly associated with a high frequency of postoperative recurrence [81].

Prognostic factors: Post-therapeutic assessment

In a large series of patients treated with radical nephroureterectomy for UTUC in USA, high tumor grade, advancing stage, Lymph node metastases, infiltrative growth pattern, and lymphovascular invasion were associated with disease recurrence [63]. The 5-year cancer-specific survival rates for patients with low-grade tumors and those with high-grade tumors were 89 versus 63 percent. The 5-year cancer-specific survival rates for patients with different stages of pT0/Ta/Tis, pT1, pT2, pT3, and pT4 disease were 94, 91, 75, 54, and 12 percent, respectively. The 5-year cancer-specific survival rates for patients with negative nodes and those with positive lymph nodes were 77 versus 35 percent [63]. Lymph node invasion is a clear independent poor prognostic factor [85]. For patients with lymph node metastatic UC, the median overall survival was 31.6 months. Negative resection margin, more lymph nodes removed, were found to be independent post-surgical prognostic factors for overall survival [91].

In Japan, independent predictive factors for all-cause mortality of patients with metastatic UTUC were age and liver metastasis [35]. In China, patients with brain and liver metastasis had significantly worse survival outcome. Multivariate analysis showed that patients with bone, lung or distant lymph node metastasis was not independent prognostic factor for patients' survival. Some highly selected patients with multiple organs of metastasis or distant lymph node involvement could benefit from surgical resection of the primary tumor, which was an independent favorable predictor for outcome. However, the presence of liver or lung metastasis could make such surgery become meaningless from the point of survival benefits [99]. In Taiwan, a retrospective study was conducted for 120 patients with metastatic UTUC after MVAC or gemcitabine/cisplatin chemotherapy. The risk factors of number of metastatic sites (hazard ratio, 2.74) and liver metastasis (HR = 1.84) as well as favorable factor of MVAC chemotherapy (HR = 0.54) were significantly correlated to survival for UTUC with statistical significance in multivariate analyses [100].

CONCLUSION

UTUC of renal pelvis and ureter is a rare, aggressive urologic cancer with a tendency towards multifocality, local recurrence, and metastasis. For patients with UTUC and without evidence of metastatic or unresectable locally advanced disease, extensive resection by nephroureterectomy with excision of a cuff of normal bladder is the preferred procedure. A neoadjuvant or an adjuvant chemotherapy added to nephroureterectomy is suggested for high-risk patients, such as metastatic, locally advanced disease, or positive lymph nodes. The preferred chemotherapy regimens include MVAC or GC. For patients with progressive disease following platinum-based chemotherapy, checkpoint inhibitor immunotherapy is an important option.

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