The Emerging Molecular Landscape of Urothelial Carcinoma

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KEYWORDS

• Ancillary testing • Urothelial carcinoma • Bladder cancer • Molecular pathology • Subclassification • Targeted therapy • Immunotherapy

Key points

- Urothelial carcinoma is one of the most complex and heterogeneous neoplasms at the molecular level, with alterations seen in a wide variety of molecular pathways and cancer-related genes.
- Historically, a two-pathway model has been used in which low-grade papillary urothelial carcinoma is associated with alterations in cell growth and proliferation pathways, whereas high-grade and invasive urothelial carcinoma is associated with alterations in cell-cycle regulation, although there now seems to be overlap in a subset of pathways.
- Currently, research groups are further subdividing urothelial carcinoma based on molecular signatures, but these are still in the research stage and application to clinical and treatment decisions remains elusive.

ABSTRACT

Although there have been many recent discoveries in the molecular alterations associated with urothelial carcinoma, current understanding of this disease lags behind many other malignancies. Historically, a two-pathway model had been applied to distinguish low- and high-grade urothelial carcinoma, although significant overlap and increasing complexity of molecular alterations has been recently described. In many cases, mutations in *HRAS* and *FGFR3* that affect the MAPK and PI3K pathways seem to be associated with noninvasive low-grade papillary tumors, whereas mutations in *TP53* and *RB* that affect the G1-S transition of the cell cycle are associated with high-grade in situ and invasive carcinoma. However, recent large-scale analyses have identified overlap in these pathways relative to morphology, and in addition, many other variants in a wide variety of oncogenes and tumor-suppressor genes have been identified. New technologies including next-generation sequencing have enabled more detailed analysis of urothelial carcinoma, and several groups have proposed molecular classification systems based on these data, although consensus is elusive. This article reviews the current understanding of alterations affecting oncogenes and tumor-suppressor genes associated with urothelial carcinoma, and their application in the context of morphology and classification schema.

OVERVIEW

With more than 73,000 projected new cases and 16,000 deaths in 2015, bladder cancer is one of the most common cancers in the United States. It is the fourth most common new cancer diagnosis in men and the twelfth most common new cancer diagnosis in women.[1] Presenting signs often include

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either macroscopic or microscopic hematuria in otherwise asymptomatic patients, whereas a subset of patients describe urinary urgency or dysuria. In the United States, the most common risk factor is smoking, although other risk factors include exposure to arsenic or nitrosylating agents.[2] There is no current screening test for bladder cancer. However, patients who present with hematuria and are suspected to harbor bladder cancer undergo an evaluation that includes cystoscopy, computed tomography imaging and urogram, and urine cytology analysis.[2]

Definitive diagnosis of urothelial carcinoma, the most common form of bladder cancer, requires pathologic evaluation of biopsy or transurethral resection material obtained at the time of cystoscopy. Once diagnosed, clinical management is chiefly determined by the histologic and morphologic characteristics of the tumor, including the tumor stage and grade.[2,3] Briefly, tumor stage is determined by the presence and depth of invasion, with invasion into the muscularis propria (detrusor muscle) representing a critical determinant of surgical versus nonsurgical management (**Fig. 1**).

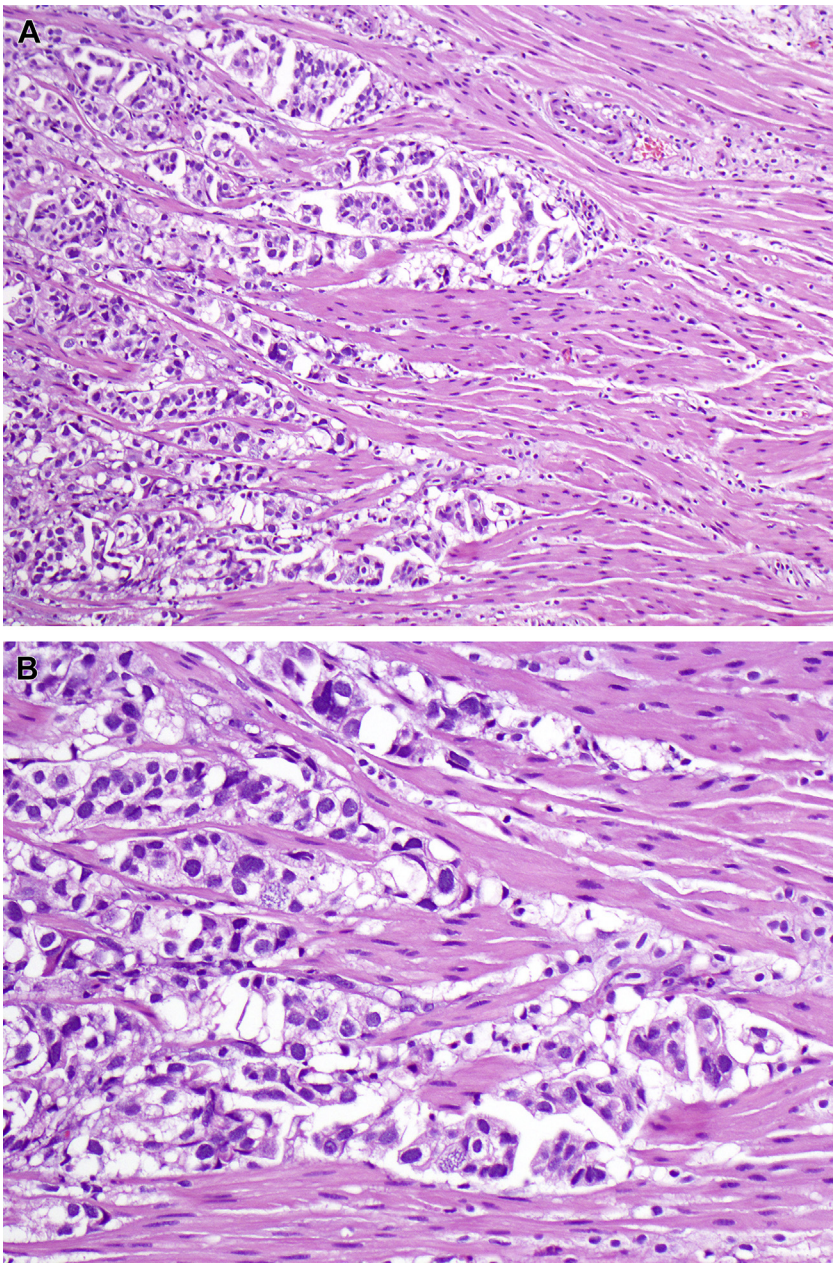

Fig. 1. Muscle-invasive urothelial carcinoma invading through and dissecting muscle bundles of the muscularis propria (detrusor muscle) (*A*, hematoxylin-eosin, original magnification ×100; *B*, hematoxylin-eosin, original magnification ×200).