BJUI
BJU INTERNATIONAL

Urothelial lesions with inverted growth patterns: histogenesis, molecular genetic findings, differential diagnosis and clinical management

Kurt B. Hodges*, Antonio Lopez-Beltran†, Gregory T. MacLennan‡, Rodolfo Montironi§ and Liang Cheng*,¶

**Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, †Department of Pathology, Case Western Reserve University, Cleveland, OH, ¶Department of Urology, Indiana University School of Medicine, Indianapolis, IN, USA, †Department of Pathology, Cordoba University, Cordoba, Spain, and §Institute of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region (Ancona), United Hospitals, Ancona, Italy*

Accepted for publication 25 May 2010

A number of well-recognized urothelial lesions with inverted morphology occur in the urinary bladder. Some are so common that they are considered normal variants of urothelium, whereas others are rare. It is important for the surgical pathologist to recognize these lesions and their overlapping morphological features, because in some cases establishing an accurate diagnosis is challenging. In this article, we review the spectrum of inverted urothelial lesions of the bladder. Emphasis is placed on differential diagnosis, molecular genetic findings, morphology and histogenesis.

What's known on the subject? and What does the study add?
Inverted lesions of the urinary bladder comprise a spectrum of changes ranging from von Brunn's nests to inverted urothelial carcinoma. Differentiating these lesions is important because their proper clinical management and their expected clinical outcomes are distinctly different.

In this article, we review the spectrum of inverted urothelial lesions of the bladder, including current morphological criteria, key differential diagnosis, molecular genetic findings and histogenesis. We have refined the diagnostic criteria for various bladder lesions with inverted growth patterns.

KEYWORDS

urinary bladder, transitional cell (urothelial) carcinoma, urothelial papilloma, molecular pathology, precursor lesions, inverted and nested TCC urothelial carcinoma, tumourigenesis(carcinogenesis), molecular genetics, fibroblast growth factor receptor 3 (FGFR3), histological variant, differential diagnosis

INTRODUCTION

Except for von Brunn's nests, inverted urothelial lesions of the bladder are uncommon. Familiarity with these lesions is important if the surgical pathologist is to avoid misdiagnoses. In the present review we will discuss the differential diagnosis, molecular genetic findings, morphology and histogenesis of benign and malignant lesions of the urinary bladder with endophytic (or inverted) growth pattern (Table 1). Von Brunn's nests, cystitis cystica/cystitis glandularis and inverted papilloma represent a spectrum of proliferative lesions, which are histogenetically related. Inverted papilloma and urothelial carcinoma with inverted growth pattern are distinct clinicopathological entities with overlapping morphological features. These represent particularly challenging lesions that if misinterpreted, could result in serious errors in patient care. While most of these lesions can be diagnosed on morphological findings, some might require ancillary studies to establish a definitive diagnosis [1].

INVERTED UROTHELIAL PAPILLOMA

Inverted papilloma of the urinary bladder accounts for less than 1% of all urothelial neoplasms [2,3]. The age range of affected patients is broad, but most are in their sixth or seventh decade of life [2,4]. Inverted papilloma is far more common in men than in women (7.3:1 ratio). Most patients present with haematuria and/or irritative voiding symptoms [2]. Rarely, patients might present with obstructive voiding symptoms.

Cystoscopically, inverted papilloma characteristically appears as a sessile or pedunculated lesion with a smooth surface. Most arise in the trigone or bladder neck [2]. They are usually small (<3 cm) but can be as large as 8 cm. Most lesions are single, although the incidence of multiple lesions ranges from 1.3 to 4.4% [2,5,6]. Inverted papilloma is associated with a low risk of recurrence (<5%), in marked contrast to the high recurrence rates of papillary urothelial neoplasms [2,6].

Morphologically, there are two main subtypes of inverted papillomas: trabecular and glandular. The trabecular subtype is the classic lesion composed of irregularly ramifying cords and sheets of urothelium arranged at various angles to the surface mucosa and arising directly from the overlying urothelium (Fig. 1A). The trabeculae are thin and orderly with a relatively uniform width. The cords of urothelium have characteristic peripheral palisading of basaloid cells. The neoplastic

FIG 1. Urothelial lesions with inverted growth pattern. ***A****, Inverted papilloma, trabecular type, with anastomosing trabeculae of urothelium extending in to the lamina propria.* ***B****, von Brunn's nests and florid von Brunn's nest proliferations (note the rounded and smooth contours).* ***C****, Cystitis glandularis of the typical type and florid cystitis glandularis (note the irregularly spaced tubular glands lined by columnar epithelium; intestinal metaplasia is also present resembling colonic glands, indicated by arrow).* ***D****, Inverted urothelial carcinoma mimicking inverted papilloma.* ***E****, Inverted urothelial carcinoma involving the renal pelvis (gross image).* ***F****, Panoramic view of the case (from image E).* ***G****, Nested variant of urothelial carcinoma growing as relatively uniform round nests.* ***H****, Verrucous squamous cell carcinoma (note the blunt pushing architecture).*

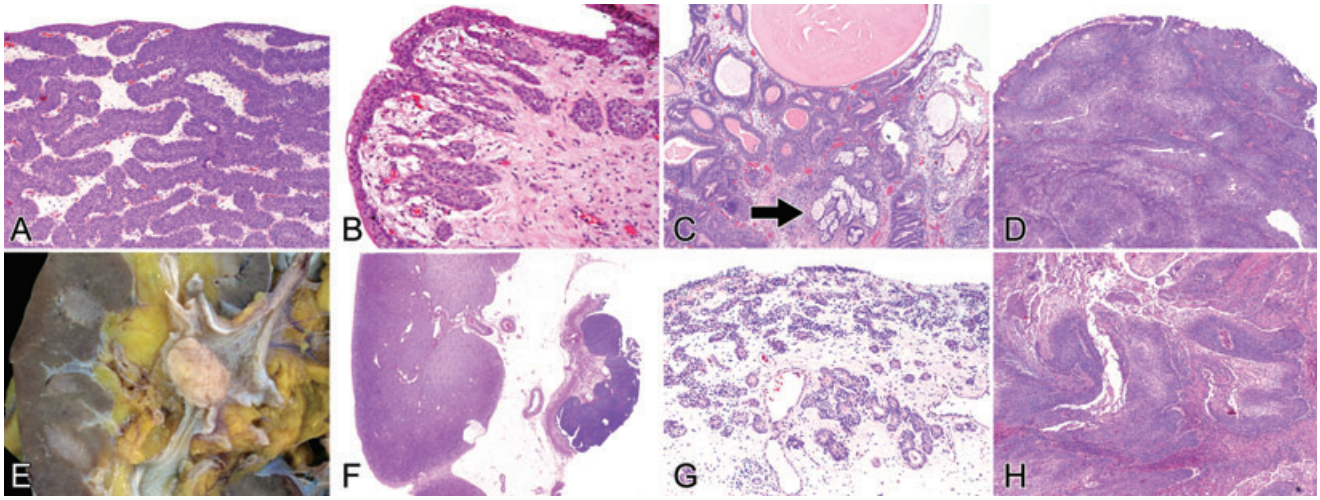

TABLE 1 Main urothelial lesions with inverted growth patterns

Benign lesions
- Inverted urothelial papilloma
- von Brunn's nests and florid von Brunn's nest proliferations
- Cystitis cystica and cystitis glandularis

Malignant lesions
- Inverted urothelial carcinoma
- Nested variant of urothelial carcinoma
- Verrucous squamous cell carcinoma

TABLE 2 Key features to recognition of inverted papilloma

- Relatively smooth surface with minimal to absent exophytic component
- Lesional circumscription with smooth base and no obvious infiltration
- Minimal to absent cytological atypia

cells within the nests and cords of urothelium often have a spindled appearance. The intervening stroma is variable in amount and can be fibrotic. Urothelial buds are frequently present at various points along the undersurface of the urothelium, protruding down into the loose stroma of the lamina propria. It is thought that these urothelial buds are the source of new tumour cords. The overlying surface urothelium can be normal, attenuated or hyperplastic, and by definition an exophytic component is either absent or minimal. Some inverted papillomas of the trabecular type are punctuated by cystic spaces lined by flattened urothelial cells and containing eosinophilic material, producing an appearance reminiscent of cystitis cystica. Foci of non-keratinizing squamous metaplasia are often present, and rare cases can show neuroendocrine differentiation [7]. Marked cytological atypia and mitotic activity are absent. An uncommon variant, designated inverted papilloma with atypia, exhibits focal mild cytological atypia, with prominent nucleoli, atypical squamous features and degenerate-appearing multinucleated giant cells. These features are not known to have any clinical significance [4,8].

The glandular subtype has morphological overlap with cystitis glandularis. It is composed of nests of mature urothelium with either pseudoglandular spaces lined by urothelium or true glandular spaces containing mucus-secreting goblet cells. The luminal secretions stain with mucicarmine. Some inverted urothelial papillomas exhibit vacuolizated or foamy cytoplasm, which might make them difficult to distinguish from urothelial carcinoma [9]. Recently, inverted papillomas with focal papillary features have been described, broadening the morphological spectrum of inverted papillomas [10]. The key diagnostic features of inverted papilloma are listed in Table 2.

Histogenetically, the trabecular subtype is thought to develop by proliferation of the basal cells of the overlying urothelium [4]. Supporting this hypothesis is the presence of bud-like basal proliferations overlying the tumor and the close resemblance between trabecular cells and normal basal cells. Microcysts, which are frequently present in the trabecular type, are pseudoglandular structures that are incapable of mucin production. Microcyst formation is most probably the result of cell necrosis within the core of the trabeculae. The glandular subtype is thought to arise from cystitis cystica and cystitis glandularis in a multi-step process [4]. This involves formation of von Brunn's nests, which undergo cystic degeneration and pseudoglandular metaplasia, resulting in cystitis cystica and cystitis glandularis, respectively, followed eventually by neoplastic transformation.

While inverted papillomas are generally considered to be benign neoplasms, there are conflicting data in the literature regarding their biological behavior [5,11,12]. Previous

studies have reported an increased incidence of urothelial carcinoma in some patients [13]. However, most of those patients had a history of previous or concurrent urothelial carcinoma. By contrast, Sung *et al.* [2] reported on 75 patients with resected inverted papilloma, none of whom had a history of previous or concurrent urothelial carcinoma. During a mean follow-up of 68 months, there was only one recurrence in these patients [4]. Therefore, complete transurethral resection of inverted papilloma appears to be adequate surgical therapy, and surveillance protocols as rigorous as those employed in the management of urothelial carcinoma seem unnecessary [5].

Molecular genetic studies, including X-chromosome inactivation, have shown that inverted papilloma is a clonal, usually diploid, neoplasm that arises from a single progenitor cell [14]. The low incidence of loss of heterozygosity in inverted papilloma is similar to normal urothelium [14,15,16]. Recently, Lott *et al.* [17] conducted fibroblast growth factor receptor 3 (FGFR3) and TP53 mutation analysis in a number of inverted papillomas. Point mutations of the FGFR3 gene were identified in 45% (nine of 20) of cases. It is notable that papillary urothelial neoplasms of low malignant potential and most low-grade urothelial carcinomas also are characterized by the FGFR3 mutations seen in inverted papilloma, and yet have substantial rates of recurrence, as well as low but still significant rates of progression to more aggressive forms of urothelial carcinoma. The underlying mechanisms that account for the different biological behaviours of these neoplasms that share a common set of mutations remain to be elucidated. Lott *et al.* [17] also found no TP53 mutations in the large cohort of inverted papillomas they studied, indicating that inverted papillomas do not harbour key genetic abnormalities predisposing to development of high-grade papillary urothelial carcinoma. As will be discussed in a later section, there are pronounced differences between inverted papillomas and inverted urothelial carcinomas, in their immunohistochemical expression of Ki-67, p53 and CD20, and in their frequency of molecular alterations in chromosomes 3, 7, 17 and 9p21 as detected by UroVysion fluorescence *in situ* hybridization (FISH) analysis, supporting the notion that inverted papillomas arise through entirely different pathogenetic mechanisms from inverted urothelial carcinoma.

The key differential diagnostic considerations are limited. Cystitis cystica is characterized by well-delineated, round nests of normal-appearing urothelium, whereas inverted papilloma shows cords with anastomosing growth patterns. In contrast to inverted papilloma, inverted urothelial carcinoma is, at least in part, exophytic, the endophytic cords and trabeculae are less uniform, and varying degrees of cytological atypia are evident [18]. The presence of cytological atypia of a degree seen in high-grade urothelial carcinoma is unacceptable in inverted papilloma, and warrants a diagnosis of inverted urothelial carcinoma.

VON BRUNN'S NESTS AND FLORID VON BRUNN'S NEST PROLIFERATIONS

Von Brunn's nests are well-circumscribed clusters of urothelial cells in the lamina propria. The nests appear to arise by the process of invagination of the overlying urothelium. The nests may or may not be demonstrably attached to the overlying urothelium [19]. Although some investigators hypothesize that von Brunn's nests arise secondary to inflammatory injury, autopsy studies have documented their presence in 85–95% of bladders, suggesting that they could be part of the spectrum of normal bladder histology [20,21]. Cystoscopically, they characteristically appear as small mucosal nodules with smooth surfaces. Microscopically, the nests typically have smooth, rounded contours but they can be slightly irregular. They are usually regularly spaced. They usually occupy the superficial lamina propria and typically are at a uniform depth, but occasionally are found deeper in the lamina propria. Cell nuclei in von Brunn's nests are bland and lack substantial atypia, although they can show reactive and metaplastic changes. Carcinoma *in situ* of the surface urothelium can extend into von Brunn's nests, but this should not be mistaken for invasion into the lamina propria.

Florid von Brunn's nests are characterized by larger nests with regular spacing (Fig. 1B) [22]. They frequently have lobular or linear configurations. Components of cystitis cystica and cystitis glandularis can be present in such proliferations. The key differential diagnostic consideration of von Brunn's nests, florid or otherwise, is the nested variant of urothelial carcinoma (see later discussion). In contrast to florid von Brunn's nests, the nested variant of urothelial carcinoma is generally characterized by smaller, crowded, irregularly spaced nests of tumour cells that appear to infiltrate deeply and haphazardly, and that usually do not exhibit a marked degree of cyst formation within the cell clusters.

CYSTITIS CYSTICA AND CYSTITIS GLANDULARIS

Cystitis cystica and cystitis glandularis represent a continuum of proliferative and presumed reactive changes that evolve from von Brunn's nests. Cystitis cystica represents von Brunn's nests in which the central cells are absent, resulting in the formation of small cystic cavities (Fig. 1C). Cystitis cystica is demonstrable in up to 60% of bladders. Cystitis cystica manifests as translucent, submucosal cysts containing clear yellow fluid. Microscopically, the cysts contain eosinophilic fluid and are lined by a few layers of urothelium or cuboidal epithelium.

Two subtypes of cystitis glandularis exist [4]. The typical (non-intestinal) subtype is characterized by glands lined by cuboidal to low columnar cells surrounded by transitional cells. The intestinal subtype has similar architecture to the typical subtype of cystitis glandularis; however, the cells lining the glands of the intestinal subtype are tall and columnar, with abundant mucin-secreting goblet cells closely resembling intestinal epithelium (we prefer the term cystitis glandularis with intestinal metaplasia when goblet cells are present; Fig. 1C, indicated by arrow). The two types of cystitis glandularis can coexist, but one form usually predominates. Although the overall incidences of the two types are not well documented, the intestinal type is much less common than the typical type of cystitis glandularis. Rare cases of florid cystitis glandularis with extensive intestinal metaplasia and mucin extravasation have been reported, and such cases can be difficult to distinguish from adenocarcinoma [23,24]. However, the degree of cytological and architectural atypicality of adenocarcinoma far exceeds that seen in florid cystitis glandularis. Adenocarcinomas usually exhibits obvious destruction of the lamina propria, and in the colloid variant, clusters of malignant cells are seen floating in pools of mucin, a feature that excludes a diagnosis of extensive intestinal metaplasia with mucin extravasation. Although cystitis glandularis

TABLE 3 Morphological, immunological and molecular genetic features of urothelial carcinoma with inverted pattern and inverted papilloma

Characteristic	Urothelial carcinoma with inverted growth	Inverted papilloma
Surface	Usually exophytic papillary lesions present	Smooth, dome-shaped, usually intact cytologically normal
Growth pattern	Endophytic, lesional circumscription variable	Endophytic, expansive, sharply delineated, anastomosing cords and trabeculae
Cytological features	Variable, nuclear pleomorphism and atypia present	Orderly polarized cells, some with spindling and palisading at the periphery. No marked atypia, mitoses rare
Biological potential	Recurrences and progression can occur	Benign, rare recurrences*
Immunohistochemistry	Variable, usually high p53 and Ki-67 proliferation index	Low p53 expression and Ki-67 proliferation index
Molecular analysis	Frequent FGFR3 mutation, chromosome 9 and 17 deletions	Rare deletions at chromosome 9 or 17, rare FGFR3 mutations, low rate of LOH

**Rare recurrences related to incomplete excision. LOH, loss of heterozygosity.*

TABLE 4 Urothelial carcinoma with inverted pattern criteria for invasion

Features	Non-invasive	Invasive
Contours of neoplastic nests/cords	Regular	Irregular
Size and shape of nests	Similar, rounded edges	Variable, irregular and jagged edges
Inflammatory and desmoplastic stroma	Absent	Present

with intestinal metaplasia has been proposed by some investigators as a precursor to adenocarcinoma, clear-cut evidence for this association is not well documented [25–27].

INVERTED UROTHELIAL CARCINOMA

Urothelial carcinoma with inverted growth pattern can be difficult to distinguish from inverted papilloma [18,28]. Distinction between these two neoplasms requires strict attention to architectural and cytological features (Table 3). Amin *et al.* [18] reported 18 cases of urothelial carcinoma with endophytic growth pattern. The mean (range) age of patients was 68 (32–94) years with a male preponderance (3.5:1 ratio). Some cases had architectural features similar to inverted papilloma (inverted papilloma-like pattern), while others had broad-pushing bulbous invaginations into the lamina propria (broad-front pattern; Fig. 1D). In some cases, both patterns coexisted. In general, the trabeculae of inverted urothelial carcinomas are wider and more variable than those of inverted papillomas. Inverted urothelial carcinoma, by definition, has substantial nuclear pleomorphism, readily apparent mitotic figures and architectural abnormalities consistent with low- or high-grade urothelial carcinoma [3]. These features are not seen in inverted papilloma. Frequently, components of otherwise typical exophytic or invasive urothelial carcinoma accompany inverted urothelial carcinoma. This raises the question of what constitutes the bona fide inverted urothelial carcinoma. We require at least 25% of the tumour to have an inverted component to be considered inverted urothelial carcinoma. Urothelial carcinoma *in situ*, if present in the surface urothelium, provides further support for a diagnosis of inverted urothelial carcinoma. Inverted urothelial carcinoma may also occur in the renal pelvis (Fig. 1E and 1F).

Immunohistochemical stains as well as FISH can further aid in making the distinction between inverted papilloma and inverted urothelial carcinoma. Jones *et al.* [29] compared specimens from 15 patients with classic inverted papillomas and specimens from 29 patients with urothelial carcinomas exhibiting an inverted growth pattern. The cases were analysed for immunohistochemical expression of Ki-67, p53 and CD20. In addition, UroVysion FISH analysis was performed to assess the tumours for alterations in chromosomes 3, 7, 17 and 9p21, which are commonly seen in bladder cancer. Inverted papillomas usually did not show immunoreactivity for Ki-67, p53 or CD20, whereas the urothelial carcinomas frequently expressed one or more of these biomarkers. In addition, the inverted papillomas did not show the classic molecular alterations typically seen in urothelial carcinomas using UroVysion FISH analysis. These findings further support the notion that inverted papillomas are benign and arise from a different pathogenetic mechanism from urothelial carcinoma.

One of the most challenging aspects when dealing with an inverted urothelial carcinoma is determining the presence or absence of invasion (Table 4). This is particularly true when there is tangential sectioning or when tumour is intermingled with delicate muscle bundles of the lamina propria. The smoothness of the epithelial–lamina propria interface is an important feature. Irregularly shaped nests with disruption or absence of the basement membrane are features of invasion. In these situations, the lamina propria can elicit a brisk inflammatory response, which could obscure the invading edge of the tumor. Desmoplasia and/or a fibrotic stromal response are reliable indicators of invasion. Paradoxical differentiation can aid in the diagnosis of early invasion. It is important to note that microinvasion usually does not elicit a stromal reaction, making its identification more difficult. In these cases, cytokeratin immunostaining can be helpful. The reason why some urothelial carcinomas develop an inverted growth pattern is not known; however, it can be related to a propensity to involve and expand von Brunn's nests.

An entity that must also be distinguished from inverted urothelial carcinoma is inverted papilloma with atypia [8]. In contrast to inverted urothelial carcinoma, inverted papilloma with atypia has only rare mitotic figures and exhibits a very low proliferation rate as estimated by Ki-67 immunostaining.

TABLE 5 Key morphological features distinguishing nested variant of urothelial carcinoma from florid von Brunn's nests

	Organization	Lumen formation	Cytologic atypia	Muscle invasion
Nested variant	Crowded, irregular glands	Yes, variable	Present	Yes, frequent
Florid von Brunn's nests	Large, regularly spaced, rounded nests	Yes, variable	Absent	No

NESTED VARIANT OF UROTHELIAL CARCINOMA

The nested variant of urothelial carcinoma is a rare, aggressive neoplasm that, particularly in limited biopsy specimens, can be notoriously difficult to distinguish from aggregates of von Brunn's nests. This cancer typically occurs in men in the fifth and sixth decades of life [28,30]. Most patients die from disease from 4 to 40 months after diagnosis despite aggressive treatment [31,32]. Although it has an innocuous appearance, it invariably contains cells with enlarged nucleoli and coarse chromatin, indicative of urothelial carcinoma, particularly in the deeper portions of the tumour (Fig. 1G). In addition, the nests have an infiltrative pattern and often fuse with one another.

Volmer *et al.* [22] compared 21 cases of florid von Brunn's nests and 11 cases of nested variant of urothelial carcinoma for biomarker expression. They found that nested urothelial carcinomas had significantly higher MIB-1 and p53 expression parameters than florid von Brunn's nests, suggesting that these immunohistochemical stains might be useful in making the distinction between these two lesions in difficult cases. Features helpful in distinguishing the nested variant of urothelial carcinoma from florid von Brunn's nests are summarized in Table 5.

VERRUCOUS SQUAMOUS CELL CARCINOMA

This is an uncommon entity that must be included in the group of bladder lesions that display an inverted growth pattern. Verrucous squamous cell carcinoma of the urinary bladder is a non-invasive neoplasm regarded as a distinct variant of squamous cell carcinoma [33,34]. Predisposing factors include recurrent cystitis, bladder diverticula and, in particular, schistosomiasis [35]. It is morphologically identical to its counterparts at other sites, including the oral cavity. It can appear grossly exophytic, papillary or warty. Histologically, the neoplasm is composed of well-differentiated keratinizing squamous epithelium with broad-based pushing deep margin (Fig. 1H). Its morphological features overlap to some degree with those of squamous papilloma and condyloma acuminatum, although both of the latter entities are predominantly exophytic lesions. Condyloma acuminatum is a squamous epithelial papillary growth that often displays koilocytosis characteristic of human papillomavirus infection. Cheng *et al.* [36] compared three cases of verrucous carcinoma to three cases of condyloma acuminatum and found that condyloma acuminatum contained HPV DNA. All cases of verrucous carcinoma were negative for HPV DNA, indicating that HPV infection does not play a role in the pathogenesis of verrucous carcinoma. The clinical history is helpful because condyloma acuminatum of the bladder is almost always associated with external genitalia lesions.

CONCLUSIONS

Inverted lesions of the urinary bladder comprise a spectrum of changes ranging from von Brunn's nests to inverted urothelial carcinoma. Differentiating these lesions is important because their proper clinical management and their expected clinical outcomes are distinctly different. Diagnostic difficulties can generally be resolved by close attention to architectural and cytological criteria. In some cases, such as differentiating the nested variant of urothelial carcinoma from von Brunn's nests, immunohistochemical stains, including MIB-1 and p53, can be helpful. Inverted papillomas are characterized by FGFR3 mutations similar to those seen in low-grade urothelial neoplasms, but overall they show a low frequency of genetic abnormalities. These findings probably account for their benign clinical behaviour and, in conjunction with a demonstrable absence of p53 mutations in inverted papillomas, support the concept that inverted papillomas arise through molecular mechanisms distinctly different from those that give rise to high-grade urothelial carcinomas. Considering the evidence gathered so far, it appears quite unlikely that inverted papilloma is a precursor of inverted urothelial carcinoma.

The most challenging aspect of assessing inverted urothelial carcinoma is the determination of the presence or absence of stromal invasion. We consider the following morphological findings to be indicators of invasion: variably sized and shaped cords and nests of tumour cells with irregular contours, particularly irregular and jagged edges, and a desmoplastic stromal response. Currently, there are insufficient data in the literature to indicate whether, on a stage-for-stage basis, patients with urothelial carcinomas with endophytic growth patterns have a better prognosis than those whose tumours are exclusively exophytic.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Cheng L, Lopez-Beltran A, MacLennan GT, Montironi R, Bostwick DG.** Neoplasms of the urinary bladder. In Bostwick DG, Cheng L eds. *Urologic Surgical Pathology*, 2nd edn. Philadelphia: Elsevier/Mosby, 2008: 259–352

2 **Sung MT, MacLennan GT, Lopez-Beltran A, Montironi R, Cheng L.** Natural history of urothelial inverted papilloma. *Cancer* 2006; **107**: 2622–7

3 **Eble JN, Epstein JI, Sauter G, Sesterhenn I.** *WHO Classification of Tumours : Pathology and Genetics. Tumours of the Urinary and Male Reproductive System.* Lyon, France: IARC Press, 2004

4 **Kunze E, Schauer A, Schmitt M.** Histology and histogenesis of two different types of inverted urothelial papillomas. *Cancer* 1983; **51**: 348–58

5 **Cheng CW, Chan LW, Chan CK *et al.*** Is surveillance necessary for inverted papilloma in the urinary bladder and urethra? *ANZ J Surg* 2005; **75**: 213–7

6 **Rozanski TA.** Inverted papilloma: an unusual recurrent, multiple and multifocal lesion. *J Urol* 1996; **155**: 1391

7 **Summers DE, Rushin JM, Frazier HA, Cotelingam JD.** Inverted papilloma of the urinary bladder with granular eosinophilic cells. An unusual neuroendocrine variant. Published erratum appears in Arch Pathol Lab Med 1991 Dec;115(12):1194. *Arch Pathol Lab Med* 1991; **115**: 802–6

8 **Broussard JN, Tan PH, Epstein JI.** Atypia in inverted urothelial papillomas: pathology and prognostic significance. *Hum Pathol* 2004; **35**: 1499–504

9 **Fine SW, Epstein JI.** Inverted urothelial papillomas with foamy or vacuolated cytoplasm. *Hum Pathol* 2006; **37**: 1577–82

10 **Albores-Saavedra J, Chable-Montero F, Hernandez-Rodriguez OX, Montante-Montes de Oca D, Angeles-Angeles A.** Inverted urothelial papilloma of the urinary bladder with focal papillary pattern: a previously undescribed feature. *Ann Diagn Pathol* 2009; **13**: 158–61

11 **Asano K, Miki J, Maeda S, Naruoka T, Takahashi H, Oishi Y.** Clinical studies on inverted papilloma of the urinary tract: report of 48 cases and review of the literature. *J Urol* 2003; **170**: 1209–12

12 **Altaffer LF III, Wilkerson SY, Jordan GH, Lynch DF.** Malignant inverted papilloma and carcinoma in situ of the bladder. *J Urol* 1982; **128**: 816–8

13 **Cheville JC, Wu K, Sebo TJ *et al.*** Inverted urothelial papilloma: is ploidy, MIB-1 proliferative activity, or p53 protein accumulation predictive of urothelial carcinoma? *Cancer* 2000; **88**: 632–6

14 **Sung MT, Eble JN, Wang M, Tan PH, Lopez-Beltran A, Cheng L.** Inverted papilloma of the urinary bladder: a molecular genetic appraisal. *Mod Pathol* 2006; **19**: 1289–94

15 **Eiber M, van Oers JM, Zwarthoff EC *et al.*** Low frequency of molecular changes and tumor recurrence in inverted papillomas of the urinary tract. *Am J Surg Pathol* 2007; **31**: 938–46

16 **Junker K, Boerner D, Schulze W, Utting M, Schubert J, Werner W.** Analysis of genetic alterations in normal bladder urothelium. *Urology* 2003; **62**: 1134–8

17 **Lott S, Wang M, Zhang S *et al.*** FGFR3 and TP53 mutation analysis in inverted urothelial papilloma: incidence and etiological considerations. *Mod Pathol* 2009; **22**: 627–32

18 **Amin MB, Gomez JA, Young RH.** Urothelial transitional cell carcinoma with endophytic growth patterns: a discussion of patterns of invasion and problems associated with assessment of invasion in 18 cases. *Am J Surg Pathol* 1997; **21**: 1057–68

19 **Goldstein AM, Fauer RB, Chinn M, Kaempf MJ.** New concepts on formation of Brunn's nests and cysts in urinary tract mucosa. *Urology* 1978; **11**: 513–7

20 **Ito N, Hirose M, Shirai T, Tsuda H, Nakanishi K, Fukushima S.** Lesions of the urinary bladder epithelium in 125 autopsy cases. *Acta Pathol Jpn* 1981; **31**: 545–57

21 **Andersen JA, Hansen BF.** The incidence of cell nests, cystitis cystica and cystitis glandularis in the lower urinary tract revealed by autopsies. *J Urol* 1972; **108**: 421–4

22 **Volmar KE, Chan TY, De Marzo AM, Epstein JI.** Florid von Brunn nests mimicking urothelial carcinoma: a morphologic and immunohistochemical comparison to the nested variant of urothelial carcinoma. *Am J Surg Pathol* 2003; **27**: 1243–52

23 **Young RH, Bostwick DG.** Florid cystitis glandularis of intestinal type with mucin extravasation: a mimic of adenocarcinoma. *Am J Surg Pathol* 1996; **20**: 1462–8

24 **Jacobs LB, Brooks JD, Epstein JI.** Differentiation of colonic metaplasia from adenocarcinoma of urinary bladder. *Hum Pathol* 1997; **28**: 1152–7

25 **Smith AK, Hansel DE, Jones JS.** Role of cystitis cystica et glandularis and intestinal metaplasia in development of bladder carcinoma. *Urology* 2008; **71**: 915–8

26 **Corica FA, Husmann DA, Churchill BM *et al.*** Intestinal metaplasia is not a strong risk factor for bladder cancer: study of 53 cases with long-term follow-up. *Urology* 1997; **50**: 427–31

27 **Cameron KM, Lupton CH.** Inverted papilloma of the lower urinary tract. *Br J Urol* 1976; **48**: 567–77

28 **Talbert ML, Young RH.** Carcinomas of the urinary bladder with deceptively benign-appearing foci. A report of three cases. *Am J Surg Pathol* 1989; **13**: 374–81

29 **Jones TD, Zhang S, Lopez-Beltran A *et al.*** Urothelial carcinoma with an inverted growth pattern can be distinguished from inverted papilloma by fluorescence in situ hybridization, immunohistochemistry, and morphologic analysis. *Am J Surg Pathol* 2007; **31**: 1861–7

30 **Lopez-Beltran A, Cheng L.** Histologic variants of urothelial carcinoma: differential diagnosis and clinical implications. *Hum Pathol* 2006; **37**: 1371–88

31 **Holmang S, Johansson SL.** The nested variant of transitional cell carcinoma – a rare neoplasm with poor prognosis. *Scand J Urol Nephrol* 2001; **35**: 102–5

32 **Drew PA, Furman J, Civantos F, Murphy WM.** The nested variant of transitional cell carcinoma: an aggressive neoplasm with innocuous histology. *Mod Pathol* 1996; **9**: 989–94

33 **Boxer RJ, Skinner DG.** Condylomata acuminata and squamous cell carcinoma. *Urology* 1977; **9**: 72–8

34 **El Sebai I, Sherif M, El Bolkainy MN, Mansour MA, Ghoneim MA.** Verrucous squamous carcinoma of bladder. *Urology* 1974; **4**: 407–10

35 **El-Bolkainy MN, Mokhtar NM, Ghoneim MA, Hussein MH.** The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer* 1981; **48**: 2643–8

36 **Cheng L, Leibovich BC, Cheville JC *et al.*** Squamous papilloma of the urinary tract is unrelated to condyloma acuminata. *Cancer* 2000; **88**: 1679–86

Correspondence: Liang Cheng, MD, Chief of Genitourinary Pathology Division, Director of Molecular Diagnostics, Indiana University School of Medicine, 350 West 11th Street, Clarian Pathology Laboratory Room 4010, Indianapolis, IN 46202, USA.
e-mail: liang_cheng@yahoo.com

Abbreviations: **FGFR3**, fibroblast growth factor receptor 3; **FISH**, fluorescence in situ hybridization.