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Seminar article

Optimizing management of upper tract urothelial carcinoma

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Abstract

Upper tract urothelial cancer (UTUC) is a rare cancer of the urothelium, comprising only a fraction of cases as compared to urothelial tumors of the bladder. As a result, systemic treatment approaches in bladder cancer are often applied to patients with UTUC. Given the anatomical location of these tumors, the age, the comorbid conditions of these patients with UTUC, and the need for radical nephroureterectomy for treatment, most patients have substantial impairment of renal reserve. There is growing evidence for the benefit of perioperative chemotherapy in this disease. Patients with UTUC have high rates of microsatellite instability and fibroblast growth factor receptor 3 mutations as compared to their bladder counterparts presenting unique, important subsets in UTUC. Immune checkpoint inhibitors targeting the programmed death receptor 1 and ligand have provided a new second-line treatment option for patients with UTUC and appear particularly well suited for patients with microsatellite instability. More work in understanding the molecular gene signatures and its relationship to response to chemotherapy, immunotherapy, and targeted therapy is needed to continually optimize care for patients with all stages of disease. Advances in UTUC are possible, when one accounts for the unique clinical and biological features of this disease.

Keywords: Upper tract; Urothelial cancer; Chemotherapy; Renal pelvis

Overview

Our understanding of the molecular tapestry of urothelial cancers is evolving. This, in addition to improving therapeutic arsenal for treating these tumors, shows promise to improve outcomes for patients with urothelial carcinoma (UC). Although the majority of the progress and focus has involved tumors that arise in the bladder, this progress will also undoubtedly shape the treatment of upper tract urothelial cancer (UTUC) as well. In this review, we will focus on the current management strategies of UTUC, the growing evidence for perioperative chemotherapy in UTUC [1–3], the developments in the molecular classification of UC and early efforts in UTUC, and we will examine the current role of immune checkpoint therapy and discuss how these agents may be optimally implemented in the coming years.

In the United States, the incidence and prevalence of UTUC is not well defined with renal pelvis tumors lumped in with cancers arising in the kidney and those arising in the ureters grouped with cancers in the very rare "other urinary organs" [4]. The most commonly cited incidence of upper tract urothelial carcinoma (UTUC) is that it represents 5% of all UCs, which in the United States translates to 2 cases per 100,000 giving a rough estimate of 3,750 cases annually [5,6]. The ratio of renal pelvis to ureter tumoral origin is estimated to be 2:1. Environmental risk factors for the development of UTUC include tobacco, occupational exposure to aromatic amines or chlorinated solvents, phenacetin, as well as Balkan endemic nephropathy and Chinese herbal nephropathy, both resulting from exposure to *Aristolochia fangchi* or *Aristolochia clematis* [7,8]. The most important hereditary condition associated with UTUC is Lynch syndrome, also known as hereditary nonpolyposis

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colorectal cancer, defined by mutation in mismatch repair proteins resulting in microsatellite instability (MSI), but MSI may also be detected in sporadic cases of UTUC and represents an important subgroup of UTUC [9,10].

Surgical considerations

Effectively staging patients with UTUC can be a significant challenge. The risk of clinically understaging patients and proceeding to upfront surgery has the potential to diminish renal function to the point where cisplatin-based chemotherapy is not possible [11]. A study by Xylinas et al. estimated less than 15% of patients who have received a radical nephroureterectomy (RNU) would be cisplatin candidates in the adjuvant setting if a creatinine clearance of 60 ml/min is used as a cutoff. In an effort to reduce the probability of surgical upstaging, Favaretto et al. [12] retrospectively evaluated 324 patients treated at single institution and proposed a predictive nomogram model to assess for risk of either muscle-invasive or lymph node–positive disease at the time of RNU. In this model, local invasion on imaging and high-grade disease detected at ureteroscopy were predictive of both adverse pathologic findings. In this model, the presence of hydronephrosis did not add to the predictive nature of the nomogram. Other groups have defined hydronephrosis as predictive for pathologically advanced disease at surgery [13,14]. Additional clinical factors independently associated with adverse cancer-specific survival at surgery were reported by the Upper Tract Urothelial Carcinoma Collaboration and have been corroborated by other studies, namely high-grade disease on biopsy, and sessile architecture [15].

Although neoadjuvant chemotherapy is increasingly being advocated for by large institutions [2,3], and is included in the UTUC guidelines for high-grade disease [16], many still consider a RNU with bladder cuff excision alone the gold standard for surgical management of localized UTUC. Given the age and common comorbidities in this patient population, ever-improving endoscopic procedures have been pioneered. Published literature to date examining the usage of these approaches has largely been through single-center series. Kidney-sparing surgeries (KSS) vary depending on the anatomic location of the tumor, i.e., renal pelvis or various locations within the ureter, and include segmental ureterectomy and ureteroscopic or percutaneous procedures. A meta-analysis published by Yokoubi et al. [17] included 8 publications and looked at end points of disease-specific and overall survival. This data did not include any randomized, prospective trials, and they found no measurable difference between RNU and KSS. However, the authors cautioned regarding the low level of evidence and the significant heterogeneity in outcomes leading to significant difficulty in interpreting this data. The current European guidelines and National Comprehensive Cancer Network (NCCN) guidelines for the management of UTUC list alternatives to RNU based on an individual's risk factors. The NCCN focuses on grade with low-grade tumors having the option for RNU vs. KSS. The European guidelines define "low-risk" UTUC as low-grade disease based on cytology and biopsy, papillary architecture, tumor size less than 1 cm, unifocal disease, and no obvious "invasive aspect" on cross-sectional imaging [18]. When all of these criteria are satisfied kidney-sparing management is considered an alternative, but is categorized as having a low level of evidence in support. A recent update from the authors of the European guidelines systemically reviewed the available literature for KSS vs. RNU in 22 retrospective series and concluded with that for low-grade UTUC and with no invasive aspect on cross-sectional imaging, ureteroscopic and percutaneous management provided similar survival outcomes as compared to RNU [19].

Chemotherapy

No prospective randomized trials for neoadjuvant or adjuvant chemotherapy UTUC have been reported to date, with the exception of 2 studies evaluating adjuvant intravesical chemotherapy for the prevention of bladder cancer after nephroureterectomy, with both showing evidence of benefit [20,21]. In muscle-invasive bladder cancer randomized, level I evidence supports the use of cisplatin-based combination neoadjuvant chemotherapy as compared to surgery alone [22]. Conversely, no level I evidence supports the use of adjuvant cisplatin-based chemotherapy in the same patient population. However, a large population-based study and meta-analysis supports the use of adjuvant cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer that did not receive chemotherapy in the neoadjuvant setting [23,24]. Both the NCCN guidelines and European guidelines support the use of neoadjuvant chemotherapy in the muscle-invasive bladder cancer setting before definitive surgery.

Given the lack of evidence, the European guidelines do not address the role of neoadjuvant chemotherapy in UTUC. An early retrospective review suggested higher rates of downstaging with neoadjuvant chemotherapy for UTUC [1]. A subsequent analysis comparing matched cohorts of patients treated at a single institution with neoadjuvant cisplatin-based chemotherapy found a significant improvement in disease-specific and overall survival [25]. One neoadjuvant trial that enrolled 16 patients with UTUC, reported similar pathologic downstaging rates and survival as has been observed with urothelial cancer of the bladder (pT0 = 38%, 5-year overall survival 72%; Figs. 1 and 2) [2].

A meta-analysis exploring the limited data with both neoadjuvant and adjuvant chemotherapy in UTUC supports the benefit of cisplatin-based chemotherapy in this setting, whereas there are no data supporting the use of non–cisplatin-based chemotherapy [26]. Interestingly more