Diagnosis and Management of Upper Tract Urothelial Carcinoma

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KEYWORDS

• Upper tract urothelial carcinoma • Kidney neoplasms • Ureteral neoplasms
• Urothelial carcinoma • Nephroureterectomy • Chemotherapy • Radiotherapy

KEY POINTS

- Upper tract urothelial carcinoma (UTUC) is a rare subset of urothelial cancers that portends a poor prognosis that has not improved in the past 2 decades.
- Numerous preoperative and postoperative prognostic factors have been identified to better predict survival outcomes and guide therapy.
- Treatment of low-risk noninvasive UTUC consists of conservative nephron-sparing surgery (eg, endoscopic treatments, segmental resection) and adjuvant topical therapies (eg, mitomycin C).
- Treatment of localized high-risk disease is most commonly open radical nephroureterectomy, although minimally invasive surgery is increasingly used, given equivalent oncologic and reduced surgical morbidity.

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- Multimodal therapy, including neoadjuvant/adjuvant chemotherapy and combined chemoradiotherapy, may improve survival outcomes.
- Metastatic disease is commonly managed with systemic chemotherapy, with limited roles for salvage/adjuvant radiotherapy and surgery.

INTRODUCTION

Epidemiology

Urothelial cell carcinoma (UCC) is the fourth most common cancer worldwide, after prostate (or breast), lung, and colorectal cancer.[1] Among UCC, upper tract urothelial carcinoma (UTUC) is rare and accounts for 5% to 10% of all urothelial carcinomas with an annual incidence of 2 cases per 100,000 inhabitants in Western countries.[2] UTUC is more common in men than in women with a male-to-female ratio of 2:1 and the mean age at the diagnosis of 65 years old.[3] It is located twice more often in the renal pelvis than in the ureter and in about 20% of the cases a concomitant urothelial carcinoma of the bladder (UCB) is present.[4] UTUC tends to recur in the bladder or progress through the lymphatic and vascular systems to distant organs. To date, much of the decision-making in UTUC comes from knowledge acquired in UCB because of its relative rarity. Over the last 5 years, a large body of evidence has proven that UTUC and UCB have common features but differ as well in a significant degree.[5]

Risk Factors

Tobacco and occupational exposure are the main UTUC exogenous risk factors in most countries. The relative risk of developing UTUC in the case of tobacco exposure has been estimated to be 2.5 to 7, depending on the number of years of exposure and the number of cigarettes smoked per day.[6] Occupational exposure to certain aromatic amines has an estimated risk of 8.3.[7] However, exposure risk decreased since the 1960s because certain chemical substances, such as benzidine and β-naphthalene, have been banned from industrial production. The most exciting discovery in the last 10 years in UTUC has been the unraveling of aristolochic acid as an iatrogenic global risk factor for UTUC development.[8]

Balkan endemic nephropathy and Chinese herbs nephropathy, which are the same disease, are specifically related to UTUC.[9–11] They are characterized by a mutation of the p53 gene as a consequence of the exposure to aristolochic acid, a potent carcinogen derived from Aristolochia plants, which is used as an herbal ingredient or remedy.[12] A significant use of this plant has also been registered in Taiwan, where the incidence of UTUC is estimated to be approximately 20% to 25% of all urothelial cancers, the highest worldwide.[13] Unfortunately, clinical trials targeting these selected populations are lacking and further efforts are required to lower the exposure to this deadly substance, which is integral in many traditional Chinese and Indian pharmacopoeia.[14]

Rare cases of UTUC linked to hereditary nonpolyposis colorectal carcinoma (HNPCC, Lynch syndrome) have also been reported. UTUC patients younger than 60 years, with a personal history of an HNPCC-associated cancer, a first-degree relative younger than 50 years of age with HNPCC-associated cancer, or 2 first-degree relatives with HNPCC-associated cancer should be screened for hereditary cancers.[15,16]