HHS Public Access

Author manuscript

Mod Pathol. Author manuscript; available in PMC 2016 September 02.

Published in final edited form as:

Mod Pathol. 2015 May ; 28(5): 612–630. doi:10.1038/modpathol.2014.158.

Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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Abstract

The International Consultations on Urological Diseases are international consensus meetings, supported by the World Health Organization and the Union Internationale Contre le Cancer, which have occurred since 1981. Each consultation has the goal of convening experts to review data and provide evidence-based recommendations to improve practice. In 2012, the selected subject was bladder cancer, a disease which remains a major public health problem with little improvement in many years. The proceedings of the 2nd International Consultation on Bladder Cancer, which included a 'Pathology of Bladder Cancer Work Group,' have recently been published; herein, we provide a summary of developments and consensus relevant to the practicing pathologist. Although the published proceedings have tackled a comprehensive set of issues regarding the pathology of bladder cancer, this update summarizes the recommendations regarding selected issues for the practicing pathologist. These include guidelines for classification and grading of urothelial neoplasia, with particular emphasis on the approach to inverted lesions, the handling of incipient papillary lesions frequently seen during surveillance of bladder cancer patients, descriptions of newer variants, and terminology for urine cytology reporting.

The International Consultation on Urological Diseases (ICUD) is a World Health Organization (WHO)-registered non-governmental organization promoting improvements in world health through sponsorship and organization of interdisciplinary international consultations on the diagnosis, classification, and management of urologic diseases, with emphasis on provision of evidence-based recommendations. Prior consultations have spanned the spectrum of neoplastic and non-neoplastic urologic diseases ranging from benign prostatic hyperplasia and erectile dysfunction to prostate and bladder cancer. Bladder cancer was previously addressed in 2004 in the 1st International Consultation on Bladder Tumors in Hawaii with proceedings published in 2005.[1] In March 2011 in Vienna, Austria, bladder cancer was revisited in the 2nd International Consultation on Bladder Cancer to provide an updated consensus and recommendations. This meeting, co-sponsored by the European Association of Urology, included a Pathology of Bladder Cancer Work Group composed of nearly 40 experts in urological pathology among a total of 10 committees formulated to address key clinical and public health questions. The 2nd Consultation on Bladder Cancer resulted in recent publication of the book, *Bladder Cancer*,[2] reporting the consultation's proceedings, as well as a number of summary papers.[3–7] From the standpoint of bladder cancer pathology, this consultation, auspiciously occurring a number of years after the discussion in 1997–1998, introduction,[8] modification,[9] and formal WHO adoption in 2004[10] of the International Society of Urologic Pathology (ISUP) classification and grading system for urothelial neoplasms of the urinary bladder, offered the opportunity to

examine the state of the art and begin to address a number of key questions regarding bladder cancer pathology and the pathologist's diagnostic approach.

As new findings and better data have become available about important areas of recurrent interest since the 2004 Blue Book, the proceedings of this bladder cancer pathology committee and working group provide guidance on a number of areas of value to practicing pathologists. The consultation's proceedings are publicly available *in toto* in electronic and print form[2] and provide a compendium of the state of the art for this disease; the pathology section proceedings alone number >100 pages with >700 references. In particular, sections describing the microanatomy of the bladder and normal, reactive, and metaplastic epithelial changes provide a useful review, as does the review of the use of immunohistochemistry. However, as these proceedings have seen relatively limited coverage in the mainstream pathology literature, herein we have endeavored to distill a 'high yield' review of selected topics of the proceedings most relevant to the practice of urologic surgical pathology. Specifically, we cover four areas of the ICUD's recommendations: (i) the classification and grading of urothelial neoplasia with a focus on application of the grading system in routine practice, including for neoplasms with inverted morphology or those with grade heterogeneity; (ii) the diagnostic approach for incipient lesions, often seen in patients under surveillance for urothelial neoplasia, which are not accurately classifiable as per the current schema; (iii) an update on the variants of urothelial carcinoma, particularly from the perspective of newer variants or established variants with increased understanding of clinical significance; and (iv) a consensus language for urine cytology. These key offerings of the ICUD proceedings are bulleted in Summary Box 1.

A historical perspective of classification and grading

Building on the longstanding efforts of the WHO in study and classification of tumors (reviewed in Mostofi *et al*[9]) and the first and second series of the Armed Forces Institute of Pathology (AFIP) Fascicles,[11] the WHO in 1973 published the first international, systematic approach to the grading of urothelial neoplasia.[12] The WHO 1973 system provided a classification of what was then called 'transitional cell carcinoma' of the bladder into three grades. Although this classification provided the modern foundation for approaching these lesions, it suffered limitations, particularly pertaining to a lack of clearly defined criteria for each grade, referring only to the degree of anaplasia and thereby resulting in diagnosis of a high prevalence of grade II 'intermediate grade' carcinomas. A number of authors have argued that from a clinical standpoint, the 1973 system was limited by focusing on morphology (without clear criteria) rather than targeted to classifying tumors into categories more relevant to management.[13–15]

In 1994, based largely on a study by Jordan *et al*,[16] the 3rd Series AFIP fascicle proposed a classification of bladder carcinoma as 'papilloma,' lowgrade, and high-grade transitional cell carcinoma,[17] adapting a broader definition of 'papilloma' to include most WHO 1973 Grade I transitional cell carcinomas. In fall 1997, anticipatory of the next WHO monograph, to be published in 1999, Dr FK Mostofi assembled a team of experts at the AFIP in Washington DC to discuss terminology used in bladder cancer and make recommendations to the WHO. Of particular interest was the issue of the nomenclature of Grade I transitional cell

carcinoma, given the growing appreciation at the time that a majority of tumors in this category did not progress.[16,17] At the AFIP meeting, the term papillary urothelial neoplasm of low malignant potential (PUNLMP) was proposed to the WHO committee, to prevent assigning these more indolent lesions the label of carcinoma but not categorically designating them as a benign lesion (papilloma) because of the presence of a distinct subset of cases that show recurrence and grade progression.

Pursuant to this important step, in March 1998, a follow-up meeting, organized under the auspices of the International Society of Urologic Pathology (ISUP), was convened at the United States and Canadian Academy of Pathology (USCAP) meeting in Boston in March, 1998, where the classification, terminology, and, importantly, criteria were refined and modified (drawing significantly from influential approaches that had been reported by Malmstroöm *et al*[18] and Murphy *et al*[17]). The proceedings of this meeting were published as the WHO/ISUP Consensus Classification of Urothelial Neoplasms of the bladder at the end of that year[8] in hopes of providing a 'universally acceptable classification system' for urothelial neoplasia. Additional contributions included the formal endorsement of the term 'urothelial' to replace 'transitional cell' in description of the epithelium of the urinary tract and tumors therefrom. The flat intraepithelial lesions with non-reactive atypia were essentially compressed from a multi-tier system of mild, moderate, severe, and carcinoma in situ (CIS), to essentially a two tier system of dysplasia and CIS. In 1999, the WHO, maintaining papilloma and PUNLMP as diagnostic categories, re-appropriated the labels of Grade I, Grade II, and Grade III urothelial carcinoma,[9] but used them to label lesions defined by criteria different from those of the 1973 WHO system.

Subsequently, after a conference in Lyon, France, during 14–18 December 2002, the WHO, in its revised 2004 'Blue Book,' Pathology and Genetics of Tumours of the Urinary System, formally adopted the 1998 ISUP system, with its four categories of papilloma, PUNLMP, low-grade, and high-grade papillary urothelial carcinoma (the latter with option to comment on diffuse anaplasia if present). This system has been termed the WHO (2004)/ISUP system, herein the 'WHO/ISUP System,' and has provided a number of advantages to the field of bladder cancer pathology (Summary Box 2). It is this system that the ICUD recommends for contemporary use, consistent with the endorsement by the 4th Series Armed Forces Institutes of Pathology Fascicle on the Urinary Bladder,[19] the 7th edition AJCC Cancer Staging Manual,[20] and several American (Association of Directors of Anatomic and Surgical Pathology, the College of American Pathologists[21]), and European protocols.[22] Two additional areas relevant to grading where the ICUD made recommendations applicable to daily practice include the application of the WHO/ISUP system to tumors with inverted architecture and the approach to the diagnosis and reporting of incipient urothelial neoplasia.

Overall ICUD recommendation: grading by WHO/ISUP system

A System Linking Histopathologic Criteria to Risk

The ISUP 1998 consensus classification, adopted by the WHO in 2004 as the WHO/ISUP system, stressed the use of diagnostic criteria for papillary lesions summarized briefly as follows. *Urothelial papilloma* was defined as a papillary lesion showing a urothelium of normal thickness, cellularity and polarization, lining on fibrovascular stalks, a diagnosis

implying an unequivocally benign lesion of low risk of recurrence and no risk for progression. Essentially similar features, seen in flat, nonpapillary mucosa, would be regarded as *normal urothelium*. The *PUNLMP* category of lesions was defined as showing normal to thickened and hyperplastic-appearing (increased number of layers and cells per unit area) urothelium with minimal architectural abnormality and minimal cellular atypia. This group was intended to imply a substantial risk of recurrence (<50%) in some series approximating that of low-grade papillary carcinoma, but with low risk of progression (<5%) such that patients could be spared a cancer diagnosis. Lesions showing this range of features in a nonpapillary lesion or biopsy would be regarded as *flat urothelial hyperplasia*.

Lesions showing a urothelium with distinct cytologic atypia (nucleomegaly, irregular nuclear contours, and irregular chromatin distribution) and variable loss of polarity, arrayed on a discrete fibrovascular core, were defined as low-grade papillary urothelial carcinoma. This category implies a high risk of recurrence of ~50% and low risk of progression of ~5–10%, both greater than in PUNLMP. When encountered in a non-papillary lesion, these histologic changes would be diagnosed as *urothelial dysplasia*. Finally, tumors demonstrating urothelium with moderate to severe cytologic atypia (nuclear pleomorphism, prominent nucleoli, and mitoses, including atypical forms, in mid to higher layers of the urothelium), arrayed on fibrovascular cores, with variable, often significant loss of polarity and discohesion, were defined as high-grade papillary urothelial carcinoma. High-grade papillary carcinomas have relatively greater risk of recurrence than low-grade carcinomas, as well as a significant risk of progression to invasive disease (15–40%). The same degree of cytologic atypia, encountered in a biopsy of flat urothelium, would be regarded as *urothelial CIS*.

ICUD Recommendation—Update for Grading Invasive Carcinoma

One key area where the recommendations of the ICUD differ, indirectly, from the WHO/ISUP system concerns the approach to histologic grading of invasive lesions. In principle, the WHO 1973, ISUP 1998, WHO 1999, and WHO(2004)/ISUP systems all recommended grading invasive carcinoma by the same system under which non-invasive carcinomas are graded; indeed, the 2004 WHO Blue Book recommends their grading by ‘the degree of nuclear anaplasia and…architectural abnormalities.’ Emerging understanding in the intervening years suggests that among tumors showing any extent of invasion of the basement membrane (pT1 or greater), the histologic grade is both less important prognostically, as reviewed recently,[2,3] as well as nearly operationally irrelevant, given the overwhelming predominance of high-grade histology (per WHO (2004)/ISUP criteria). For instance, in a study by Cao *et al*,[23] 41/42 tumors showing stromal invasion were graded as high-grade under the current WHO/ISUP system. Thus, the prevalence of ‘low-grade’ pT1 was too low to evaluate, whereas even application of the 1973 criteria resulted in a non-significant difference in recurrence-free, progression-free, and overall survival. Similarly, in a larger cohort, Otto *et al*[24] found that of over 300 pT1 stage tumors, 96% were graded as high-grade under the WHO/ISUP system, whereas recurrence-free, cancer-free, and overall survival again did not differ between low- and high-grade (stage pT1 invasive) carcinomas.

In the end, this finding should not be surprising in that the criteria involved in recognizing stromal (or muscularis propria) invasion (retraction artifact, single cells, irregularly shaped clusters, paradoxical inverse maturation) essentially by definition exclude retention of the architectural features necessary for a low-grade designation (preservation of a modicum of polarity within the urothelium). Even tumors at the lower end of the spectrum of cytologic atypia in invasive tumors, the so-called 'deceptively bland' variants (nested etc), once muscle invasive show overall prognoses similar to stage-matched tumors with conventional morphology.

Thus, based on the growing experience and understanding of criteria subsequent to the introduction of the WHO (2004)/ISUP system, the ICUD recommends that invasive urothelial carcinomas, independent of the degree of invasion, be generally graded as high-grade. This recommendation comes with the understanding that there are uncommon variants of invasive urothelial carcinoma that may demonstrate idiosyncratic low-grade cytologic features (including the small and large nested variants—see below) and which require careful consideration and communication with clinical colleagues. Additionally, this ICUD recommendation comes with the consideration voiced by some panelists, especially European colleagues, that a number of protocols and institutional standard practices ascribe grades to invasive carcinomas using criteria from prior grading systems—principally WHO 1973 defined solely on degree of 'anaplasia.'[12] Thus, while recognizing that, in any case, stage trumps grade, grading of invasive urothelial carcinoma may be resorted to in very select situations based on existing institutional or clinical protocols.

ICUD Recommendation—Update for Grading Inverted Neoplasms

One of the themes in the approach to grading urothelial neoplasms in general, considered at length in the deliberations of the ICUD, was the analogy between morphologic features of papillary and flat lesions (Table 1). For instance, beginning with the descriptions and criteria first proposed in the 1998 ISUP Consensus Classification, there was an appreciation that similar degrees of cytologic changes were appreciable between flat and papillary non-invasive lesions, such that normal urothelium and papilloma were analogous, flat urothelial hyperplasia and PUNLMP were analogous, dysplasia and low-grade papillary urothelial carcinoma were analogous, and urothelial CIS and high-grade papillary urothelial carcinoma were analogous. Although the 1998 ISUP included a definition of inverted papilloma and referenced a contemporary report of urothelial neoplasms with inverted or endophytic architecture,[25] it did not address the applicability of the grading system to inverted neoplasms. For that matter, the WHO (2004) /ISUP system,[10] despite recognizing the existence of inverted papilloma, did not address grading any other inverted lesions and only considered the issue that inverted/endophytic growth patterns may simulate invasion.[25,26]

Inverted neoplasms have been the source of some difficulty in urological pathology, as already recognized in the 1998 WHO/ISUP Consensus.[8] In ICUD deliberations, it became apparent that a formal approach for grading neoplasms showing an inverted growth pattern, particularly those demonstrating predominant or exclusive inverted growth,[27] was not available under the existing grading systems. The ICUD proceedings note that this deficiency has resulted in these neoplasms, especially ones with features of PUNLMP but

with inverted growth, being reported under a number of terminologies.[25,26,28–30] Thus, a recommendation was made to appropriate the existing WHO/ISUP system criteria and analogy between flat and exophytic papillary neoplasms to inverted/endophytic papillary lesions.

Although data to support the validity of the application of the WHO/ISUP System of histologic grading to inverted neoplasms, particularly PUNLMP,[31,32] have only begun to accumulate, the ICUD recommends use of the criteria of the WHO/ISUP system to grade inverted lesions, which include *inverted papilloma* (Figure 1a and b), *inverted PUNLMP* (Figure 1c and d), *inverted papillary urothelial carcinoma, low-grade* (Figure 2a and b), and *inverted papillary urothelial carcinoma, high-grade* (Figure 2c and d, which may be invasive or noninvasive); see Table 1. Though the ICUD noted that the limited understanding of the prospective significance of such diagnoses should be recognized and conveyed to clinicians, the use of standardized criteria and terminology will enable the future studies necessary to better understand these neoplasms going forward. For that matter, in clinical practice, it is not uncommon to see tumors with both exophytic/papillary and endophytic/inverted growth; it is only when the inverted pattern is prominent or predominant that this proposed terminology should be used.

ICUD Recommendation: Update for Grading Papillary Neoplasia with Grade Heterogeneity

Heterogeneity in the grade of urothelial neoplasms is not infrequent, with some studies reporting as much as ~40%.[33–36] Under the current (and ICUD recommended) WHO/ISUP system, the recommendation was made to render a grade based on the highest grade area identified in the tumor.[10] The ICUD workgroup acknowledged that some studies have promulgated ignoring less than 5% of a higher grade neoplasm,[34,36] though it did not endorse this approach. Additionally, the proceedings reviewed the results of studies that have identified significant differences between the prognosis of non-invasive papillary carcinomas with predominant high-grade histology and carcinomas with admixed low-grade components.[33,35,36] Overall, the proceedings acknowledged that prospective studies of grade heterogeneity, approaches to its reporting, and the relationship of these parameters to outcomes are needed.

Heterogeneity in lesions that show morphology varying between PUNLMP and papillary urothelial carcinoma, low-grade, pose a less critical clinical distinction given their relatively similar recurrence rates. In contrast, the implications of mixed low-grade and high-grade morphology are more clinically important, though both PUNLMP/low-grade and low-grade/high-grade mixed patterns are encountered.[36] More importantly, one of the documented reasons behind the interobserver variability in the diagnosis of high-grade papillary carcinoma is that a focus of higher grade histology may be counted as sufficient for diagnosis by one observer but not another.[15] To provide a more complete diagnostic description of such a process, the ICUD noted that some authors use terminology such as, '*high-grade papillary urothelial carcinoma arising in a background of low-grade papillary urothelial carcinoma*.'

Because the distinction of low-grade and high-grade tumors is clinically significant, the ICUD recommends that when assigning a grade to a borderline lesion (between low- and

high-grade), a number of additional factors, including historical data (grade of prior urothelial neoplasia, frequency of recurrence), as well as salient clinical (size, focality/multifocality) and pathologic (concurrent CIS, urine cytology results) observations may be considered. The ICUD recommends consideration of the presence or absence of such factors as part of the pathologist's decision whether or not to 'upgrade' a borderline lesion to a higher grade, which is reasonable in light of the ICUD noting that urologists often approach management of a case based on such factors. In reviewing cases with 'cusp' patterns, it is important to make the assessment on thin, well stained H&E sections, and judicious ordering of recuts may be helpful in such cases. Finally, the sharing of difficult or borderline cases with colleagues is strongly recommended, especially as there are no reliable immunohistochemical or molecular markers that may be recommended, at present, as validated adjuncts to help make this important determination. A number of experts have raised concerns regarding increased tendency of practicing pathologists to grade noninvasive lesions as high-grade; future efforts such as the upcoming new edition of the WHO 'Blue Book' will likely focus on tightening diagnostic criteria.

ICUD recommendation: approach and terminology for incipient lesions encountered during surveillance

A recurring difficulty concerns what terminology to use in cases of incipient lesions or 'formes frustes' of papillary urothelial neoplasia that present in the form of generally small, proliferative, and hyperplastic lesions as are encountered with some frequency in patients under endoscopic surveillance for urothelial neoplasia.[37] For instance, *papillary urothelial hyperplasia*, described as lesions showing a urothelium with increased thickness or cell density and an undulated or 'tented' border (importantly, *lacking* fibrovascular cores or cytologic atypia) were described,[38] confirmed as a clonal process[39] and formally adopted as a diagnostic category in the 1998 WHO/ISUP Consensus.[8] In the 2004 WHO 'Blue Book,' papillary urothelial hyperplasia was not specifically identified as a distinct category, but mentioned as a morphologic variation in the spectrum of hyperplasia.[10] The ICUD Consultation endorsed this entity and term.[2,3] However, it bears consideration that the definition of papillary hyperplasia excludes lesions with cytologic atypia, raising the question of how to diagnostically approach lesions with low- or high-grade cytologic atypia or even abortive or rudimentary fibrovascular core formation, such as those sampled during surveillance.

A number of reports have described similar changes in urothelial neoplasia induced by intravesical therapies, termed as 'truncated papillae of treated papillary carcinoma'[40] or as 'atypical papillary urothelial hyperplasia.'[41] Such changes may be induced by the local abrasive effect of intravesical agents.[40] Under increased clinical scrutiny and sampling of patients following contemporary protocols, such lesions pose a challenge to the practicing pathologist regarding diagnostic approach and terminology. Unfortunately, there is no molecular or immunohistochemical biomarker that may be recommended at this time to help sort out any given case definitively. Thus, based on the experience of the bladder pathology workgroup members, the ICUD recommends a general approach to apply when such lesions are encountered rather than a particular terminology.

First, the consultation recommends the use of strict criteria for diagnosis of flat urothelial hyperplasia as opposed to focal or incipient papillary urothelial neoplasia, in particular, requiring the complete lack of true fibrovascular cores to render a straightforward diagnosis of flat hyperplasia. Thin fibrovascular cores are a hallmark of urothelial neoplasia,[17] and their presence, even in rudimentary form, in a biopsy under surveillance, is worrisome for neoplastic persistence or recurrence. Second, reflective of the desire to employ standardized criteria, the ICUD recommends use of the criteria and terminology of the WHO/ISUP system to describe the degree of atypia of the proliferative or hyperplastic flat urothelium such that cases be described in terms of *dysplasia* or CIS, based on the degree of the cytologic atypia of the urothelium.

Perhaps most importantly, correlation with the clinical setting, particularly the cystoscopic impression, is essential to determine whether such a forme fruste lesion was thought to be a papillary lesion. For instance, in the appropriate clinical scenario, which might include a prior non-invasive low-grade papillary urothelial carcinoma diagnosis and a clinically exophytic lesion identified, a patch of hyperplastic urothelium with distinct but mild cytologic atypia and mild-to-moderate loss of polarity, with only focally to poorly formed fibrovascular cores may be interpreted as a small low-grade papillary urothelial carcinoma. However, in the absence of histologic documentation of well-formed exophytic growth and in the absence of clinical documentation of a papillary lesion, descriptive terminology such as '*dysplasia with early papillary formations*' (Figure 3a and b) or '*CIS with early papillary formations*' to describe low- and high-grade cases (Figure 3c and d), is recommended. The fact that these terms are descriptive diagnoses needs to be communicated with the treating urologist, in as much as there are limited data supporting their validity as entities or their prognostic significance.

ICUD recommendation: update on approach to variants and new patterns

Overall recommendation

The remarkable morphologic plasticity of urothelial carcinoma has been studied in detail, with numerous patterns of variant morphology and differentiation reported, as reviewed recently,[42,43] and as considered exhaustively by the ICUD proceedings.[2] A comprehensive review of the full range of variants of urothelial carcinoma is beyond the scope of this review; instead, we provide a focused update regarding variants of urothelial carcinoma that are not detailed in the 2004 WHO Blue Book,[10] including the large nested variant, urothelial carcinoma with small tubules, urothelial carcinoma with rhabdoid features, and urothelial carcinoma with chordoid features. Additionally, we provide an update on one key variant, micropapillary urothelial carcinoma, where new diagnostic, clinical, and molecular data are available and increasingly relevant to ongoing practice of urologic surgical pathology.

Importantly, the ICUD makes a general recommendation in favor of reporting variant morphology for urothelial carcinoma, especially as recent studies suggest it may be underreported in routine practice.[44] Reporting of variants will not only inform clinicians but also enable prospective study and allow correlation with any subsequent recurrence.[45] Additionally, similar to the College of American Pathologists reporting approach, in cases

where multiple variant morphologies coexist, the recommendation is made to report each variant and the estimated percentage of each variant present.

The Large Nested Variant of Urothelial Carcinoma

The *large nested variant of urothelial carcinoma*,[46] along with the (small) nested variant of urothelial carcinoma,[47] is one of the variants that may present a 'pseudo benign' (deceptively bland) appearance. Though the potential of benign proliferations such as von Brunn's nests to simulate carcinoma is well known,[48] awareness of the large nested variant is important given that it may simulate a urothelial neoplasm with inverted growth despite being invasive, often deeply, of the bladder wall. These carcinomas are composed of large nests of cells that are cytologically bland (see Figure 4a – c). They show a broad, pushing pattern of invasion, sometimes evocative of the pattern of verrucous carcinomas. In contrast to the small nested variant, a surface component has been identified with some frequency, which also often appears low-grade. In the series reported by Cox *et al*,[46] follow-up data were obtained in 17/23 patients with large nested variant urothelial carcinoma, showing persistent/progressive disease in 6/17, suggesting that the low-grade appearance is deceptive.

Larger, additional cohorts will be necessary to better understand this variant, its prevalence, and its prognostic significance;[49] however, a number of features have been identified to assist in its discrimination from potential simulants. First, although these lesions appear low grade compared with 'garden variety' invasive urothelial carcinoma, the degree of atypia is more in keeping with a low-grade urothelial carcinoma and generally exceeds that of nests of von Brunn, even in a reactive setting. In the case of small nested carcinoma, the degree of atypia is usually greater at the deeper aspect of these lesions, somewhat the opposite of that expected for benign proliferative lesions. Features to consider in support of a large nested carcinoma include the haphazard and irregular distribution of the nests in the wall of the bladder (Figure 5a), which is unexpected for embryologic duct remnants (urachal, etc) or even orifices of duplicated or tangentially sectioned ureteral collecting systems. The infiltrative appearance of the nests in the wall, especially deep in the muscularis propria, directly juxtaposed to large caliber bundles of muscularis propria (Figure 5b), is very useful, because non-invasive inverted urothelial neoplasia should not invade the muscularis propria. Finally, observation of foci of conventional invasion, apparent in approximately one third of cases reported previously,[46] can be helpful to confirm invasion (Figure 5c).

Urothelial Carcinoma with Small Tubules

Urothelial carcinoma with small tubules[50–52] is a rare neoplasm characterized by infiltrative, small tubules which may be admixed with solid small nests, often showing the low-grade morphology described in nested cases (Figure 6a – c). The epithelium may be attenuated and does not show overt glandular or columnar differentiation, and a surface component may not be present. Given the smaller size of these tubules, generally smaller than that observed in microcystic urothelial carcinoma,[53] this variant may be mistaken for nephrogenic adenoma, adenocarcinoma of the prostate,[54] or even cystitis cystica et glandularis, though generally these carcinomas show a degree of infiltrative growth, often involving the muscularis propria, and cytologic atypia, at least focally, exceeding that allowable in nephrogenic adenoma or other benign lesions in the differential. Also in the differential diagnoses are

primary adenocarcinomas of the bladder (which generally show more explicit glandular features, higher grade, variability in acinar size, mucin, and surface/precursor lesions) and prostatic adenocarcinoma (which may be readily excluded by use of immunohistochemistry). The importance of this variant remains its recognition and distinction from benign or malignant processes, as sufficient cases have not yet been studied to estimate its biologic potential or treatment implications.

Urothelial Carcinoma with Rhabdoid Features

Urothelial carcinoma with rhabdoid features[55,56] is another infrequent variant at the undifferentiated end of the spectrum of urothelial carcinoma. These tumors merit distinction from malignant extrarenal rhabdoid tumors of soft tissue, which are pathogenetically unrelated sarcomas generally of the pediatric population,[57] with which they share histomorphologic features. These tumors are rare and often present as a pattern observed in an otherwise poorly differentiated to undifferentiated urothelial carcinoma. Generally, carcinomas with rhabdoid features show a friable, discohesive appearance composed of sheets of cells with characteristic high-grade features, eccentrically located vesicular nuclei with prominent nucleoli and hyaline cytoplasmic inclusions; identification of a conventional urothelial component or contemporary urothelialassociated markers[58–61] may be helpful (Figure 7a – c). In the differential diagnosis, one must consider the rare malignant extrarenal rhabdoid tumors of soft tissue that have been reported in the bladder;[62] these tumors do not express immunohistochemical markers associated with urothelial carcinoma[58] and show prevalent alteration or loss of expression of the gene SMARCB1 (INI1).[63]

Invasive Urothelial Carcinoma with Chordoid Features

Urothelial carcinoma with chordoid features[64] were noted during a retrospective review of >160 urothelial carcinomas to identify cases with a morphology reminiscent of chordoma, extraskeletal myxoid chondrosarcoma, myoepithelioma of soft tissue, or yolk sac tumor. Though at least focal identifiable conventional urothelial carcinoma was seen in all cases, a striking pattern of cellular cording was present within an abundant myxoid matrix[64] (Figure 8a – c). This stromal change, which may be prominent in conventional urothelial carcinoma and has been described as ‘urothelial carcinoma with prominent myxoid stroma,’[65] suggests that tumors reported as ‘with chordoid features,’ or ‘associated with prominent myxoid stroma’ are within a similar spectrum of histopathology. Given the lesions in the differential diagnosis, all these neoplasms show expression of urothelial-associated markers such as p63 and high molecular weight cytokeratin, which may be useful to confirm the diagnosis. In contrast, markers associated with tumors in the differential, including calponin, glial fibrillary acidic protein (myoepithelioma), glypican-3 (yolk sac), and brachyury (chordoma) are negative. Three quarters of the tumors characterized by Cox *et* al[64] showed extension into perivesical fat or adjacent organs and lymph node metastases. The majority of patients had persistent disease or died of disease at follow-up.

Micropapillary Urothelial Carcinoma

Though covered in the 2004 WHO Blue Book, recent years have seen several developments in our understanding of the *micropapillary variant of urothelial carcinoma*. Although other variant morphologies have been reported to be associated with aggressive course, especially

high-stage disease,[42] micropapillary urothelial carcinoma remains the variant where the prognostic implications are more clearly defined and where therapeutic, and, recently, molecular considerations are most salient. The ICUD noted that there is not a firm criterion for the proportion of micropapillary histology required to designate a case as micropapillary; series have studied cases ranging from focal to almost pure micropapillary histology.[66,67] There are indications that the extent of micropapillary differentiation is prognostically significant, with the proportion of micropapillary morphology identified on transurethral resection shown to predict stage,[68] disease-specific survival,[66] or both.[69] For this reason, the general ICUD recommendation is to both report this variant morphology and estimate its proportion (as above).

These carcinomas were originally described as reminiscent of papillary serous adenocarcinomas of the ovary,[70] a differential diagnostic consideration which, along with micropapillary variant carcinomas of the breast and other sites, remains salient today. The morphology is described as slender, delicate filiform processes or small clusters of cells, generally without true fibrovascular cores (hence the ‘micro’), which appear tightly clustered in lacunar spaces arrayed in an infiltrative growth pattern[70] (Figure 9a). Particularly when this morphology is extensive, lymphovascular invasion is almost invariably present, showing a similar pattern of clustered micropapillae present within vascular spaces.[71] Proceeding from data that variants of urothelial carcinoma, including micropapillary, may be under[44] or over-recognized in the practice of surgical pathology and a desire to better characterize its diagnostic features, Sangoi *et al*[72] performed an interobserver reproducibility study of micropapillary urothelial carcinomas, sharing cases among a number of experts of the field. Although a number of features were identified as sensitive markers of micropapillary carcinoma, especially prominent retraction artifact, which may be seen in conventional urothelial carcinomas that do not meet criteria for the micropapillary variant (Figure 9b), the features that were identified as most specific to consensus micropapillary cases studied were the features of ‘multiple nests in the same lacuna’ (Figure 9c), ‘intracytoplasmic vacuolization,’ and related ‘epithelial ring forms’ (Figure 9d).[72] These features will be of use for prospective evaluation of clinical cases.

Lastly, the clinical significance of micropapillary urothelial carcinoma has evolved substantially in the past few years. Consistent with observations of predominant high-stage disease, including deep, extensive invasion and positive lymph nodes,[66–70] the recommendation for early cystectomy (rather than trial of intravesical therapy) has been advocated by some, even when muscle invasion has not been documented.[73] However, other groups have retrospectively reviewed their experience with micropapillary cases and noted locally advanced disease with nodal metastasis, even in cases without pre-cystectomy documentation of muscle invasion, suggesting consideration of neoadjuvant chemotherapy.[74] In contrast, other groups have questioned the need for aggressive management (by whatever means) particularly in cases showing a low percentage of micropapillary morphology, lack of associated CIS, and lack of muscle invasion.[68,75] There is far from a consensus regarding the clinical implications of diagnosis of micropapillary urothelial carcinoma and its most appropriate management algorithm. This variant should be approached with clear criteria and documentation of the percentage of micropapillary component (as with other morphologic variants), emphasis on careful communication with clinicians, and awareness

that implications may be significant, depending on institutional practices. Most promising for this disease, going forward, are recent molecular observations, which suggest a high prevalence of lesions involving *ERBB2*, the HER2 oncogene, which may be amplified[76,77] or mutated,[78] providing a therapeutically tractable target. Of note, *ERBB2* abnormalities in urothelial neoplasms are not limited to micropapillary carcinoma. In a recent integrative analysis of 97 high-grade invasive urothelial carcinomas, none of the five tumors harboring amplification exhibited any micropapillary histology.[79]

ICUD recommendation: urine cytology reporting

One final area where the ICUD consultation proceedings impact directly on practice in pathology concerns urine cytology. We recommend the reader to review the consultation's proceedings and related summaries for coverage of its recommendations for the role of cytology in screening and monitoring bladder cancer patients, as well as for commentary regarding the role for molecular assays in cytology.[2,3] The ICUD recommends a specific approach and terminology for reporting urine cytology results, which is summarized in Table 2. This approach, which is modeled after the Papanicolaou Society of Cytopathology Practice and Guidelines Task Force recommendations, provides a format that mimics the Bethesda 2001 System for reporting cervical cytology.[80] In particular, the recommendations emphasize inclusion within the diagnostic section of a statement documenting the anatomic site of origin of the urinary tract specimen (bladder, urethra, ureter, or renal pelvis), as well as a statement documenting the technique whereby the sample was obtained (voided urine, washings, brushings, etc). Finally, the recommendation is made to employ a comment section, which could be used at the discretion of the cytopathologist, to list additional findings or to clarify any findings listed in the diagnostic categories.

The ICUD proceedings specifically addressed issues regarding several of the recommended diagnostic terms. In particular, in the group of diagnoses related to epithelial cell abnormalities, the relationship of the diagnostic categories *atypical urothelial cells* and *low-grade urothelial carcinoma* was addressed. The consultation clarified that because of the lack of specific criteria for identification of low-grade urothelial carcinoma, most such cases would be included within the *atypical urothelial cells* group. Additionally, as regards the *atypical urothelial cells* diagnostic category, the ICUD acknowledged that there remains a lack of consensus as to what criteria are appropriate to define inclusion in this category. Despite this lack of clarity, the consultation noted that recent reports suggest that this category may be substratified into two classes, implying differential acuity of follow-up. These two subclasses are *atypical urothelial cells of undetermined significance*, the implication being to follow with repeat urine cytology, as compared with *atypical urothelial cells, cannot rule out high-grade carcinoma* or *atypical urothelial cells, favor neoplasm*, which imply the need for endoscopic evaluation.[81,82]

Subsequent to the published ICUD proceedings, the International Academy of Cytology (IAC) in its 2013 congress in Paris proposed new consensus guidelines for urologic cytology samples, which includes reporting urinary cytopathology. These guidelines will be known as 'The Paris System for Reporting Urinary Cytopathology' and will be published in 2016.

Conclusion

The Second International Consultation on Bladder Cancer, conducted nearly 10 years since the first consultation and the WHO Blue Book update in 2004[10] represents a body of work and consensus, developed over a decade, the summary of which is provided here (Summary Box 1), available online, and in other summaries. We recommend that surgical pathologists in practice avail themselves not only to the review of the state of the art of bladder cancer pathology provided in the document, but also to reviews and recommendations regarding screening and surveillance protocols, molecular biomarkers, stage-specific clinical guidelines, chemotherapy, and non-urothelial bladder cancers. The entire consultation text is available as a downloadable document file at no cost, providing a comprehensive textbook of the disease. Given the ICUD's stressing evidence-based recommendations, areas where evidence or consensus is *lacking* are noted and represent opportunities for future clinical and translational investigation.

Finally, it bears consideration that the updated WHO 'Blue Book' classification of the pathology of tumors of urinary system and male genital organs, including as it did in 2004 a classification of tumors of the bladder,[10] is rapidly approaching. As deliberations occur and result in a revised WHO monograph to be widely available within the next 2 years, the ICUD recommendations can provide an interim update for use in practice and for consideration for formal adoption.

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Summary Box 1: Key ICUD updates and recommendations

1. The grading system of choice for papillary and flat non-invasive urothelial neoplasia is the WHO (2004)/ISUP System.
2. Generally, invasive urothelial carcinoma should be graded as high-grade, irrespective of the depth of invasion. *Recognizing that this issue is not completely resolved, invasive tumors may be further graded as required by institutional or clinical trial protocols*.
3. The criteria used in the WHO/ISUP System can be extrapolated to inverted neoplasia, which are classified as *inverted papilloma; inverted PUNLMP; inverted urothelial carcinoma, low-grade, non-invasive; inverted urothelial carcinoma, high-grade, non-invasive; inverted urothelial carcinoma, high-grade, invasive*.
4. Diagnostic terminology for incipient papillary lesions not accurately classifiable per the current system seen in patients under surveillance include *dysplasia with early papillary formations and carcinoma in situ with early papillary formations*. Correlation with cystoscopic findings is a prerequisite.
5. Approach for neoplasms with grade heterogeneity:
   - **a.** Assign by highest grade component, as per the WHO/ISUP System.
   - **b.** In equivocal cases, consider key clinicopathologic data, including focality/multifocality, grade of prior diagnoses, size of lesions, frequency of recurrence, presence/absence of concurrent CIS, cytologic impressions; these parameters may help in deciding whether to ‘upgrade’ an equivocal lesion.
   - **c.** There is no established role for immuno-histochemical or molecular assays in this setting.
6. Variants of urothelial carcinoma not reviewed in the WHO 2004 include:
   - **a.** Large nested variant.
   - **b.** Urothelial carcinoma with small tubules.
   - **c.** Undifferentiated carcinoma with rhabdoid features.
   - **d.** Urothelial carcinoma with chordoid features.
7. Micropapillary urothelial carcinoma has received much attention for:
   - **a.** Refined criteria for increased diagnostic reproducibility; key features include ‘multiple nests in the same lacuna’ and ‘epithelial ring forms’

	b.	Clinical implications: controversy over role for early cystectomy.
	c.	Distinctive molecular features: ERBB2 mutation and amplification.
8.	Recommendation of diagnostic terminology for urine cytology:	
	a.	Document anatomic source/site of specimen in diagnosis.
	b.	Document technique used for sampling.
	c.	Recommended diagnostic terminology—See Table 2.

Summary Box 2: Major contributions of the WHO (2004)/ISUP System

1. Establishment of uniform terminology, definitions, and criteria for papillary neoplasia, removing ambiguity of the WHO 1973 system (eg, transitional cell carcinoma grade I-II, transitional cell carcinoma grade II-III)
2. Simplification of flat urothelial lesions with non-reactive atypia into dysplasia and CIS
3. Application of similar overall criteria, by analogy, between papillary and flat lesions, underpinning of the ICUD recommendation for use in inverted lesions
4. Creation of a category of tumor that identifies a tumor with a negligible risk of progression (PUNLMP), whereby patients avoid the label of carcinoma but are not given ‘benign’ diagnosis obviating follow-up
5. Identification of a clinically high risk group who are candidates for intravesical management (high-grade papillary urothelial carcinoma, urothelial CIS)
6. Identification of a larger group of patients, relative to WHO 1973 grade III, who are at increased risk for invasive disease and merit closer follow up
7. Overall stratification of bladder tumors into prognostically significant categories
8. The classification system has been widely accepted by the ICUD, UICC, AJCC, AFIP Fascicles, and American (CAP, ADASP) and European protocols.

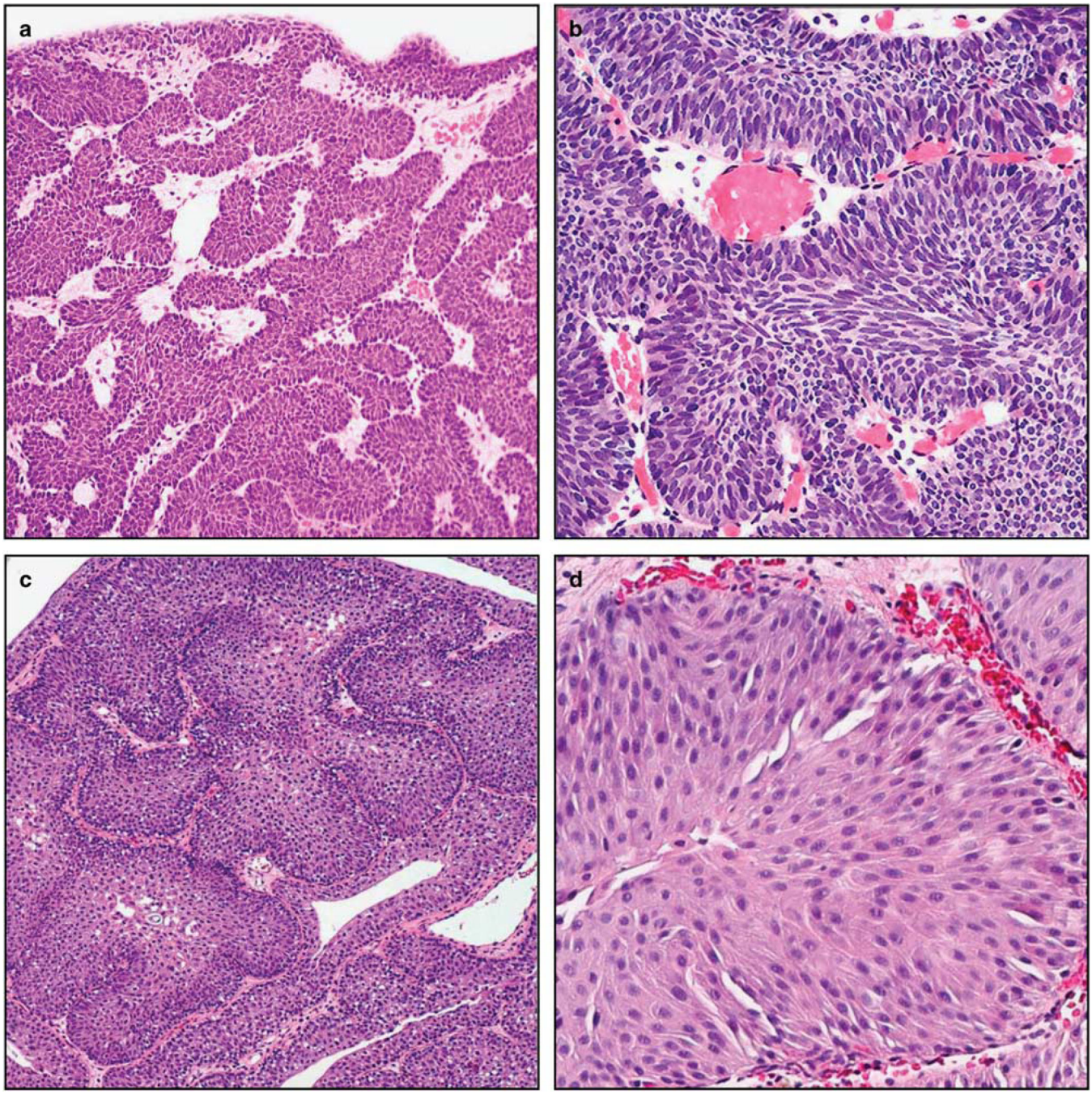

Figure 1.

Inverted papilloma and inverted papillary urothelial neoplasm of low malignant potential (PUNLMP). (**a**) An inverted urothelial papilloma shows endophytic growth of non-hyperplastic, non-atypical urothelium. (**b**) Often a suggestion of peripheral palisading is apparent, while the epithelium may frequently take on a bland, spindled appearance. (**c**) An inverted PUNLMP, similar to exophytic PUNLMP is composed of a hyperplastic (increased cells per unit area and/or increased thickness) urothelium growing in an endophytic pattern.

(**d**) By definition, PUNLMP demonstrates no more than mild atypia and rare mitoses within a urothelium with preserved polarity.

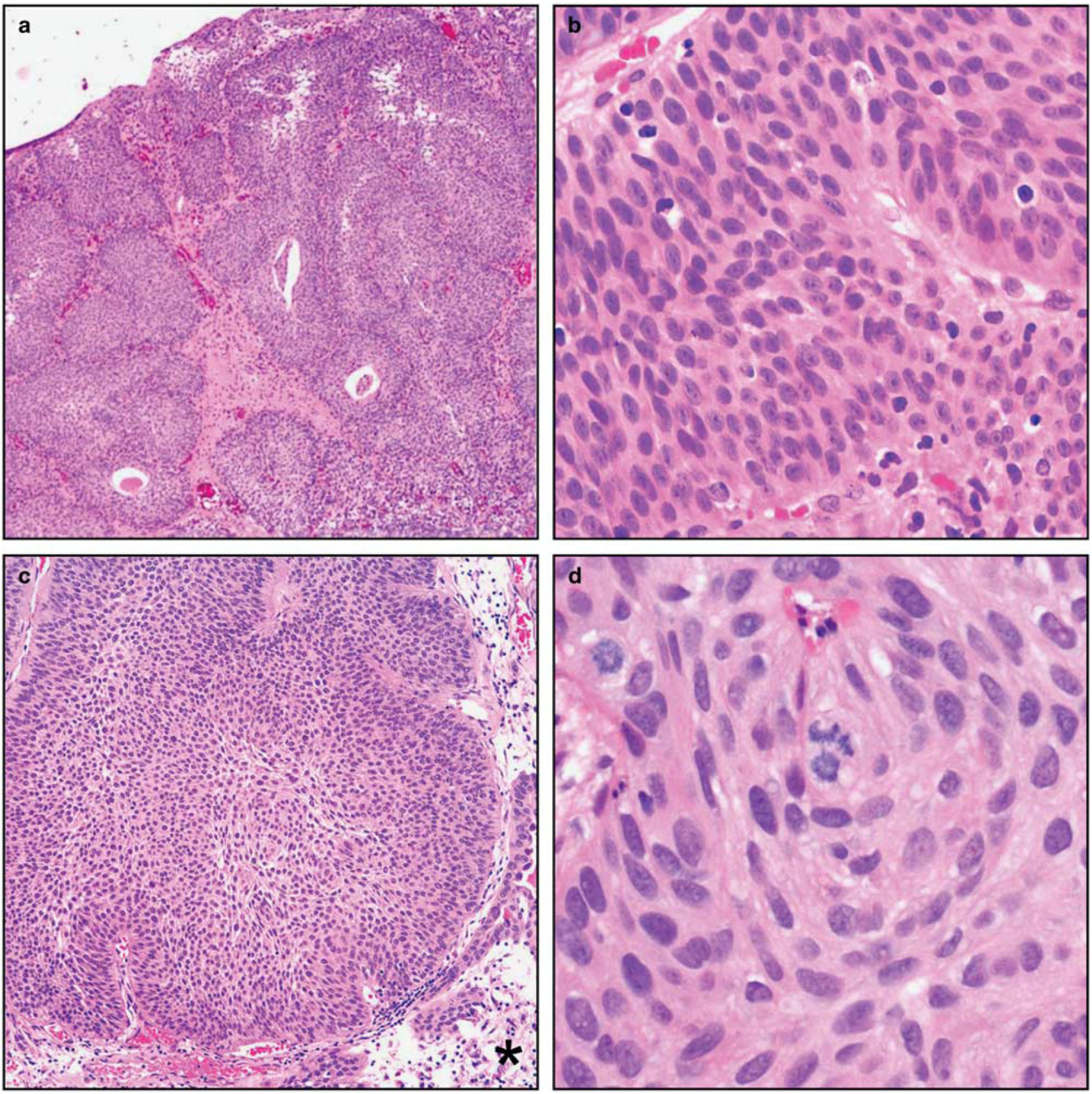

Figure 2.

Inverted papillary urothelial carcinoma, low-grade and high-grade. (**a**) Papillary urothelial carcinoma, low-grade, with predominant inverted growth shows a degree of cellularity and loss of polarity beyond that allowable in a PUNLMP. (**b**) Distinct, mild to moderate cytologic atypia is apparent. (**c**) Papillary urothelial carcinoma, high-grade, with predominant inverted growth shows even greater loss of order in the epithelium. This example showed foci of lamina propria invasion (asterisked), more extensive in adjacent fields, illustrated here to mainly contrast with the predominantly non-invasive component.

(**d**) Loss of polarization with respect to the basement membrane is increased, while greater nuclear atypia is apparent; an atypical mitosis is identified.

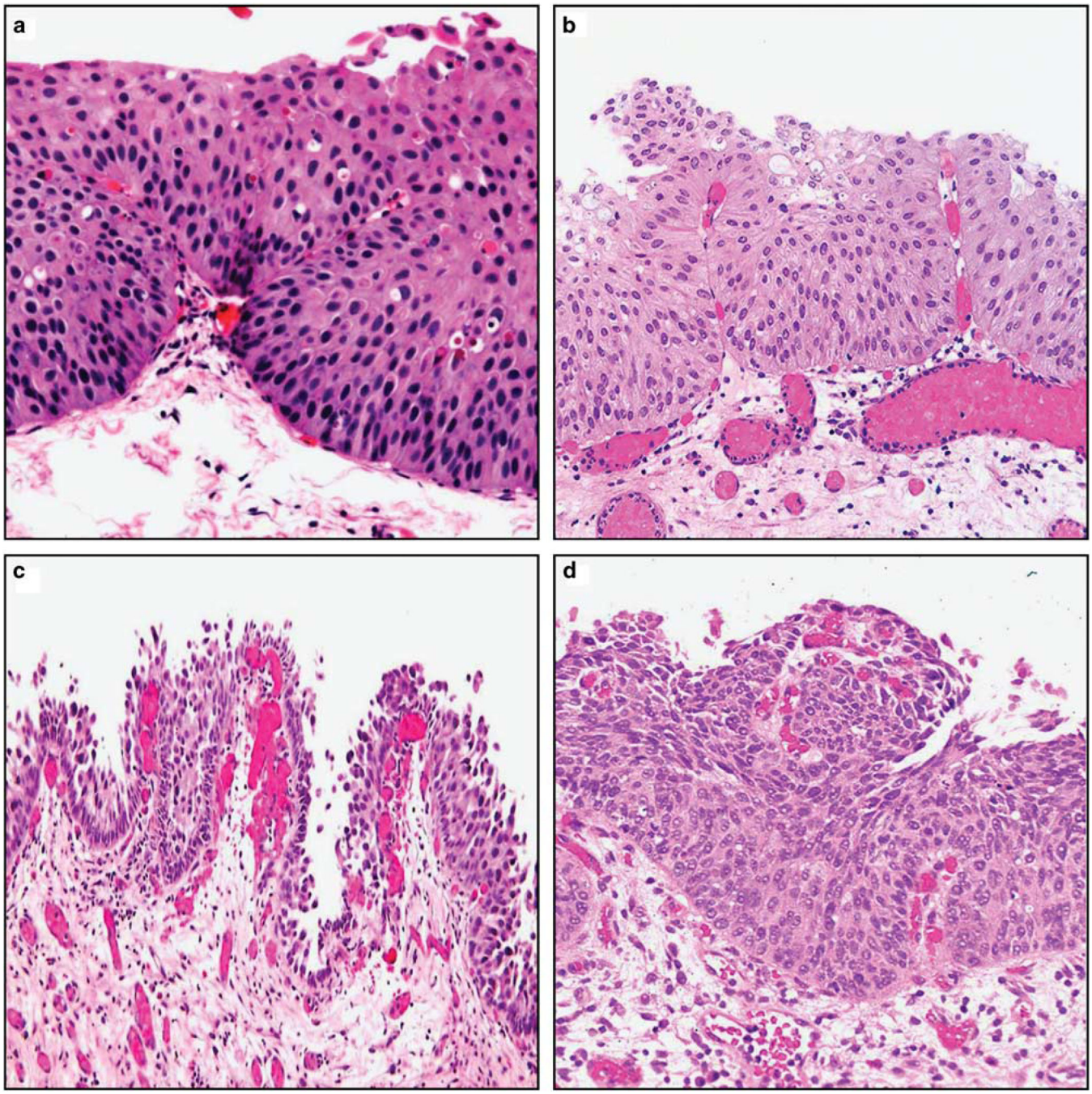

Figure 3.

Update on 'formes frustes' of papillary neoplasia. (**a** and **b**) Two examples of lesions that, if encountered in a biopsy of a patient under surveillance for papillary urothelial neoplasia, without a clinical impression of a papillary lesion may be termed '*urothelial dysplasia with early papillary formations*.' Correlation with cystoscopic impression is key, as a lesion such as (**b**) may be diagnosed outright as papillary carcinoma, low-grade if clinically documented as a tumor. (**c** and **d**) Two examples of lesions that, if encountered in a similar scenario would be termed '*urothelial carcinoma in situ with early papillary formations*'; the lesion in

(**d**) is better developed such that it may be considered sufficient to diagnose papillary urothelial carcinoma, high-grade, particularly if there is any endoscopic suspicion for a lesion. The ICUD notes that clinicopathologic correlation is essential to use these diagnostic terms.

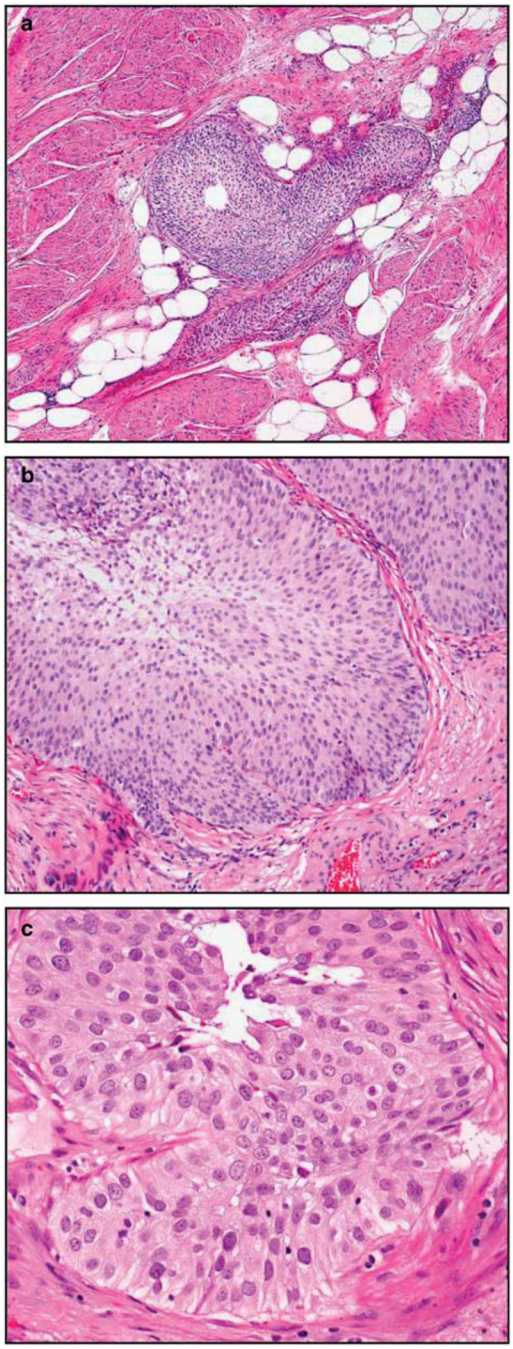

Figure 4.

(**a**) The large nested variant of urothelial carcinoma may be high stage, as illustrated by deep muscularis propria invasion. (**b**) Despite the aggressive growth pattern, a well-polarized epithelium is preserved. (**c**) Atypia is less than expected for invasive carcinoma and raises consideration of low-grade inverted neoplasia.

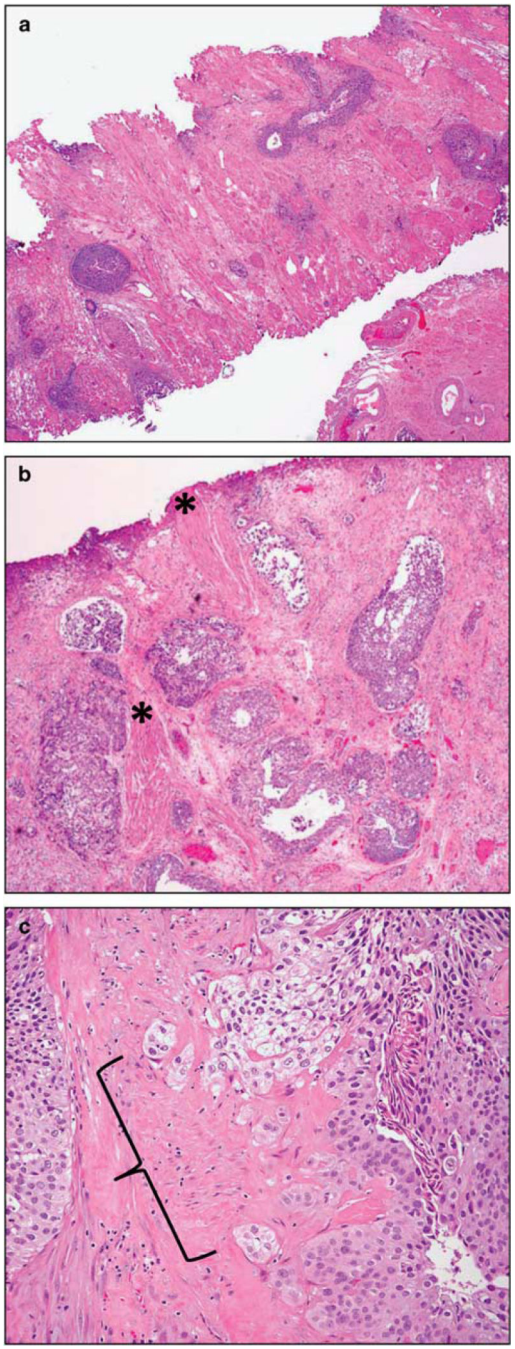

Figure 5.

Difficulties in diagnostic approach to large nested lesions. (**a**) This example of a muscularis propria invasive large nested urothelial carcinoma illustrates the diagnostic challenges, given cautery and crush artifacts and the low-grade appearance. If the lesions were not multifocally involving the muscularis propria, benign mimics such as urachal remnants or orifices of duplicated or tangentially sectioned ureters could be considered. (**b**) In another large nested case, the haphazard pattern of the nests is helpful in exclusion of benign anatomic or vestigial structures, as is their direct juxtaposition to large compact muscle

bundles of muscularis propria (asterisked). Noninvasive inverted neoplasms should not generally extend into the muscularis propria. (**c**) Observation of a focus of conventional-type invasion (bracketed), consisting of irregularly sized and shaped invasive cell clusters, can be very helpful to exclude a non-invasive inverted neoplasm.

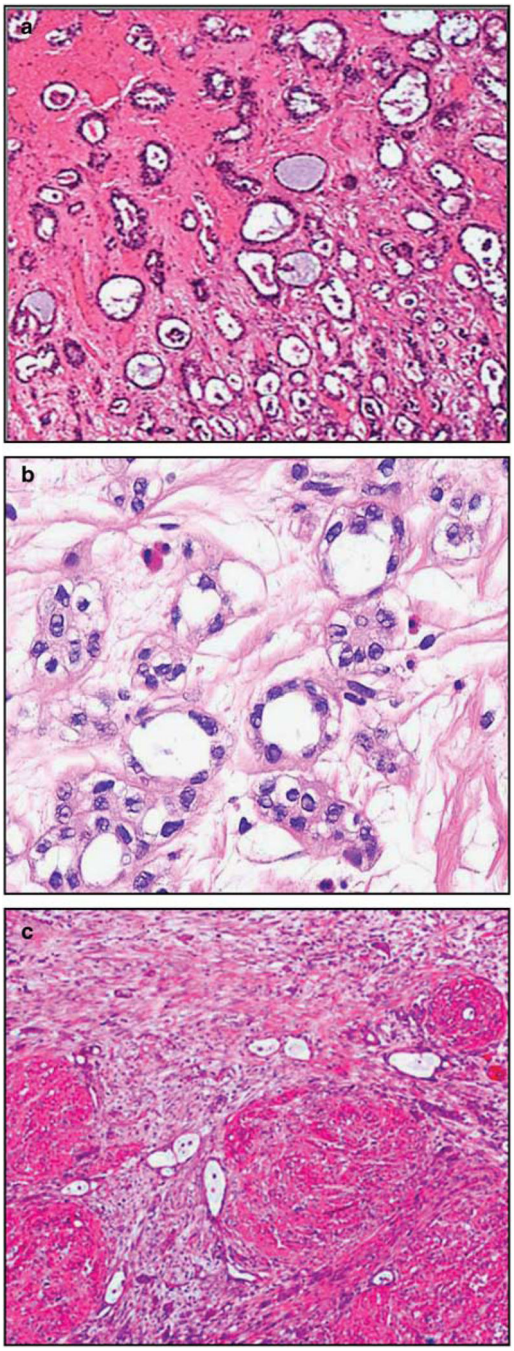

Figure 6.

(**a**) Urothelial carcinoma with small tubules presents an infiltrative pattern of variably sized small tubules. (**b**) The epithelium lining the tubules is frequently attenuated, prompting consideration of nephrogenic adenoma or other processes. (**c**) These lesions may be deeply invasive of muscularis propria despite the low-grade appearance.

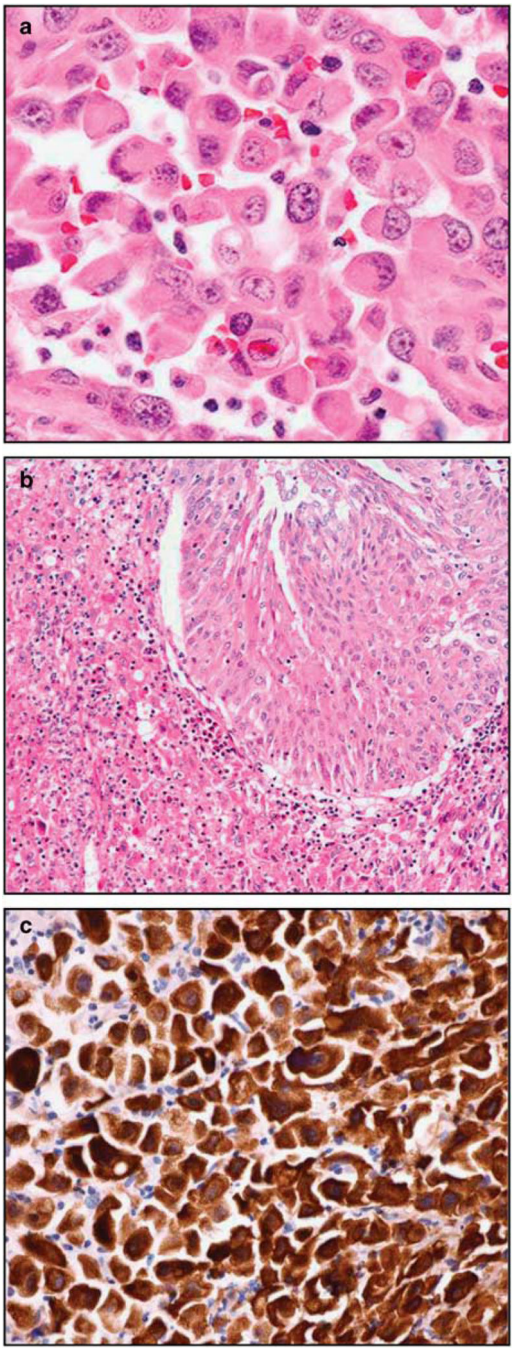

Figure 7.

(**a**) Urothelial carcinoma with rhabdoid features is a pattern on the spectrum of poorly differentiated to undifferentiated urothelial carcinoma showing ‘rhabdoid’ morphology of discohe-sive cells with eccentric nuclei with prominent nucleoli and inclusion-like eosinophilic cytoplasmic inclusions. (**b**) Identification of a recognizable conventional urothelial carcinoma is helpful. (**c**) Expression of the urothelial carcinoma-associated marker, S100P, was diffuse, as were uroplakin II and GATA3 in this case.

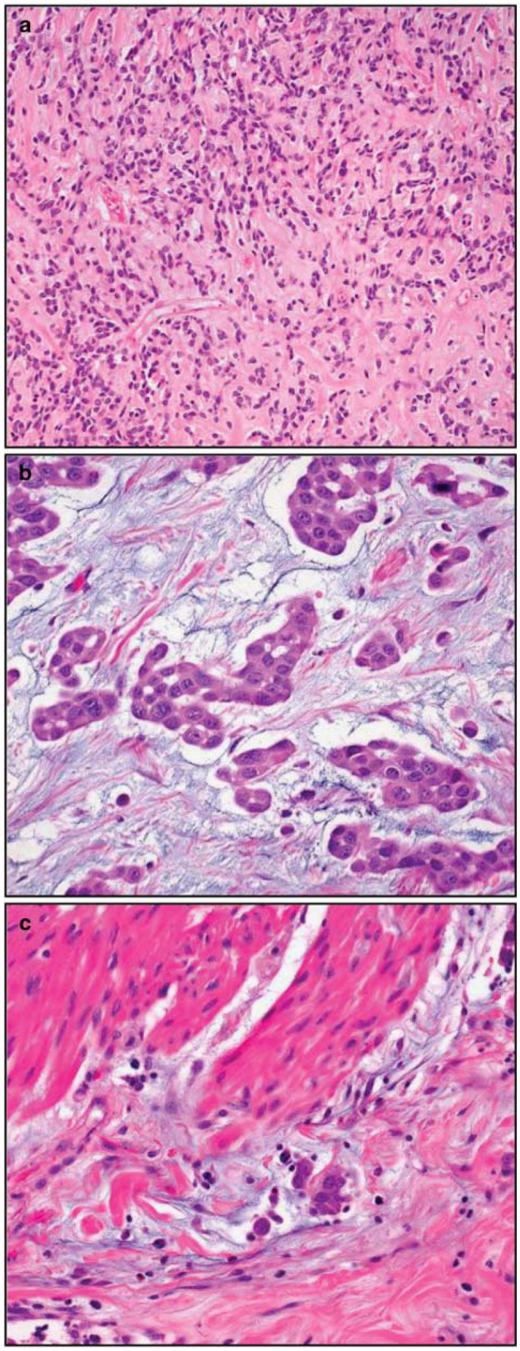

Figure 8.

(**a**) Urothelial carcinoma with chordoid features shows cords to reticular growth of epithelial cells in a myxoid stroma evocative of extraskeletal myxoid chondrosarcoma. (**b**) Another case shows clustered cells in abundant myxoid stroma. (**c**) These cases often present with high stage.

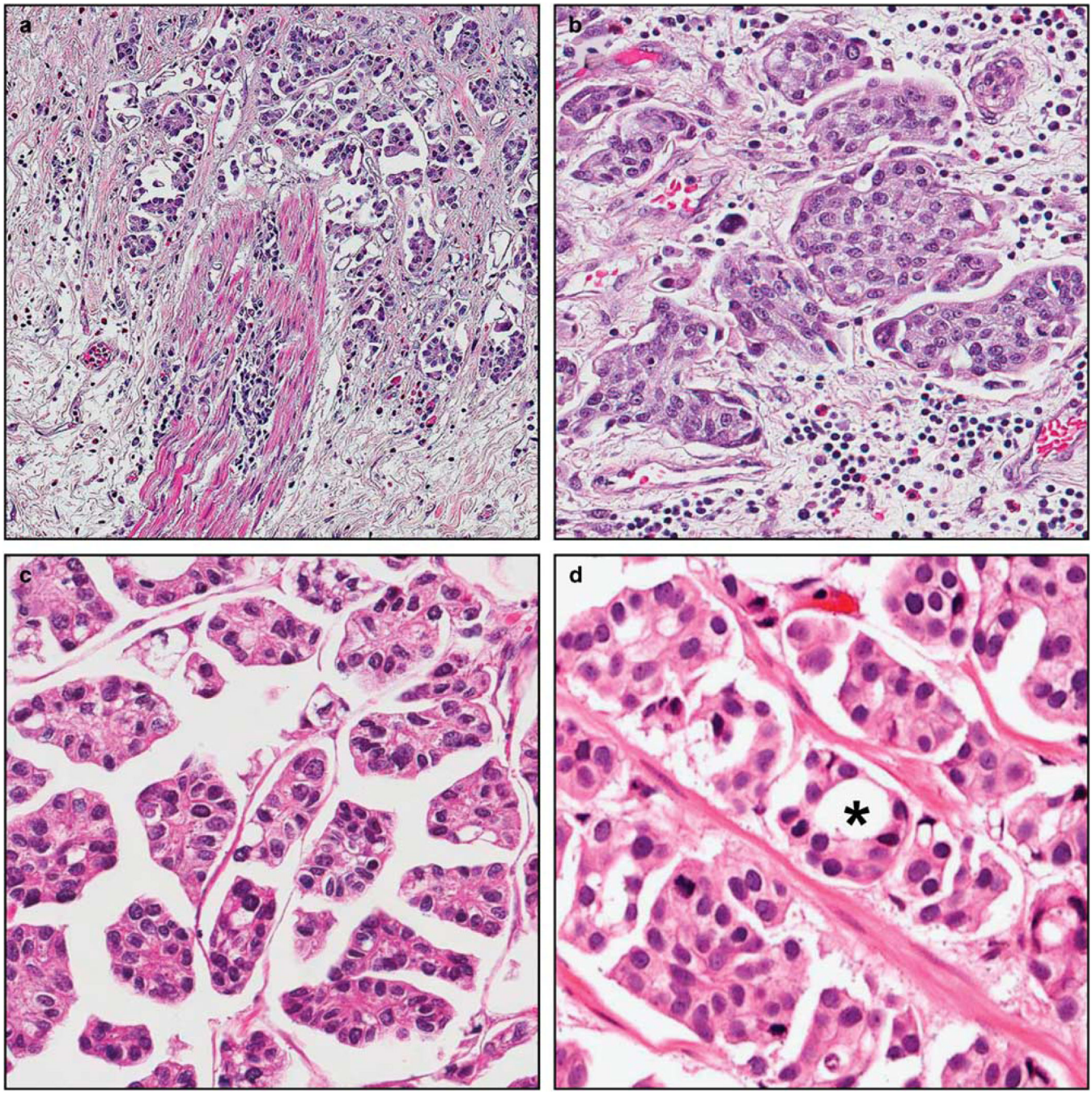

Figure 9.

Update on features of micropapillary urothelial carcinoma. (**a**) Micropapillary urothelial carcinoma with invasion of the muscularis propria. (**b**) Prominent retraction artifact, apparent in this conventional urothelial carcinoma, may simulate micropapillary carcinoma. (**c**) Two specific features of micropapillary urothelial carcinoma illustrated here are ‘multiple nests in the same lacuna’ and ‘inverse polarization’ of the epithelium with peripherally

oriented nuclei. (**d**) ‘Epithelial ring forms,’ asterisked at center, are another highly specific feature helpful in diagnosis.

Table 1

Analogy for application of WHO/ISUP system to inverted neoplasia

Degree of atypia	Exophytic papillary lesions	Flat lesions	Endophytic/inverted papillary lesions[a]
None	Papilloma	Normal	Inverted papilloma
Minimal	PUNLMP[b]	Urothelial hyperplasia	Inverted PUNLMP[b]
Distinct, mild-moderate	Papillary urothelial carcinoma, low-grade, non-invasive	Urothelial dysplasia	Inverted papillary urothelial carcinoma, low-grade, non-invasive
Moderate-severe	Papillary urothelial carcinoma, high-grade, non-invasive	Urothelial CIS	Inverted papillary urothelial carcinoma, high-grade, non-invasive
Severe	Papillary urothelial carcinoma, high-grade, invasive	Urothelial carcinoma, high-grade, invasive	Inverted papillary urothelial carcinoma, high-grade, invasive

[a] Inverted lesions may show areas with both exophytic and endophytic growth, but should be at least predominantly inverted to be designated as such.

[b] Papillary urothelial neoplasm of low malignant potential.

Table 2

ICUD recommended format and nomenclature for urine cytology

I.	*Adequacy statement (optional)*	
		Satisfactory for evaluation
		List any quality factors affecting specimen
		Unsatisfactory for evaluation (give reason)
II.	*General categorization*	
		Negative for epithelial cell abnormality (see Descriptive diagnoses)
		Epithelial cell abnormality present (see Descriptive diagnosis)
III.	*Descriptive diagnosis*	
		Negative for epithelial cell abnormality
		Infectious agents
		Bacterial organisms
		Fungal organisms
		Viral changes (CMV, herpes, adenovirus, polyomavirus)
		Nonspecific inflammatory changes
		Acute inflammation
		Chronic inflammation
		Changes consistent with xanthogranulomatous pyelonephritis
		Cellular changes associated with:
		Chemotherapeutic agents
		Radiation
		Epithelial Cell Abnormalities
		Atypical urothelial cells (*see comment)
		Low-grade urothelial carcinoma
		High-grade urothelial carcinoma (invasive carcinoma vs carcinoma in situ)
		Squamous cell carcinoma
		Adenocarcinoma
		Other malignant neoplasms (specify type)
IV.	Other—Any molecular findings	
V.	Comment—Use at cytopathologist discretion to report or clarify other findings	