Morphologic and Molecular Characteristics of Bladder Cancer

James P. Solomon, MD, PhD[a], Donna E. Hansel, MD, PhD[b,*]

KEYWORDS

• Bladdder cancer • Urothelial cancers • Molecular alterations • Hematuria

ABSTRACT

Bladder cancer is the fourth most common cancer in men, and is associated with significant morbidity and mortality. Pathologic evaluation of urothelial cancers relies predominantly on histomorphologic features but can be aided in a small subset of cases by immunohistochemical analyses. Distinction of papillary versus flat lesions, low-grade versus high-grade cytology, and histologic variants and the presence or absence of invasive tumor is important for proper clinical management. Advances in the molecular alterations associated with the various subtypes of urothelial carcinoma have been made but such studies are ongoing.

OVERVIEW

With more than 74,000 new cases and more than 15,000 deaths each year, urothelial carcinoma of the bladder is one of the most common cancers in the United States. It affects men at a rate 3 times that of women and is the fourth most common cancer diagnosis in men.[1] Hematuria, either gross or microscopic, is the most often presenting symptom, but patients may also experience other nonspecific symptoms, including urinary urgency or dysuria. Smoking is a well-established risk factor for the disease, increasing risk of development by approximately 4-fold.[1] There is no current screening test for urothelial carcinoma, but patients who present with symptoms suspicious for bladder neoplasia undergo a clinical work-up that includes imaging of the upper urinary tracts, urine cytology on voided urine, and white light cystoscopy with bladder biopsy.[2] Once diagnosed, the treatment of urothelial carcinoma depends on the pathologic stage and grade of the tumor (see also Harshman et al, Diagnosis of Bladder Carcinoma: A Clinician's Perspective, Surgical Pathology Clinics, 2015, Volume 8, Issue 4). Surgical excision of tumor burden, either used alone or in combination with intravesicular treatments, such as bacillus Calmette-Guérin, is the mainstay of early-stage cancers. Advanced cancers invasive into the muscularis propria (detrusor muscle) of the bladder are often treated with radical cystectomy, and outcomes are improved with neoadjuvent systemic chemotherapy or radiation treatment.[2] Although the prognosis for noninvasive tumors is good, with a 96% 5-year survival, invasive tumors carry a much worse prognosis, with 70% and 33% 5-year survival rates for localized and regional disease, respectively.[1] Because of the differences in management strategies and prognosis, accurate histopathologic characterization of bladder tumors is of the utmost importance. Great strides have been made in understanding the pathophysiology of urothelial carcinoma; however, the disease seems to have a heterogeneous biology, and various molecular pathways and mutations in many genes are likely involved in tumorigenesis. Nevertheless, the molecular characterization of urothelial carcinoma is currently not performed in routine clinical practice. Additionally, the lack of available predictive biomarkers re-emphasizes

[a] Department of Pathology, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA; [b] Division of Anatomic Pathology, Department of Pathology, University of California, San Diego, 9500 Gilman Drive, MC 0612, La Jolla, CA 92093, USA
* Corresponding author.
E-mail address: dhansel@ucsd.edu

Surgical Pathology 8 (2015) 663–676
http://dx.doi.org/10.1016/j.path.2015.07.003
1875-9181/15/$ – see front matter

the importance of accurate histopathologic staging and grading.

GROSS FEATURES

There are 2 main growth patterns of urothelial lesions: papillary and flat. The growth patterns are thought to have different molecular mechanisms of growth (discussed later). On cystoscopy or in gross resection specimens, papillary lesions often appear as an exophytic mass with papillary fronds growing outward into the bladder lumen. The lesion may have a cauliflower-like appearance, and there may also be areas of necrosis or ulceration within the lesion. On the other hand, flat, or in situ, lesions, often have a red or velvety gross appearance, contrasting with the smooth tan-gray appearance of normal mucosa, and these areas should be thoroughly sampled.

MICROSCOPIC FEATURES

CLASSIFICATION AND GRADING OF UROTHELIAL NEOPLASIA

The classification system of urothelial neoplasia has undergone several revisions since its official inception in 1973. Revisions in 1998 and 1999 preceded the current recommendation established in 2004 by the World Health Organization/International Society of Urologic Pathology (WHO/ISUP). These classifications determined in 2004 have strict diagnostic criteria, with each of the described lesions having different risks of progression and recurrence.[3] These diagnostic criteria are summarized in **Table 1**.

In general, papillary lesions are classified by their growth pattern and complexity of fibrovascular cores as well as the cytologic features of the overlying epithelium. Urothelial papilloma is a papillary lesion with fine, nonbranching fibrovascular cores and is characterized by a urothelium that is less than 7 cell layers thick with normal polarization with no cellular atypia. These lesions have the lowest risk of recurrence and the lowest risk of progression. A papillary urothelial neoplasm of low malignant potential (PUNLMP) has nonbranching fibrovascular cores and an overlying urothelium that may be hyperplastic (**Fig. 1**A, B). The hyperplastic urothelium has an increased number of cell layers but retains its polarity with minimal cellular atypia. There may be a substantial risk of recurrence but a low risk of progression and, therefore, this term was developed so as to not label patients with a cancer diagnosis. Nevertheless, a PUNLMP diagnosis should not represent more than 10% of all papillary urothelial diagnoses. In contrast, low-grade papillary urothelial carcinoma may have branching fibrovascular cores and a urothelium that has lost some cell polarity (see **Fig. 1**C, D). Mild atypia can be seen, including nucleomegaly and irregular nuclear

Table 1
Pathologic key features of urothelial carcinoma

	Pathologic Features
Normal urothelium	No more than 7 cell layers thick, with polarization from basal layer to overlying superficial layer of umbrella cells
Papillary lesions	
Papilloma	Discrete exophytic lesion with fine, nonbranching fibrovascular cores with overlying normal-appearing urothelium
PUNLMP	Nonbranching fibrovascular cores with overlying hyperplastic epithelium with preserved polarity and minimal nuclear atypia
Low-grade papillary urothelial carcinoma	Minimal branching of fibrovascular cores and overlying urothelium with loss of polarity and slight variability in nuclear size and shape
High-grade papillary urothelial carcinoma	Complex papillary architecture and overlying urothelium with highly atypical cells, including high nuclear-to-cytoplasmic ratio, nuclear pleomorphism, prominent nucleoli, and abundant high-riding mitoses
Flat lesions	
Urothelial hyperplasia	Thickened mucosa with normal polarization and no cytologic atypia
Urothelial dysplasia	Slight loss of polarity with mild atypia, including irregular nuclear borders and dense chromatin
CIS	Flat lesion with extensive architectural disorder with large, pleomorphic, hyperchromatic nuclei, prominent nucleoli, and abundant high-riding and/or abnormal mitoses