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Urothelial carcinoma; an overview of histology, molecular subtypes, and clinical implications based on the latest WHO classification

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ABSTRACT

The incidence of urothelial carcinoma is increasing worldwide (including in Iran). Bladder cancer can be classified in various manners according to the standardized histomorphology set by the World Health Organization (WHO). Various genetic modifications occurring at the DNA level and the resulting variations in RNA expression give rise to different subcategories that have important implications for diagnosis, prognosis, and treatment. The molecular basis of these morphologic variances is now better understood because of recent developments in molecular biology. With updates on the genetic and clinical characteristics, we highlight the histologic traits of the divergent differentiation and subtypes recognized by the most recent WHO classification (5th edition). Molecular subtypes of lower and upper tract cancer can be used to characterize their clinical behaviors and determine therapeutic responses to neoadjuvant chemotherapy. In this overview article, we also present a preliminary analysis of our ongoing data collection on molecular features of urothelial carcinoma.

Review

Implication for health policy/practice/research/medical education:
This review evaluates the current knowledge on urothelial carcinoma and the implications of patient management that can guide therapeutic decisions. The updated WHO classification of bladder cancer subtypes helps standardize clinical practice and research. Preliminary data in our institute reveals variations in the frequency and types of mutations between lower tract urothelial carcinoma and upper tract urothelial carcinoma. Further research on molecular features of urothelial carcinoma is warranted to identify novel therapeutic targets.

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Introduction

The sixth most prevalent type of cancer in the USA is urothelial carcinoma (1). Some data suggest a higher incidence in the developed countries (2). Bladder cancer is more prevalent in males worldwide, with a 1.1% lifetime risk in men compared to 0.27% for women (3). The lifetime risks for women and men in the United States are 1.2% and 3.9%, respectively (4). Recent studies reveal an increased incidence of urothelial carcinoma worldwide (3). The lower urinary system (bladder and urethra) accounts for about 90–95% of urothelial carcinoma cases, while the upper urinary tract (renal pelvis and ureter) accounts for the remaining 5–10% (5).

Smoking (including cigarettes, opium, and e-cigarette) and advanced age are the most established risk factors for bladder cancer. In contrast, other risk factors include occupational exposure (i.e., benzene and aromatic amines), ingestion (i.e., heavy metals and arsenic), chronic inflammation (i.e., bacterial and parasitic infections, especially Schistosomiasis), and chronic indwelling foley catheter (6-10). Bladder cancer diagnosis is more prevalent in men, occurring 3 to 4 times more frequently than in women. This higher incidence has traditionally been attributed to occupational exposures and lifestyle factors. However, the risk may also be increased in men with prostatic enlargement and urinary retention due to the stagnation of carcinogens (11). The lifetime risk of upper urinary tract urothelial cancers is thought to range from 0.4% to 20% in people with Lynch syndrome. In a recent meta-analysis, increased bladder cancer risk was identified

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in overweight men but not in overweight women. Obese men and women showed elevated risk (pooled RR=1.14, 95% CI: 1.06-1.22) and mortality (pooled RR=1.19, 95% CI: 1.02-1.38), respectively (12).

Pathophysiology and molecular biology

From a histological perspective, the majority (75%) of bladder cancer cases consist of pure urothelial carcinoma. In comparison, the remaining 25% of bladder cancer cases display histological subtypes, which contributes to the complexity of managing the disease (13). Bladder cancer can be categorized in several ways. Based on standardized histomorphology established by the WHO, urothelial carcinoma is divided into high-grade and low-grade carcinomas. The tumor stage is assigned to measure the depth of invasion into the bladder wall. Non-muscle-invasive bladder cancer (NMIBC) refers to tumors that are limited to the urothelium (stage Ta) or the lamina propria (stage T1) and are treated differently from muscle-invasive bladder cancer (MIBC) that invade the muscle (stage T2) or beyond (stages T3 and T4). A high-grade flat noninvasive lesion with notably high recurrence and progression rates is known as urothelial carcinoma in situ.

Underlying these phenotypes are genetic alterations at the DNA and subsequent RNA expression levels, forming distinct molecular subtypes with diagnostic, prognostic, and therapeutic implications. Multiple studies have found common mutations in low-grade NMIBC (*FGFR3, STAG2, PIK3CA, RTK/RAS/RAF* pathway genes) and high-grade MIBC/advanced disease (*ERBB2, RB1, TP53* , *MDM2, KDM6A, CDKN2A, ARID1A*).

Bladder cancer can also be divided into three molecular subtypes using next-generation sequencing (NGS), called luminal, basal, and p53-wild-type (14,15). Each subtype reveals different clinical behavior, rate of response to immunotherapy and conventional chemotherapy, and progression rate. The features in support of basal phenotype include squamous differentiation (presence of intracellular keratin, dyskeratosis, keratin pearl formation, or evidence of intercellular bridges) and expression of CK5/6, CD44, and CK14 immunohistochemical markers. The more aggressive illness at presentation and activation of p63 are characteristics of the basal subtype, and these tumors appear to reveal a worse clinical prognosis.

Luminal phenotype is characterized by expressions of GATA3, HER-2, and CK20 immunohistochemical markers and has activated *PPAR-γ* and *FGFR3* mutations with enriched epithelial markers and bears a better clinical prognosis. The p53-wild-type subtype exhibits chemotherapy resistance because of an active *TP53* gene (16,17).

Despite having similar morphologies, lower tract urothelial carcinoma (LTUC) and upper tract urothelial carcinoma (UTCU) differ from one another in terms of epidemiology, tumor behavior, molecular alterations, and prognosis (18,19). At diagnosis, UTCU is more frequently invasive, and molecular studies have shown some biological distinctions between UTCU and LTUC (20). In a study by Yang et al, *TP53, PIK3CA,* and *FGFR3* mutations were noted to be the driving genes for upper tract urothelial carcinoma, and upper tract urothelial carcinoma had greater clonal and sub-clonal mutation

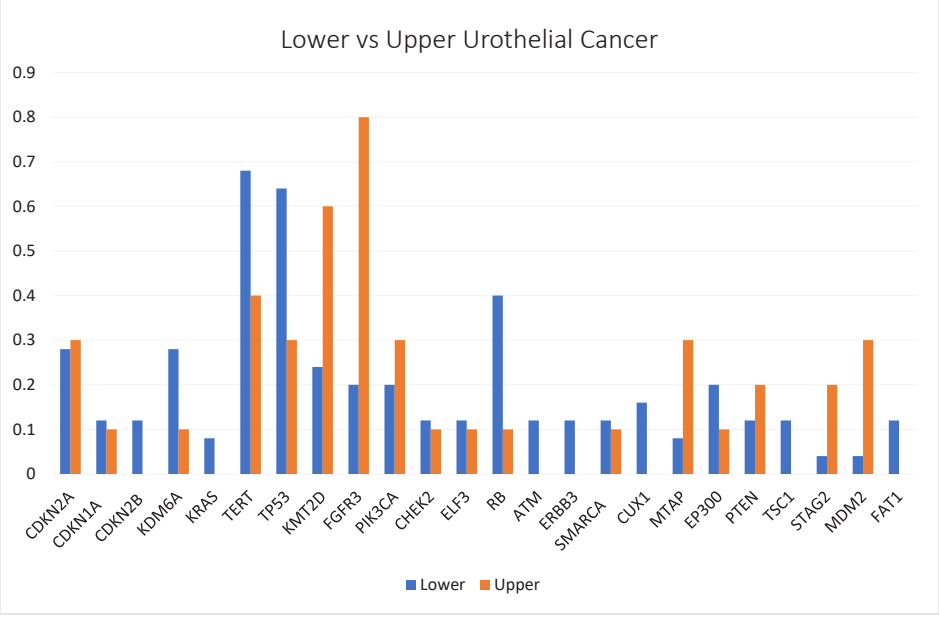

Figure 1. Molecular alterations in urothelial carcinoma. The figure shows the frequency and type of mutations in upper tract urothelial carcinoma and lower tract urothelial carcinoma cases.

numbers than LTUC (21).

As shown in Figure 1, in a preliminary analysis of the collected data at Brown University, we have provided a review of molecular alterations of 45 MIBC cases, including 28 LTUC (25 high-grade and three low-grade), 10 UTUC (8 high-grade and two low-grade) and 7 cases with concomitant UTUC and LTUC using the available NGS platforms with analysis of matched tumor and germline DNA for up to 648 cancer-associated genes. Our results revealed that the frequency and type of mutations differed between upper tract urothelial carcinoma and LTUC. In upper tract urothelial carcinoma cases, the most frequently mutated genes included *FGFR3* (80%), *KMT2D* (60%), *TERT* (40%), *CDKN2A*, *TP53*, *PIK3CA*, *MDM2*, and *MTAP* with a frequency of 30%. In 28 LTUC cases, the most frequently mutated genes included *TERT* (68%), *TP53* (64%), *RB* (40%), *CDKN2A* (28%), and *KDM6A* (28%). We also identified 7 cases with concomitant upper tract urothelial carcinoma and LTUC. In the last group, the most frequently mutated genes included *TERT*, *FGFR3*, *RB*, *TP53*, and *KMT2D*. Enhanced comprehension of the molecular biology and genetics of bladder cancer has revolutionized the diagnosis and treatment of both localized and advanced stages of the disease (22).

Urothelial carcinomas are classified based on architecture, morphology, and grade. Architecturally, they are divided into papillary, flat, and inverted lesions.

Papillary lesions grow in an exophytic pattern as a fingerlike projection with a central fibrovascular core. All exophytic lesions have an endophytic counterpart (inverted lesions). The grade of lesion is determined based on the level of atypia in the urothelium. Papillary (and inverted) lesions lined by normal urothelium are called papillomas, these are small lesions with few, non-branching papillary fronds (inverted papilloma if endophytic). Urothelium in these lesions reveal normal thickness (3-5 cell layers) and a re devoid of any atypia or evidence of overgrowth (overgrowth is defined by increased number of layers, elevated mitotic activity and apoptosis). Papillomas (and inverted papillomas) are considered benign neoplasms. Papillary urothelial neoplasm of low malignant potential reveals increased layering of urothelium with no atypia or brisk mitotic activity. These usually reveal more papillary fronds, often with branching. Low-grade papillary urothelial carcinoma harbors urothelium with mild atypia (defined as nuclear size variation/enlargement, irregularity of nuclear membrane, chromatin clumping, hyperchromasia and conspicuous mitotic activity). The atypia in low grade UC is not detectable in low-power magnification microscopy. High-grade urothelial carcinoma reveals loss of polarity and urothelial atypia that is easily detectable in low-power magnification microscopy, including marked nuclear enlargement (5 times the size of a normal lymphocyte), hyperchromasia, elevated mitotic activity and apoptosis with/out necrosis and urothelial denudation. It is of note that mitotic activity per se is not a reliable feature for detection of cancer or determining the grade in urothelial carcinoma because several non-malignant entities including inflammation and regeneration can reveal increased mitotic activity.

Overall, papillary lesions are far more common due to better clinical detection. Flat lesions are thought to be underdiagnosed clinically. Flat lesions include reactive urothelial atypia, dysplasia, and carcinoma in situ. Carcinoma in situ is a lesion that reveals prominent nuclear atypia compatible with high-grade urothelial carcinoma (nuclear enlargement five times the size of lymphocytes, hyperchromasia, elevated mitotic activity, and apoptosis with/out urothelial denudation). Any atypical lesion that does not meet the carcinoma in situ criteria and lacks other underlying etiologies (intraepithelial inflammation, history of radiation or chemotherapy) is considered dysplasia.

Urothelial carcinoma commonly shows divergent differentiation, including squamous, glandular, trophoblastic, and Müllerian differentiations. Urothelial carcinoma with squamous differentiation is prevalent (seen in 30 to 40% of urothelial carcinoma) and harbors intercellular bridges with/out keratinization. Glandular differentiation is less common (seen in up to 18% of tumors). It may complicate the diagnosis by adding to the differential list other glandular lesions including prostate cancer in males, GYN organ cancer in female, and colon cancer. The other divergent differentiations are less common. In general, when compared stage for stage, the presence of divergent differentiation does not affect the outcome of the tumor (23).

Based on the WHO 2022 classification of urothelial carcinomas, several histological subtypes can be seen in urothelial carcinoma, including micropapillary, nested, tubular and microcystic, large nested, plasmacytoid, sarcomatoid, lipid-rich, lymphoepithelioma-like, clear-cell, giant cell, and poorly differentiated urothelial carcinomas (23). Figure 2 shows different Subtypes of urothelial carcinoma.

Some subtypes of urothelial carcinoma are thought to present a more aggressive clinical course, including micropapillary urothelial carcinoma and plasmacytoid urothelial carcinoma, where the chance of local and distant spread is higher due to discohesive tumor clusters. In the micropapillary subtype, numerous small tumor clusters (devoid of fibrovascular cores) located within empty lacunar spaces in at least 20% of the tumor confirms the diagnosis. The most useful diagnostic criterion is identifying numerous micropapillary clusters within a

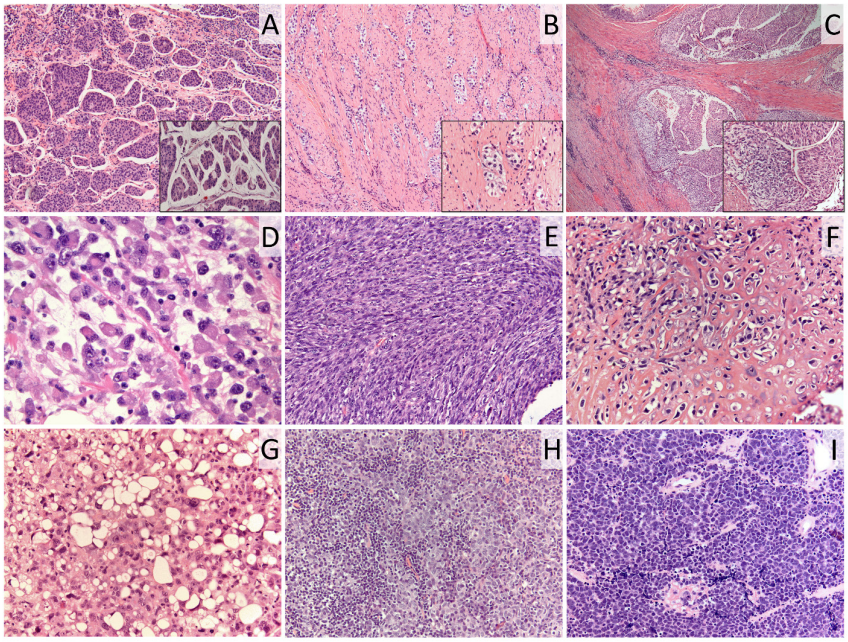

Figure 2. Subtypes of urothelial carcinoma. **(A)** Micropapillary subtype of urothelial carcinoma. Note several micropapillary clusters in one lacunar space in the inset. (H&E, 10×, inset 20×). **(B)** Nested subtype of urothelial carcinoma. Note nests of tumor cells infiltrating muscularis propria, and lack of cellular atypia in the inset. (H&E, 10×; inset: 20×). **(C)** Large nested subtype of urothelial carcinoma in the ureter. Note large nests of tumor cells in between muscularis propria, and lack of cellular atypia (in the inset). (H&E, 10×, inset: 20×). **(D)** Plasmacytoid subtype of urothelial carcinoma. (H&E, 40×). **(E)** Sarcomatoid subtype of urothelial carcinoma. Note high-grade spindle cell morphology and abundance of mitotic activity. (H&E, 10×). **(F)** Sarcomatoid subtype with heterologous component (chondrosarcoma). Note the chondroid matrix containing tumor cells. (H&E, 10×). **(G)** Lipid-rich subtype of urothelial carcinoma. Note lipoblast-like neoplastic cells with vacuolated cytoplasm and nuclear indentations. (H&E, 10×). **(H)** Lymphoepithelioma-like subtype of urothelial carcinoma. (H&E, 10×) I) Small cell carcinoma of the urinary tract (H&E, 10×).

single lacunar space (24). Studies have revealed frequent mutation of the *ERBB2* gene in micropapillary urothelial carcinoma (25). Individual discohesive tumor cells with plasmacytoid/rhabdoid or signet ring-like morphology are diagnostic in the plasmacytoid subtype. Studies have revealed a mutation in *CDH1* in plasmacytoid urothelial carcinoma (26).

Sarcomatoid urothelial carcinoma (carcinosarcoma) also represents a very aggressive subtype of urothelial carcinoma, revealing an aggressive, often undifferentiated spindle cell component with/out heterologous components (chondrosarcoma, osteosarcoma, rhabdomyosarcoma) admixed with conventional high-grade urothelial carcinoma. A prior history of surgical exploration or radiation of the pelvis can raise the chance of sarcomatoid urothelial carcinoma (24,27). Nested and large nested subtypes may pose a diagnostic challenge in small biopsies due to the lack of prominent cytological atypia; however, demonstration of infiltrative growth pattern (invasion into muscularis propria layer) or identification of common urothelial carcinoma mutations (i.e., *TERT*) in the biopsy material can help in differentiation (23). In radical surgery specimens, demonstration of muscle invasion by the low-grade-looking tumor nests is diagnostic of these subtypes.

Lymphoepithelioma-like urothelial carcinoma, demonstrates a better response to chemotherapy, therefore better prognosis (28). Finally, clear-cell urothelial carcinoma should be differentiated from clear-cell adenocarcinoma of the bladder and secondary clear-cell carcinomas (i.e., renal origin).

Clinical course, prognosis, and outcome

Although men are more likely to develop bladder cancer, at the time of diagnosis, women often present with more advanced tumors than men (29). In patients with MIBC, Mori et al, conducted a study that revealed a slight association between the female sex and lower overall survival (pooled hazard ratio [HR], 1.02; 95% confidence interval [CI], 1.00-1.05) as well as lower cancer-specific survival (pooled HR, 1.21; 95% CI, 1.11-1.31). However, when explicitly considering patients with NMIBC, the study did not find any significant link between sex and cancer-free survival (HR 1.04; 95% CI, 1.24) or recurrence-free survival (HR 1.06; 95% CI, 0.98-1.16) (30).

The methods for diagnosing and treating localized and advanced diseases have changed as a result of advances in our understanding of the molecular biology and genetics of bladder cancer. The standard of care for intermediate- and high-risk NMIBC remains intravesical therapy (i.e., BCG, mitomycin). However, the range of advanced

disease treatment options has been enhanced, including immunotherapy with checkpoint inhibitors, antibody-drug conjugates, and targeted therapies (22). The gold standard treatment for MIBC is radical cystectomy (31). Before radical cystectomy, molecular categorization of bladder cancer can be used to characterize their clinical behaviors and determine therapeutic responses to neoadjuvant chemotherapy (32,33). In a study of 118 patients with metastatic urothelial carcinoma, Tanaka et al showed that molecular alteration might be used to predict chemoradiation therapy response (34). For MIBC patients, a more aggressive approach to treatment is necessary to mitigate the risks of metastasis and disease-specific mortality. This typically involves either radical cystectomy with urinary diversion or trimodal therapy consisting of maximal endoscopic resection, radio-sensitizing chemotherapy, and radiation (22). Currently, the gold standard for treating UTUCs is radical nephroureterectomy (RNU) (35), which harbors 20–50% chance of intravesical tumor recurrence after RNU (36). In a study conducted by Audenet et al, the authors found that patients with UTUC who had alterations in *FGFR3* (HR = 3.00, 95% CI: 1.58–5.68; $P = 0.001$) and *KDM6A* (HR = 2.27, 95% CI: 1.29–4.02; $P = 0.005$) were significantly linked to a greater chance of a subsequent bladder tumor developing; however, *TP53* alterations were associated with a lower risk (HR = 0.32, 95% CI: 0.13–0.80; $P = 0.014$) (37).

Recent studies suggest that risk factors for postoperative LTUC recurrence in UTUC include advanced tumor stage, the existence of high-grade carcinoma, preoperative ureteroscopy, and diabetes without metformin use (38,39). Notably, 82-89% of LTUC recurrences occur within two years after RNU, and 44% of patients with LTUC recurrence have an invasive disease (pT1 stage) (40). The treatment landscape for patients with advanced bladder cancer is rapidly evolving, with the introduction of immunotherapy using checkpoint inhibitors, targeted therapies, and antibody-drug conjugates. These novel treatment options have become viable alternatives for specific patients at different stages of the disease (22).

Conclusion

In this article, we provided an overview of epidemiology, risk factors, classification, molecular subtyping, and prognosis of urothelial carcinoma. Molecular subtypes of lower and upper tract cancer can be used to characterize their clinical behaviors and determine therapeutic responses to neoadjuvant chemotherapy. The preliminary analysis of our ongoing data collection showed different molecular features in upper and LTUC, which reinforces the importance of using molecular subtyping in predicting prognosis and making therapeutic decisions.

Authors' contribution

Conceptualization: Ali Amin, Fateme Khalatbari.
Data curation: Fateme Khalatbari.
Formal analysis: Fateme Khalatbari, Miremad Moafi-Madani.
Investigation: Fateme Khalatbari.
Methodology: Ali Amin, Fateme Khalatbari, Miremad Moafi-Madani.
Project administration: Ali Amin.
Supervision: Ali Amin.
Visualization: Ali Amin.
Writing-original draft: Fateme Khalatbari.
Writing-review and editing: Ali Amin.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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