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Papillary Urothelial Neoplasms: Clinical, Histologic, and Prognostic Features

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Cite this chapter as: Yu Y, Downes MR. Papillary Urothelial Neoplasms: Clinical, Histologic, and Prognostic Features. In: Barber N and Ali A, editors. *Urologic Cancers*. Brisbane (AU): Exon Publications. ISBN: 978-0-6453320-5-6. Online first 27 May 2022.

Doi: https://doi.org/10.36255/exon-publications-urologic-cancers-papillary-urothelial-neoplasms

Abstract: Primary bladder neoplasms can be divided into two broad categories: flat and papillary lesions. In this chapter, we provide a review of non-invasive papillary urothelial neoplasms of the bladder: urothelial papilloma, inverted urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive low grade papillary urothelial carcinoma, and non-invasive high grade papillary urothelial carcinoma. The following is discussed for each entity: clinical features, etiology, microscopic description, ancillary tests, molecular alterations, and prognostic factors.

Keywords: inverted urothelial papilloma; non-invasive papillary urothelial carcinoma; papillary urothelial neoplasm of low malignant potential; papillary urothelial neoplasms; PUNLMP

In: Barber N, Ali A (Editors). *Urologic Cancers*. Exon Publications, Brisbane, Australia. ISBN: 978-0-6453320-5-6. Doi: https://doi.org/10.36255/exon-publications-urologic-cancers

INTRODUCTION

Non-invasive urothelial neoplasms of the bladder can be divided into two categories: those that are flat and those with papillary configuration. Papillary neoplasms can further be sub-divided into urothelial papilloma, inverted urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive low grade papillary urothelial carcinoma, and non-invasive high grade papillary urothelial carcinoma. This chapter discusses each of the aforementioned entities in detail including their clinical features, etiology, microscopic description, ancillary tests, molecular alterations and prognostic factors.

UROTHELIAL PAPILLOMA

Urothelial papilloma is a neoplasm with papillae which contains delicate fibrovascular cores lined by normal urothelium. Urothelial papilloma is a rare benign papillary urothelial neoplasm that accounts for less than 4% of non-invasive urothelial neoplasms (1). It has been described in a wide age range, but patients tend to be younger, and it can be seen in children (2). The exact etiology is largely unknown at this time (3). It is believed that urothelial papilloma shares similar etiologic factors with other urological neoplasms which include smoking (4), occupational exposure to chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, aromatic amines, and arsenic (5, 6). These neoplasms are exophytic lesions with a papillary configuration and normal thickness urothelium (Figure 1A). Dilated lymphatic channels may be found in the fibrovascular cores. There should be no architectural disorder with cells oriented perpendicular to the basement membrane. Umbrella cells are usually present and may display nucleomegaly and multinucleation.

Cytologically, the urothelial cells are bland with no atypia. Mitoses are absent. Immunohistochemistry is not required for the diagnosis. These lesions show positive CK20 expression in the umbrella cells only, similar to the expression of normal urothelium (Table 1). MIB-1 proliferation is usually low (<5%) (1). Urothelial papillomas have *FGFR3* mutations (7). Alterations involving *TP53* have not been described. The recurrence rate of urothelial papilloma varies from 8 to 14% and the rate of progression to cancer is less than 1% (1, 2, 8). For non-muscle invasive bladder neoplasms, the WHO/ISUP histologic grade correlates with the biological behaviour; higher grade tumours have higher likelihood of recurrence and progression. In the different iterations of the WHO/ISUP grading systems, papilloma is considered a benign neoplasm with a favourable clinical course.

INVERTED UROTHELIAL PAPILLOMA

Inverted urothelial papilloma is a non-invasive urothelial neoplasm with an endophytic or inverted growth pattern and absent or minimal cytological atypia. This is a rare and benign entity. Inverted urothelial papillomas (Figure 1B) are rare and account for less than 1% of all urothelial neoplasms in the bladder (1). Patients typically present in in their fifth to sixth decade and there is a stronger

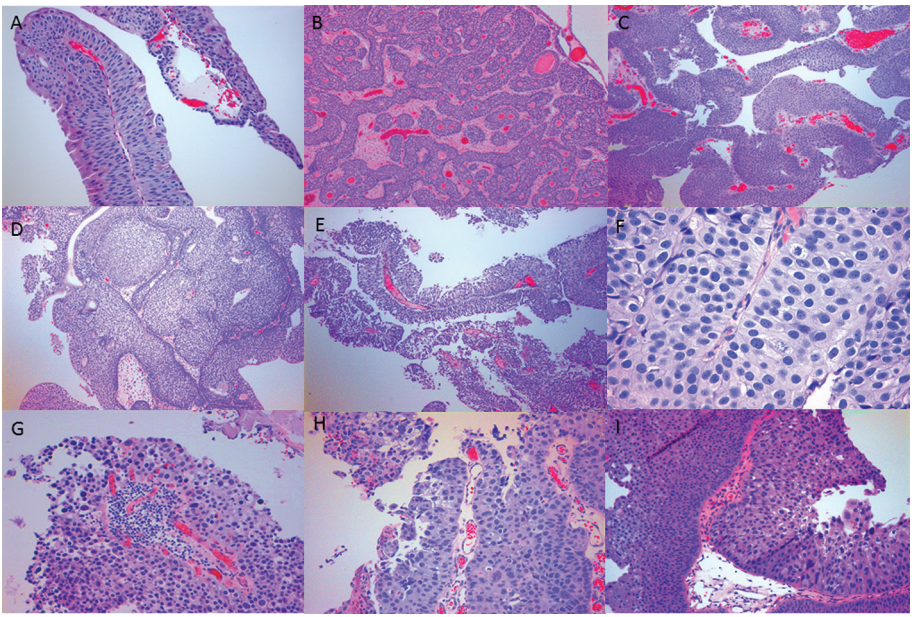

Figure 1. Papillary Urothelial Neoplasms. A, Urothelial papilloma with normal thickness urothelium, no architectural disorder and bland cytology. **B,** Inverted urothelial papilloma with an endophytic growth pattern with urothelium organized in trabeculae and anastomosing cords. **C,** Papillary urothelial neoplasm of low malignant potential (PUNLMP) has thickened urothelium, orderly architecture and uniform cytology. **D**, An inverted form of PUNLMP. **E**, Low grade non-invasive papillary urothelial carcinoma with long, slender papillae, higher magnification (**F**) shows mild loss of polarity, mild cytologic pleomorphism and mitoses in the lower half of the urothelium. **G** and **H**, High grade non-invasive papillary urothelial carcinoma with complex papillae with and fused architecture. Architectural disorder and nuclear pleomorphism are visible on low power. **I,** Concurrent low grade and high-grade lesions can be found.

TABLE 1 Expected Immunoprofile of Papillary Urothelial Neoplasms

Entity	Immunoprofile
Papilloma	CK20+ in umbrella cells only, low Ki-67 proliferation
Inverted papilloma	CK20-, low Ki-67 proliferation
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	CK20+ (superficial), FGFR3+/-, low Ki-67 proliferation
Non-invasive low grade papillary urothelial carcinoma	GATA-3+, p63+, high molecular weight cytokeratin+, CK5/6+ (basal layer) and CK7+. Can have STAG2 loss. Mismatch repair proteins can be lost (Lynch syndrome-associated tumours)
Non-invasive high grade papillary urothelial carcinoma	GATA3+, CK5/6+, CK7+, CK20+, high molecular weight cytokeratin+, p63+; compared to low grade lesions, can have increased p53 and Ki-67 expression

predilection for males than females (ratio of 5.8 to 1) (9, 10). The most common clinical presentations include hematuria and less commonly, lower urinary tract obstructive symptoms. The most common sites are bladder neck, trigone, lateral and posterior wall (1). On cystoscopy they may appear as raised, polypoid lesions with a smooth surface. The treatment is surgical resection via transurethral approach. Etiology is similar to other urothelial papillary neoplasms which include smoking, occupational exposure to chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, aromatic amines, and arsenic (4–6).

Histologically, these neoplasms exhibit trabeculae and anastomosing cords of urothelium with an endophytic growth pattern that invaginate into the lamina propria (Figure 1B). Peripheral palisading of the basal cell layer may be seen. There should be a smooth interface with the stroma. The urothelium has normal thickness and lacks cytoarchitectural atypia. Immunohistochemistry is not required for the diagnosis. These neoplasms are usually CK20 negative and show low Ki-67 proliferation index (Table 1). Genetic alterations which have been reported in inverted urothelial papillomas include: *FGFR3* mutations, 9p deletions, 9q deletions, 17p deletions, and *HRAS* mutations (11–13). For non-invasive urothelial neoplasms, the WHO/ISUP histologic grade is a strong prognostic factor. As with conventional urothelial papilloma, inverted papilloma is deemed a benign neoplasm and is not assigned a WHO/ISUP histologic grade. This is a benign neoplasm and reported recurrence rate is less than 1 percent (1).

PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL

Papillary urothelial neoplasm of low malignant potential (PUNLMP) is a papillary urothelial neoplasm with increased thickness urothelium and minimal cytologic atypia. PUNLMP is a rare tumour, the prevalence is approximately 3 per 100,000 people per year (1). There is a strong male predominance, the male-to-female ratio is 5:1; the mean patient age is 64.6 years (3). The clinical presentation is usually gross or microscopic hematuria. Urine cytology is negative in the majority of cases. On cystoscopy, single or multiple intraluminal bladder papillary masses of variable size may be visualized. The most common locations for PUNLMPs are the lateral and posterior walls of the bladder, although it may be found anywhere along the urinary tract that has urothelium. Treatment option is surgical via transurethral resection. The etiology is similar to other papillary urothelial neoplasms. Specific factors include smoking (4), occupational exposure to certain chemicals such as chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, aromatic amines, and arsenic (5, 6).

Histologically, PUNLMPs are papillary neoplasms with thicker and/or more cellular urothelium (Figure 1C). The architecture has no loss of order or polarity (14–18). The cytology is uniform and monotonous with cells appearing similar to each other. There may be some nuclear crowding and slight enlargement compared to the normal counterparts. Nucleoli should be inconspicuous, and chromatin is evenly distributed. Mitotic activity should be extremely rare and limited to the basal layer (1). An inverted form may also occur (Figure 1D). Immunohistochemistry is not required for the diagnosis of PUNLMP.

Some non-recurrent lesions may show strong positive staining pattern in FGFR3, superficial staining for CK20 and low MIB-1 proliferation index (Table 1) (14). The genetic and cytogenetic changes in PUNLMPs include mutations in *FGFR3*, *TERT* promoter mutations and chromosome 9 loss (1, 15, 16). Tumours with nuclear expression of *TP53* are correlated with early-onset disease (age less than 45 years old) (17). The WHO/ISUP histologic grade is an important prognostic factor for non-muscle invasive urothelial neoplasms. Very few studies in the literature have looked at prognostic factors specifically for PUNLMPs. A recent study has shown that PUNLMPs have a recurrence rate of 18% and progression rate of 2% (18). Nevertheless, these lesions have a favourable outcome (1). Due to the risk of recurrence, patients typically have long-term follow up (19).

NON-INVASIVE LOW GRADE PAPILLARY UROTHELIAL CARCINOMA

Non-invasive low grade papillary urothelial carcinomas have low grade architectural and cytologic abnormality. It is essential that high grade features and invasion through the basement membrane are absent. The incidence of low grade papillary urothelial carcinomas is 5 per 100,000 people per year (3). There is a higher predilection for male (3:1 male-to-female ratio) and the median age is 70 years Patients with Lynch syndrome may present with earlier stage and low-grade disease (20). Most of the lesions are found in the lateral and posterior walls of the bladder. Painless gross or microscopic hematuria is the most common clinical presentation. Patients who present with gross hematuria may have more advanced disease (21). Patients may initially be diagnosed via cystoscopy, CT urography, ultrasound, or urine cytology. Intraluminal masses, hydronephrosis or filling defects may be detected on imaging (22). Treatment options include transurethral surgical resection and intravesical therapy such as Bacille-Calmette-Guerin or mitomycin C (23). Smoking has been associated with low grade papillary urothelial carcinoma (4). Other etiologic factors include occupational exposure to certain chemicals such as chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, aromatic amines, and arsenic (5, 6).

Histologically, low grade papillary urothelial carcinoma has fibrovascular cores lined by neoplastic urothelium (Figure 1E). Long and slender papillae usually show minimal branching or fusing. At low magnification, the architecture appears mostly orderly. At higher magnification, mild loss of polarity can be seen with some mild cytologic pleomorphism. There may be slight difference in cell size but no significant nucleomegaly or nuclear pleomorphism. Nuclear contour may be slightly irregular. Mitoses may be seen and are usually in the lower half of the urothelium (Figure 1F). There should be no atypical mitotic figures. Inverted growth patterns with both endophytic and exophytic components may also be present. Immunohistochemistry is not routinely utilized in the diagnosis of low grade papillary urothelial carcinomas. GATA-3 is positive in 97.5% of papillary urothelial neoplasms (24). These lesions can show positive staining in p63, high molecular weight cytokeratin, CK5/6 in the basal layer, and CK7 (25–28). STAG2 has been reported to show negative staining in upper tract urothelial malignancies (29). Mismatch repair proteins can be lost in Lynch syndrome-associated tumours (Table 1).

The initial step in the proposed pathogenesis of low-grade urothelial carcinoma involves loss of chromosome 9, which subsequently causes normal urothelium to become hyperplastic. Further genetic alterations such as *FGFR3* mutations, which then activates downstream mitogenic activated protein (MAP) kinase pathway, leading to further development of low grade papillary urothelial carcinoma (15). Mutations in the *TERT* promoter has been shown to be present in 50% of low grade papillary urothelial carcinomas; and these are more likely associated with *FGFR3* mutated tumours (16). *STAG2,* a cohesion complex gene, has been shown to have inactivating mutations in 32 to 36% of low grade and low tumour stage lesions (29). Other genetic alterations include mutations in *CCND1,* loss of 11p chromosome, *PIK3CA* mutations and microRNA alterations (30). Epigenetic silencing via promoter hypermethylation of select tumour suppressor genes have also been reported (31). Adverse prognostic factors for low grade papillary urothelial carcinoma, beyond the WHO/ISUP histologic grade, include multifocal disease, tumour size and the presence of concomitant urothelial carcinoma in situ (1, 23). Multifocal disease is associated with disease progression and higher disease associated mortality. Urothelial carcinoma in situ is associated with higher recurrence rate. High MIB-1 proliferation index is associated with poor prognosis (32). Mutations in *FGFR3 and PIK3CA* associated tumours show lower rates of recurrence (33); while tumours with *PTEN* deletions show increased rates of recurrence (34).

NON-INVASIVE HIGH GRADE PAPILLARY UROTHELIAL CARCINOMA

Non-invasive high grade papillary urothelial carcinomas are urothelial neoplasms with a papillary configuration and moderate to severe cytoarchitectural disorder. There is no invasion through the basement membrane. There is a stronger predilection for male than female (male-to-female ratio 6 to 8:1) and the mean age of patients is 70 years (1). These lesions are most commonly found in the lateral and posterior walls of the bladder; but it may arise from anywhere on the urinary tract with urothelium. For lesions arising from the renal pelvis, 85% are papillary and 66% are high grade (35). Patients typically present with intermittent, painless hematuria; gross hematuria is associated with higher pathologic stage diseases (21). High grade papillary urothelial carcinomas are associated with high rate of progression to invasion. Patients are diagnosed via cystoscopy, imaging modalities such as CT urography, ultrasound, or urine cytology. On cystoscopy, single or multiple exophytic lesions may be seen. Imaging typically shows filling defects, hydronephrosis or intraluminal masses (22). Treatment options include surgical transurethral resection tumour, intravesical immunotherapy with Bacillus Calmette-Guerin or intravesical chemotherapy with mitomycin C or thiotepa. Similar etiologic factors have been implicated in both high grade and low grade non-invasive papillary urothelial carcinomas: smoking (4), occupational exposure to chlorinated hydrocarbons, polycyclic aromatic hydrocarbons, aromatic amines, and arsenic (5, 6).

Non-invasive high grade papillary urothelial carcinomas show complex papillae with solid to fused architecture (Figures 1G and H). Neoplastic urothelium line fibrovascular cores. On low power, the architectural disorder and nuclear

pleomorphism are visible. The neoplastic cells tend to be crowded and overlapping, with dyscohesion and partial denudation of the epithelium. The nuclei are enlarged with irregular and coarse chromatin. Prominent nucleoli can be present. Mitotic activity may be brisk and atypical forms can be found. Inverted growth pattern with both endophytic and exophytic patterns may also be seen (36).

It is important to note that concurrent low-grade lesions can be found (Figure 1I). Grade heterogeneity is common and can be found in up to one third of non-invasive papillary urothelial carcinomas (37, 38). The grade of the lesion is assigned based on the highest-grade component identified. The general accepted approach is to designate a lesion "high grade" if there is at least 5% high grade histology identified (39). If a lesion comprises less than 5% high grade, it is reported as low-grade tumour with a quantification of the high-grade component present. This is important since such tumours may be more akin to low grade neoplasms in prognosis (38, 40); however, this is still debated (41, 42). Immunohistochemistry is not required for the diagnosis of non-invasive high grade papillary urothelial carcinomas. These lesions are positive for GATA3, CK5/6, CK7, CK20, high molecular weight cytokeratin, and p63 (Table 1). Compared to low grade lesions, high grade papillary urothelial carcinomas can have increased p53 and MIB-1 expression (43). A subset of high-grade lesions will show loss of staining in CK5/6 (44).

Non-invasive high grade urothelial carcinomas have genetic or epigenetic alterations involving the *TP53* gene or *CDKN2A* gene. Somatic mutations in *TERT* have been reported to be present in 70–80% of non-invasive urothelial carcinomas (1). Mutations in *PIK3CA, TSC1, HRAS, APC* genes have been reported. Epigenetic silencing via promoter hypermethylation of select tumour suppressor genes are also identified (31). MicroRNA changes and loss of chromosome 9 have been described (30).

The WHO/ISUP histologic grade is an important prognostic factor for non-invasive high grade papillary urothelial carcinomas (45). The presence of nuclear anaplasia is correlated with disease progression and faster recurrence (1). Other adverse prognostic factors include multifocal disease and the presence of concomitant urothelial carcinoma in situ (1). Multifocal disease is associated with disease progression and higher disease associated mortality. Urothelial carcinoma in situ is associated with higher recurrence rate. High MIB-1 proliferation index is associated with poor prognosis (32). Tumours with *PTEN* deletions show increased rates of recurrence (34). Tumours with *TP53* and *RB* mutations have worse prognosis (46).

CONCLUSION

Papillary urothelial neoplasms are commonly encountered genitourinary specimens by the surgical pathologist. Familiarity and an understanding with the clinical features, etiologic factors, histologic appearance, relevant ancillary workup, molecular alterations, and prognosis is important for arriving at the correct diagnosis and guiding appropriate clinical management. A brief overview of what is currently known about papillary urothelial neoplasms is provided in this chapter.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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