# Kidney, Ureteral, and Bladder Cancer

## A Primer for the Internist

Hans C. Arora, MD, PhD[a], Michele Fascelli, MD[a], JJ.H. Zhang, MD[a], Sudhir Isharwal, MD[a], Steven C. Campbell, MD, PhD[b,*]

**KEYWORDS**

• Kidney cancer • Bladder cancer • Ureteral cancer • Urothelial carcinoma
• Renal cell carcinoma • Evaluation • Surgery • Treatment

**KEY POINTS**

- Hematuria (gross or microscopic) is a common presenting symptom in kidney, bladder, and ureteral cancer.
- High-quality contrast-enhanced cross-sectional abdominal imaging, such as computed tomography urogram or magnetic resonance urogram, is the most sensitive radiological studies for evaluation of suspected renal or upper tract malignancy.
- Cystoscopy is an important component of the evaluation of any patient with gross or microscopic hematuria.
- Early recognition and referral to an urologist for further work-up and management is critical to optimize prognosis.

## INTRODUCTION

Malignancies of the urinary tract (kidney, ureter, and bladder) differ in their cellular origins and thus represent distinct clinical entities. The overarching term kidney cancer most commonly refers to malignancies of the renal parenchyma. Renal cell carcinoma (RCC) is by far the most common type of kidney cancer, accounting for 90% of renal malignancies. Cancers of the renal pelvis, ureter, and bladder are predominantly urothelial carcinoma (UC; formerly known as transitional cell carcinoma) and also represent a major source of morbidity and mortality.

RCC and UC differ in their presentation and management. In the current era, RCC is most often detected incidentally during the imaging work-up for unrelated symptoms.

Disclosure Statement: None.
[a] Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Q10-1, Cleveland, OH 44195, USA; [b] Center for Urologic Oncology, Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Q10-1, Cleveland, OH 44195, USA
* Corresponding author.
*E-mail address:* campbes3@ccf.org

Med Clin N Am 102 (2018) 231–249
https://doi.org/10.1016/j.mcna.2017.10.002
0025-7125/18/

In contrast, patients with UC often present with gross or microscopic hematuria. Even though UC of the upper urinary tract and bladder are histologically similar, they differ in their management and prognosis. A high index of suspicion with prompt referral to an experienced urologist is critical for early detection and treatment, and to prevent local or systemic progression of these malignancies. The objective of this article is to provide an overview of the evaluation and management of malignancies of the urinary tract.

## KIDNEY CANCER: RENAL CELL CARCINOMA

The term renal mass encompasses a biologically diverse group of tumors ranging from benign lesions to aggressive cancers.[1–3] The incidence of RCC in the United States has been increasing in recent decades with nearly 64,000 new cases and more than 14,000 deaths expected in 2017.[4] Increased use of imaging studies resulting in increased early-stage detection is a suggested contributor to the increased incidence of renal masses.[5] The major environmental risk factors for RCC include smoking, hypertension, and obesity.[6–9] Acquired renal cystic disease, often presenting in end-stage renal disease patients, also confers an increased risk for RCC, specifically papillary RCC.[3] RCC can be hereditary in 3% to 5% of cases and, in this setting, typically presents in a younger age group and may be part of a clinical syndrome complex.

### *Patient History*

Historically, renal masses were diagnosed with the classic triad of symptoms: flank pain, hematuria, and a palpable abdominal or flank mass. Currently, more than 50% of renal masses are diagnosed incidentally during imaging studies, with only 10% or less presenting with the classic triad, which often indicates locally advanced or metastatic disease.[3] Despite increased detection of renal masses at earlier stages, the incidence of metastatic disease on initial presentation has remained 20% to 30% across population-based studies.[1,10] RCC can present with several paraneoplastic conditions, including anemia, polycythemia, hypercalcemia, constitutional symptoms (fever, weight loss, cachexia), and elevated erythrocyte sedimentation rate or C-reactive protein.[3] A reversible hepatitis (Stauffer syndrome) may also be observed in RCC even in the absence of liver metastases, and elevated liver enzyme levels may improve after tumor resection. RCC has been termed the internist's tumor owing to the diversity of potential presentations related to these paraneoplastic syndromes.

### *Pathophysiology*

The major subtypes of RCC are clear cell, papillary, chromophobe, and collecting duct. These subtypes differ in their genetic origin, histologic appearance, and metastatic potential (**Table 1**).[3,11,12] Familial hereditary syndromes can present with either renal-related symptoms or extrarenal manifestations, such as skin lesions or spontaneous pneumothoraces, and are typically associated with specific subtypes of RCC (**Table 2**).

RCC is often associated with increased tumor neovascularity, particularly for clear cell variants. Inactivation of the *VHL* tumor suppressor gene results in the accumulation of hypoxia-inducible factor (HIF)-related proteins, which leads to overexpression of vascular endothelial growth factor (VEGF) and increased angiogenesis.[3] Another important pathway is that of mammalian target of rapamycin (mTOR) kinase, an upstream activator of HIF-1 protein expression that leads to cell growth and angiogenesis.[3,13] Many of these pathways can now be targeted with tyrosine kinase or mTOR inhibitors, improving outcomes for patients with advanced RCC.