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TOPIC PAPER

SIU–ICUD on bladder cancer: pathology

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Abstract
Many changes have been made during these last years and concepts for understanding bladder cancer have evolved. We make an update with the latest findings of the WHO (World Health Organistaion) 2016, ICCR (International Collaboration on Cancer Reporting) and other official organisms and try to show the latest developments. In this document we provide new consensus guidelines and insights. We kept this document short and concise providing consensus guidelines to clinicians for the best patient care, it should be easy to understand for a non pathologists. We focussed on several burning issues, such as the anatomical and histological understanding of the bladder wall, the prognostic significance of grading and the most challenging problems in staging, we underline our needs from the clinicians such as clinical information, we further discuss the histological subtypes of bladder cancer, which is an extremely important issue in the light of molecular classifications and give prognostic insights. Furthermore, we discuss the ICCR worldwide consensus reporting, urinary cytology with the Paris system and several issues such as frozen section specimen.

Keywords Pathology · Stage · Grade · Histology

Introduction

Advancing insights in pathology and molecular-genetic basis of bladder cancer have led to a number of changes in pathology reporting. We provide an update on the latest changes and new concepts of the 2016 WHO (World Health Organization) classification of bladder cancer. Furthermore, we refer to the ICCR (International Collaboration on Cancer Reporting; www.ICCR-cancer.org) founded to produce internationally standardized and evidence-based datasets for the pathology reporting of cancer, and to consensus meetings organised by the ISUP (International Society of Uro Pathology) (Table 1).

An optimal pathology diagnosis of bladder cancer requires relevant information to be provided by the clinician [1, 2]. This includes previous disease of the urogenital

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Table 1 Required and recommended items in a pathology report according to the ICCR (www.ICCR-cancer.org)

Item	Recommended	Required
Clinical information	✓	✓
Specimen site	–	✓
Additional specimens submitted	–	✓
Operative procedure	–	+
Bloc identification key	✓ (TURB)	✓
Histological tumor type	–	✓
Presence of invasive carcinoma	–	✓
Associated epithelial lesions (depends on operative procedure)	✓	✓
Histological grade	–	✓
Extent of invasion	–	✓
Macroscopic extent of invasion	–	✓
Microscopic extent of invasion	–	✓
Tumor focality	✓	–
Substaging T1 disease	✓	–
Lymphovascular invasion	–	✓
Only for cystectomies		
Response to neoadjuvant therapy	–	✓
Margin status	–	✓
Lymph node status	–	✓
Histologically confirmed metastasis	–	✓
Coexistent pathology	✓	–
Histological staging (if applicable)	✓	–

tract, prior intravesical, radiation or surgical treatments and chemotherapy, the gross presentation, the site of the tumor and the technique used for procuring the specimens.

Gross handling of bladder tissue specimens

With regards to the gross handling, no standard protocol exists how much material/samples should be taken neither in TURB nor in cystectomies, biopsy are completely included. Monobloc resections allow a better overview of the whole specimen [3]. The gross handling of lymph node (LN) dissections, the best method for staging the LN status is not standardised either. Counting inguinal LN is a difficult issue in uropathology. Concepts like the "lymph node density" are surgery dependent, but metastatic LN invasion is obvious in gross findings. Nodal cancer volume, the size of the largest metastatic tumor deposit and extranodal extension play a role for the prognosis [4]. Routine reporting on the LN metastatic size and extranodal extension are recommended by the ICCR.

Fresh Frozen intraoperative examination of histologic specimens for urinary bladder is relatively rare and only exceptionally indicated, especially when constructing a neobladder [5].

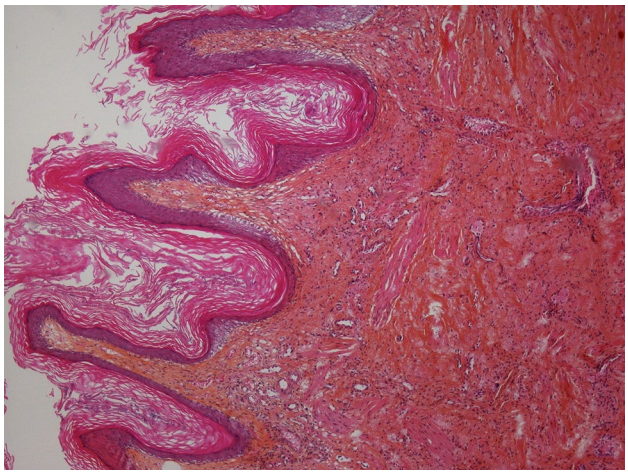

Fig. 1 Keratinising metaplasia, keratin on top of the lesion. The urothelium is replaced by a squamous metaplasia without atypia

Topography

The composition of the urinary bladder wall differs by topographic region. These regional histoanatomic differences can have an impact on the pathological staging and prognosis of UC. The muscularis mucosae (MM) layer in the lamina propria, considered a landmark proposed for one of the pT1 substaging systems is often not discernable at the trigone [2]. The detrusor muscle also displays several differences, e.g., in the trigonal region where the ureters are inserted. These variations in size and location of muscularis propria may compound the pathological stage assignment at these sites. Some data suggest that tumors in the trigone and bladder neck have greater risk for progression [6]. Involvement of prostatic urethra, bladder neck, trigone and posterior wall were significantly related to a shorter recurrence-free interval [7]. Similarly, cancers at the trigone showed a higher risk for lymph node metastasis and decreased cancer-specific survival [7].

Flat lesions of the bladder mucosa

Urothelial denudation may be caused by instrumentation and intravesical therapy, but carcinoma in situ (*Cis*), can also lead to extensive denudation. Abundant vascularization of a denuded area should at least evoke the thought of a possible *Cis* or a high-grade lesion and must be reported [8]. Concurrent urine cytology is very helpful, since a positive urine cytology further supports the diagnosis of *Cis* in spite of negative histology [7].

Squamous metaplasia is a common finding without clinical significance, but keratinizing squamous metaplasia is considered as a precancerous lesion and must, therefore, be reported as such (Fig. 1). Glandular metaplasia might

be seen as a response to chronic irritation or inflammation, such as neurogenic overactive bladder, bladder extrophy, long-term catheterization or history of calculi, data on the value of as a precancerous lesion are discordant. Nephrogenic metaplasia is a benign lesion, seen in bladder walls with history of injuries, e.g., by previous urological instrumentation [9].

Urothelial proliferation of unknown malignant potential (previously flat urothelial hyperplasia) is considered when the urothelium is thickened (> 7 layers), without cytologic atypia. The lesion might surround LG (low grade) pTa tumors. Since reactive and neoplastic hyperplasia cannot be distinguished by morphology criteria alone its terminology was changed by the WHO 2016 [9].

Flat lesions with atypia such as reactive atypia (RA), are seen in an inflammatory context and the clinical history usually helps to diagnose these lesions and not to misdiagnose as *Cis*.

Urothelial atypia with unknown significance is not a very well defined term and this diagnosis should only rarely be made. Urologists must be aware that this diagnosis requires prompt treatment and new biopsies to allow a final diagnosis. Therapy associated reactive atypia such as reactive atypia are commonly seen and should not be mistaken as *Cis* [9]. The microscopic changes, especially after radiation can be very misleading and even result in a misdiagnosis of invasive carcinoma. Radiation cystitis might persist for years after therapy [10].

Dysplasia is defined by presence of cytonuclear and architectural abnormalities that fall short of a diagnosis of *Cis* with as main differential diagnoses reactive atypia and *Cis*. Immunohistochemistry can help solving this issue in some cases. Urologists generally do not treat patients with isolated dysplasia [11].

Carcinoma in situ is defined as a flat non-invasive lesion with marked atypia, and therefore, considered as a HG (high grade) lesion (Fig. 2). Different histological patterns of *Cis* exist without need to subclassify, because they do not make any difference in clinical follow-up. Diagnosis of isolated *Cis* is rare and generally associated with positive urine cytology. *Cis* of urethra may extend into underlying prostate ducts and acini, and *Cis* of the renal upper urinary tract may propagate into renal collecting ducts; both extensions must be considered as *Cis*. Development of true invasion with worse prognosis is seen in 20–30% of patients with primary isolated *Cis* [12, 13]. The ISUP recommends the use of a

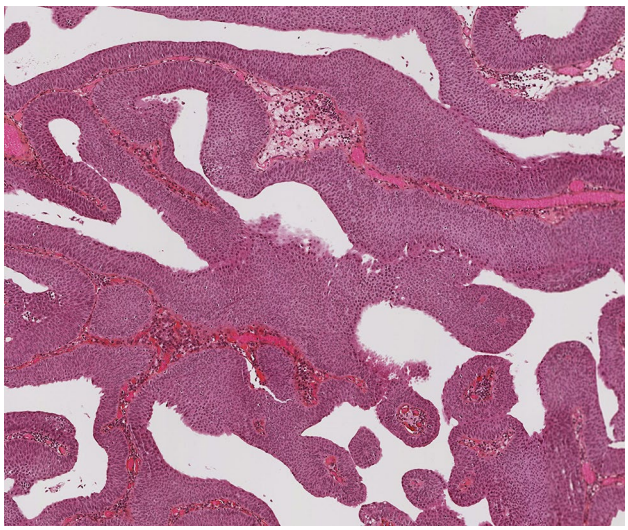

Fig. 3 Papillary urothelial neoplasm of low malignant potential. The criteria for diagnosis are very strict, slender papillae without atypia are required

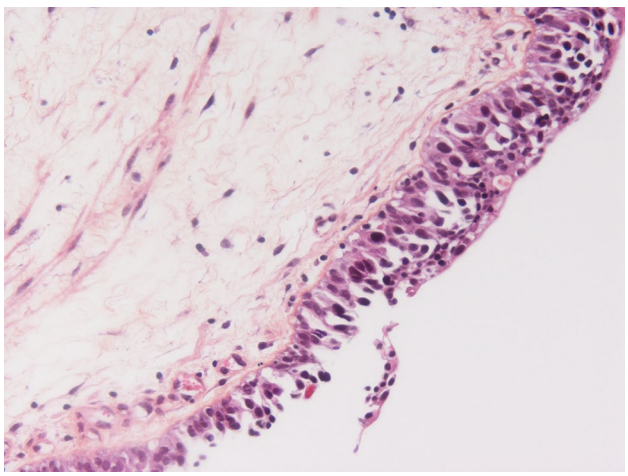

Fig. 2 Carcinoma in situ. The cells display discohesive features and discohesive atypia

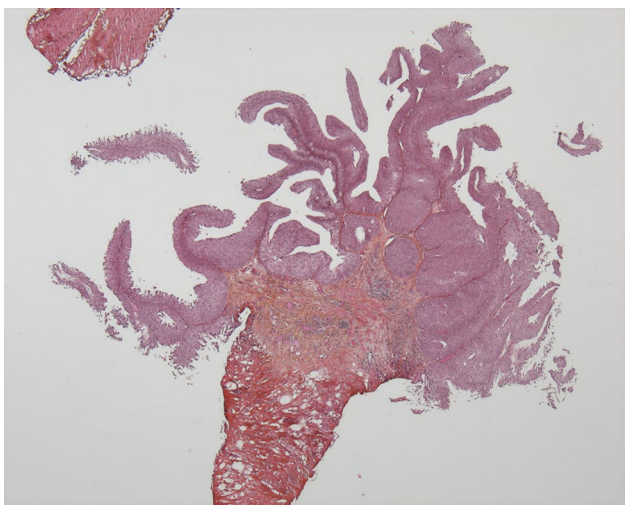

Fig. 4 pTa low-grade lesion of non invasive papillary urothelial carcinoma. Typical aspect of resection specimen

panel of markers such as CK 20, p53 protein, MIB-1 and CD44 in case of doubt [14].

Papillary bladder neoplasms

Urothelial papilloma is a benign papillary lesion lined by unremarkable urothelium of normal thickness and often covered by hypertrophic vacuolated umbrella cells. Among the non-muscle invasive bladder cancers (NIMBC), the non-invasive (pTa) bladder neoplasms the categories papillary urothelial neoplasm of low malignant potential(PUNLMP) (Fig. 3), low grade (LG) (Fig. 4) and high grade (HG papillary UC must be distinguished according to the 2004 and 2016 WHO classification [9].

PUNLMP was adopted by the 2004 WHO, lacks the label of "cancer" and is more frequently present in younger patients. Cytological atypia is minimal, the prognosis is very good, with a low risk of recurrence and progression. Non-invasive papillary LG urothelial carcinoma is characterized by orderly arranged urothelium of increased thickness lining the papillary formations, and rare mitoses. Non-invasive papillary HG UC are characterized by a more disordered urothelial lining, more pronounced cytonuclear atypia and increased mitotic activity often in a suprabasal position. The spectrum of pleomorphism of HG UC can vary [9, 15].

Inverted urothelial neoplasms can have variable degrees of inverted or endophytic growth component, they should not involve the muscularis propria and do not display the typical features of invasion. Grading should be done in the same way as the other UC. These UC with inverted growth pattern must be distinguished from inverted papilloma, a distinct benign tumor with low-recurrence rate (< 2%) lacking an exophytic papillary component [16].

Grading of non-muscle invasive bladder cancer

With regards to the grading of UC, currently, two grading systems co-exist, the 1973 WHO and the 2004 WHO/ISUP grading system. Grading has a particularly strong clinical relevance for NMIBC. Current guidelines of the most influential urological societies [European Association of Urology (EAU), American Urological Association(AUA)] differ in their recommendation on grading of NMIBCs [1, 17]. The EAU recommends the pathology reporting of both the 1973 and 2004 WHO grading systems for NMIBC, whereas the AUA mentions that the WHO 2004 classification should be used. The EAU motivates its recommendation to use the 1973 and 2004 grading in parallel by pointing at the limited evidence that one of the systems would be superior to the other [1, 18].

The different components of 2004 WHO (1998 ISUP/WHO) grading system for urothelial neoplasms have been the subject of several clinic-pathological validation studies. Main criticism of the 1973 grading system was (1) lack of detailed grading criteria resulting in low inter-observer reproducibility, (2) predominance of absolute number of patients showing progression to muscle-invasive UC (MIBC) in the grade 2 category rather than the grade 3 category and (3) the attribution of the carcinoma label to the subset of bladder tumors (i.e., PUNLMP) considered at very low risk of progression [19]. The 2004 WHO grading system tried to address the lack of reproducibility among pathologists by 1) reducing the number of carcinoma categories to two grades, a LG and a HG category and 2) by specifying in more detail the various categories. It was thought that the 2004 WHO grading would result in a better correlation of histopathology and cytology.

The differing histopathological criteria of the 1973 and 2004 WHO classifications preclude a direct translation of one system into the other, requiring a pathology review, except for the extremes of the spectrum (1973 grades 1 and 3) (Fig. 5).

Low-grade papillary carcinoma represented the largest grade category by the 2004 WHO system which comprised 36–74% of the papillary tumors, and G2 (31–84%) the largest in the 1973 WHO system. HG NMIBC (2004 WHO) are more frequent than G3 (1973 WHO). More patients with NMIBC are now in the HG category as

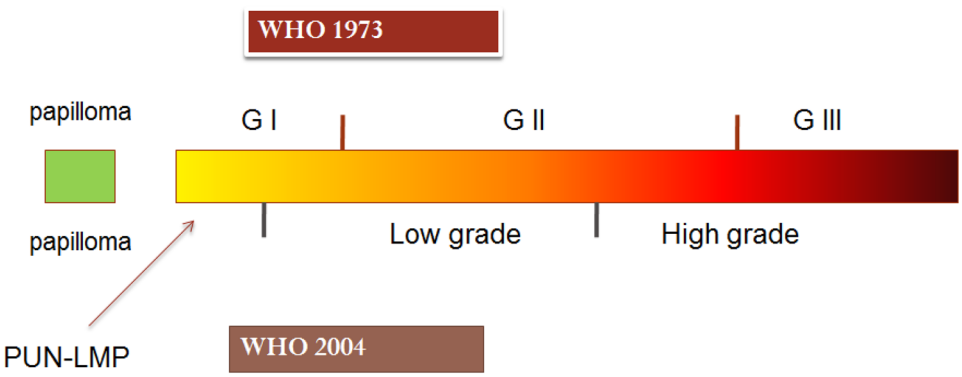

Fig. 5 Comparison of the WHO 1973 and WHO/ISUP 2004 grading system

compared to grade 3 (1973 WHO), resulting in more patients getting BCG treatment [20].

When looking at the literature, the distribution of NMIBC according to 2004 WHO/ISUP and 1973 WHO grading systems, the range for the WHO 2004 classification is from 36 to 74% for LG pTa and 4–64% of HG pTa tumors. PUNLMPs were found in 0–38%. The grade distribution of the WHO 1973 ranges from 9 to 58% G1, 31–84% G2 and 1–23% G3 pTa tumors [20].

Several studies compared the impact on disease outcome of the 2004 WHO system and the 1973 WHO system in cohorts of non-invasive (pTa) papillary urothelial neoplasms [21]. Some studies have shown a limited advantage for the 2004 WHO grading [22]. Other studies did not show a clear-cut advantage in terms of impact to outcome for the 2004 WHO system over the 1973 WHO grading system [23]. Separate analyses showed both 2004 WHO system and 1973 WHO system independently predicted progression ($p = 0.003$ and $p = 0.002$, respectively) together with tumor size. Based on their systematic literature review, Soukup et al. concluded that both grading systems predict progression and recurrence, although pathologists vary in their reporting [18].

Grading of T1 and T2 bladder cancer

To date, only three studies compared the prognostic value of the two grading systems for pT1 UCs [22, 24, 25]. Cao et al. noted no significant differences in recurrence-free survival, progression-free survival or overall survival between G2 and G3 pT1 tumors. The next two larger studies on 134 and 310 pT1 UC patients confirmed that LG pT1 carcinomas were very uncommon, reducing the 2004 WHO grading essentially to a single grade system. One study demonstrated that 1973 WHO approached significance as a prognosticator for progression to muscle-invasive carcinoma, whereas the other larger study demonstrated that the 1973 WHO grading was a prognosticator for disease-specific survival, with 10-year disease-specific survival of 96% for grade 2 and 78% for grade 3 pT1 UCs ($p < 0.001$) [22, 24, 25].

For muscle-invasive UCs the prognostic impact of grading of both grading systems is even more limited than in pT1 UCs. The WHO 2016 classification recognizes that the overwhelming majority of invasive UCs are high grade.

In terms of impact to disease outcome, both grading systems provide important prognostic information, with the 2004 WHO generally demonstrating essentially similar results as the 1973 WHO grading. Morphologic and/or molecular sub-categorization might help to refine the grading systems and improve reproducibility.

Inter-observer variation of grading

Most published observer variability studies show that both WHO grading systems suffer from substantial inter-observer agreement, with only moderate agreement [26].

Reasons for lack of reproducibility are the lack of clearly definable hallmarks, and maybe tumor heterogeneity.

Admixture of at least two different grades in papillary urothelial neoplasms is not uncommon, and is reported in 3%–43% of tumors [27, 28]. The WHO 2004/2016 classifications suggested to report the highest grade [29], but lack of consensus on whether to use a threshold of the percentage of HG cancer remains [8]. Some studies suggested a 5 or 10% minimum cut-off [23, 27]. An argument to report the presence of a minor (< 5%) HG component in an otherwise LGUC are distinct genetic abnormalities associated with aggressive cancer even in the LG component [28]. The lack of strong outcome data, precludes a strong recommendation regarding the reporting of 'mixed grade" NMIBC. A reasonable approach would be to perform grading based on the highest grade and communicate the HG percentage in the pathology report.

Sub staging of T1 and T2 bladder cancer

For a pathologist, the term 'invasive UC' indicates the presence of any tumor cells/nests beneath the urothelial basement membrane including invasion limited to the lamina propria (pT1). Confusingly, urologists use this term in their daily practice to refer to muscle invasive disease (pT2). pT1 tumors progress more frequently than their pTa counterparts, they tend to be more aggressive, and early cystectomy may even be considered for some pT1 tumors with high-risk features [30]. Assessment of invasion of the lamina propria can be challenging and is sample dependent [31]. The terminology of microinvasive cancer is now obsolete, with any tumors infiltrating the lamina propria considered as pT1.

HG carcinomas with invasion of the subepithelial tissue have different outcomes according to the depth of invasion, therefore, a subdivision of category T1 was advocated. Some studies divided pT1 into pT1a and b, based on the depth of invasion using the muscularis mucosal as landmark. pT1b tumors had a significantly worse recurrence–progression and cancer-specific survival [31, 32].

Other methods measuring the depth or diameter in mm, for instance micro-invasion (T1 m) as a single invasive focus < 0.5 mm and T1 extensive-invasive (T1e) as ≥ 0.5 mm have subsequently been advocated [33]. The 2016 WHO recommends substaging pT1 tumors without indicating which method. The ICCR group recommends to report either the diameter and extension or pT1a/b (staging according to the MM.

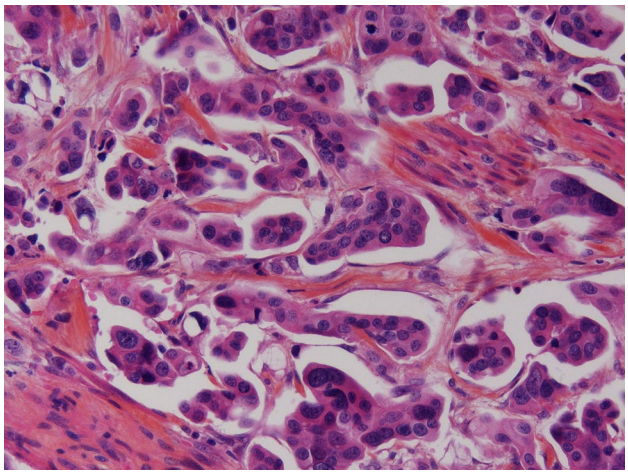

Fig. 6 Typical aspect of a micropapillary urothelial carcinoma. Retraction artifacts around the cancerous micropapillae

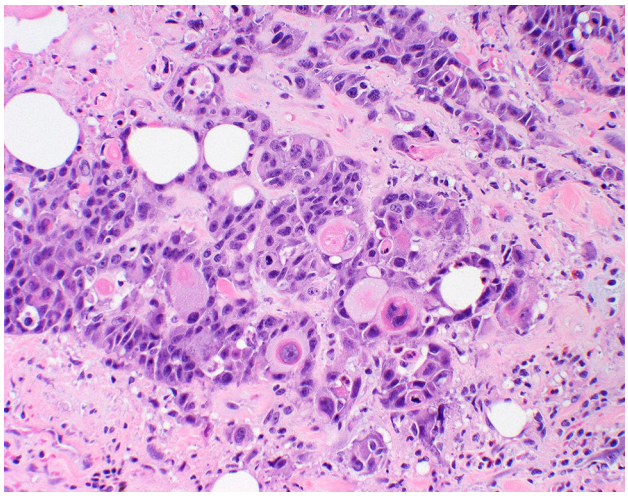

Fig. 7 Urothelial carcinoma with squamous differentiation, the atypia of tumor cells is important

In a recent study, uropathologists annotated lamina propria invasion on virtual slides in TURB specimens of problematic cases. A majority consensus in 72% of the 25 cases and a multi-rater kappa score of 0.47 was found [34].

In muscle invasive carcinomas and cystectomy staging is easier, but distinguishing pT2b and pT3a in tumors surrounded by a fibrotic or desmoplastic stroma without adipocytes is challenging [2]. Distinction of T2b and T3a has clinical significance [35].

Complementary prognostic factors are lymphovascular invasion (14.7–56% of invasive carcinomas have lymphovascular invasion) [36]. The criteria for the recognition of microvascular invasion must be as strict.

Variant histology

Variant histologies (VH) of UC represent a divergent differentiation of UC. Reporting VH is recommended because of prognostic and therapeutic implications. A recent paper including 779 patients could demonstrate that VH occur in approximatively 27.3% [37]. Micropapillary carcinoma (MPC) and squamous differentiation were the most frequent VH (Fig. 6). Poor agreement was reported for atypical MPC ($\kappa = 0.54$), although in their classical form an agreement of 93% was found [38]. Several VH are underreported, especially the lymphoepithelial, plasmacytoid and nested carcinomas [39].

UC with squamous cell differentiation seem to have a better outcome compared to MPC and nested variant carcinomas [40]. Some authors suggested in cT1N0M0 MPC an immediate cystectomy with a disease-specific survival of 100%, patients with delayed cystectomies display 45% of progression and 35% will be N + [41]. Some data suggest that the molecular basal type of UC which have morphologically squamous cell carcinomas (SCC) features may benefit from neoadjuvant chemotherapy [42]. Variants identified at one time in sampling may differ from those identified at another time point because of tumor heterogeneity. Recent molecular data support this notion. Whenever variant morphology is identified, the ICCR requires the reporting, including the percentage of each variant.

Emerging molecular evidence has identified relevant alterations in some variants and subtypes, although many of these findings have not yet modified routine clinical practice [43]. Precision medicine continues to evolve, deeper understanding of pathogenesis and disease outcomes in the setting of VH is needed to better define commonalities and differences to conventional UC.

UC with divergent differentiation are tumors with foci other tumor differentiation, they are the most common VH. These carcinomas are diagnosed as "UC with this/that/XY/ differentiation" and the percentage of the VH reported (Fig. 7). Behavior is similar to conventional UC. Five percent of bladder cancers represent pure SCC [9].

MPC, relatively well known (see above) occurs in up to 8% of UCs. MPC terminology should only be applied in the context of invasive disease, it is frequently admixed with conventional UC. No ancillary test is currently recommended for the diagnosis of MPC. Amplification and/or overexpression of *ERBB2* (*HER2*) occurs at a higher frequency in MPC than in conventional UC [44]. MPC often presents at a higher stage than conventional UC and may be associated with an increased risk of lymph node and distant metastasis [45].

Some variants such as the nested/large nested UC are problematic because of their bland features. Diagnosis may be delayed due to lack of overt malignant features,

especially in small biopsy samples [46]. In pT2 outcomes may be similar to conventional UC [9].

The plasmacytoid UC shows a clinical presentation with diffuse growth and peritoneal carcinomatosis [10]. The bladder is often diffusely involved. The signet ring component has newly been added in the WHO 2016 classification [9]. This carcinoma presents at an advanced stage and is commonly associated with diffuse bladder wall involvement, carcinomatosis, and positive surgical margins [14, 47–50].

Rare entities with < 3% incidence are the microcystic UC, which often presents at an advanced pathological stage [9], outcomes are similar to conventional UC. The lymphoepithelioma-like cells are admixed with a dense inflammation [9], in pure forms their outcome seems good. Others like the lipid-rich UC, giant-cell, clear cell, poorly differentiated and sarcomatoid UC all display poor outcome, especially in the sarcomatoïd variant metastatic spread is frequent [9].

Pure primary bladder adenocarcinoma is rare, various grading systems, have been employed [9]. Since these tumors commonly present with locally advanced disease, the clinical value of grading the tumor is questionable [9]. There are no reliable immunohistochemical markers to distinguish between primary adenocarcinoma or metastasis from an adenocarcinoma [9].

Neuroendocrine carcinoma (NEC) of the bladder occurs in pure form or mixed with other carcinoma types, most often UC [9]. Large and small cell variants exist, accounting for less than 10% of urinary UC, occurring at any age. NEC appear to behave aggressively with high metastatic potential and mostly fatal outcome, they often present at an advanced stage, with up to 94% of cases having muscularis propria invasion or extravesical extension. Metastasis at time of presentation are in regional lymph nodes, liver, bone, and lung. Mean survival ranges from 6 to 34.9 months, the 5-year survival rate ranges from 8 to 40%. If organ-confined the survival is better. Prognosis is influenced by disease extent at diagnosis, employment of chemotherapy and the patient's performance status [51].

In most cases of UC the diagnosis is readily accomplished based on the morphologic features. In some situations, immunohistochemistry may be helpful in determining the urothelial nature of a tumor, such as not specific morphology or if metastasis from another location is considered. In 2014 the ISUP published recommendations on the utility of immunohistochemistry in urinary bladder lesions [14]. With regard to markers for urothelial differentiation, the committee found that there is no ideal marker or established panel to confirm urothelial differentiation. On the basis of the differential diagnostic consideration, positivity for GATA3, CK20, p63, and either high-molecular weight CK (HMWCK) or CK5/6 is of value in proving urothelial differentiation in the appropriate morphologic and clinical context. With regard to the role of IHC in the distinction of reactive atypia from urothelial carcinoma in situ, the committee recommended that morphology remains the gold standard in this differential diagnosis and that, at best, the IHC panel of CK20/p53/CD44 has potential utility but is variably used and has limitations. The immunostaining pattern must be interpreted with strict morphologic correlation, because overreliance on IHC may be misleading, particularly in the post treatment setting. IHC has no role in the distinction of dysplasia versus carcinoma in situ and in the grading of papillary urothelial carcinoma. IHC may have a limited but distinct role in staging of bladder cancer. In a subset of cases, depending on the clinical and histologic context, broad-spectrum CKs (to identify early or obscured invasion) and desmin (distinction of muscle from desmoplasia and to highlight muscle contours for subclassification) may be helpful. In the workup of a spindle cell proliferation of the bladder and in limited specimens, we recommend an immunohistochemical panel of six markers including ALK1, SMA, desmin, CK (AE1/AE3), and p63 with either of HMWCK or CK5/6. Currently, there are no prognostic immunohistochemical or molecular studies that are recommended to be routinely performed on biopsy or resection specimens.

Considering the most important stains, briefly, Uroplakin II and III are the most specific marker of urothelial differentiation, but a lack of sensitivity and lose expression if poorly differentiated. GATA-3 is a highly sensitive marker of urothelial differentiation, being expressed in 80–100% of HGUCs. The major limiting factor is its lack of specificity. One of the most characteristic features of UC is the co-expression of CKs 7 and 20. Expression is grade dependent and in HGUC CK 7 is expressed more often. The lack of CK 20 expression is a feature of the so-called basal phenotype of UC. The basal cell phenotype have reduced GATA-3 and

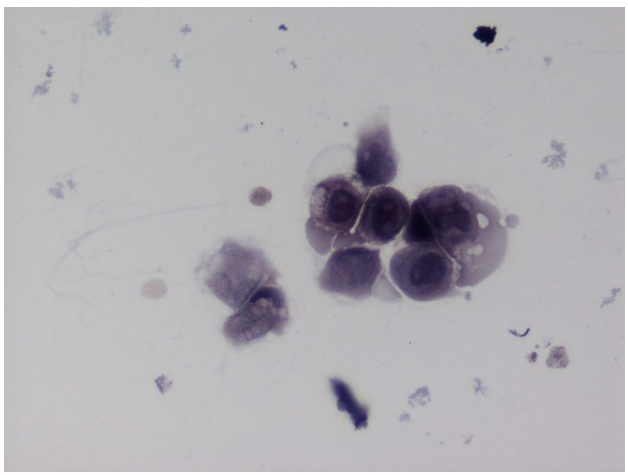

Fig. 8 Cytology of a high-grade urothelial carcinoma. Size of nuclei is > 0.7, chromatin and nuclear membrane irregular

uroplakin II expression. The p63 protein is highly sensitive and expressed in 81%–92% of UCs. With regard to VHs, the expression of the above markers has been similar in most variants as in usual UC. In areas of squamous or glandular differentiation, expression of immunomarkers will vary according to the phenotype [14].

Urine cytology Paris system

The College of American Pathologists encouraged the use of standardization terminology in the reporting of urine cytology, which led to the Paris System (PS) [52]. Urine cytology is a simple, noninvasive and inexpensive tool in the diagnosis and follow-up of patients with HGUC (Fig. 8). A negative cytology result and normal cystoscopy is quite specific and reassuring as for the absence of a high-grade lesion. A positive result accompanied by a negative cystoscopy or biopsy is usually an indication for a more aggressive follow-up and repeat biopsy with the potential evaluation of the upper urinary tract.

Urine cytology has high specificity for HGUC, but the clinical relevance of non-definitive cytological diagnoses such as 'atypical urothelial cells (AUC)' remained ambiguous [53]. The PS provides a needed uniformity in the terminology and criteria used for urine cytology reporting.

The diagnostic categories are: 1—nondiagnostic/unsatisfactory, 2—negative for HGUC (NHGUC), 3—Atypical Urothelial Cells (AUC), 4—suspicious for HGUC (SHGUC), 5—HGUC, 6—low-grade urothelial neoplasm (LGUN) and 7—secondary malignancies [52].

The NHGUC category was designed to include the majority of cases, including cells with minimal atypia due to urolithiasis, infection, chemotherapy, radiation, UCG treatment, or polyoma (BK virus) infection. The other categories are based on well-defined criteria, such as increased nuclear–cytoplasmic ratio (> 0.5), severe hyperchromasia, with either irregular nuclear membranes, clumpy chromatin pattern or both. The aim of the PS was to minimize the rate of AUC diagnoses and to transform this category into a standardized, reproducible and clinically meaningful category [53]. FISH examination can still be employed in difficult cases, nevertheless with the robust PS provides good definitions and decreases the necessity of ancillary testing.

ICCR standardized reporting

The ICCR with the aim of standardized reporting, produces common, internationally validated and evidence-based pathology datasets for cancer reporting. Standardization of pathology reports is an essential step in the process of improving patient care. The main goal was to produce internationally standardized and evidence-based datasets for the pathology reporting of cancer to improve cancer patient outcomes worldwide and to advance international benchmarking in cancer management. The website has important advantages such as a bookmarked guide and a hyperlinked guide, with explanatory texts on requested elements.

Conclusion

The WHO 2016 has introduced several changes which we tried to report to update knowledge about pathology. We also introduce standardised reporting published by the ICCR and explained the latest concepts of grading and staging.

Author contributions Protocol/project development: EC. Data collection or management: EC, MB, FA, MA, FB, DG, DH, OH, BM, VR, TK. Data analysis EC, MB, FA, MA, FB, DG, DH, OH, BM, VR, TK. Manuscript writing/editing EC, MB, FA, MA, FB, DG, DH, OH, BM, VR, TK/editing EC, MB, TK.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Research involving human participants and/or animals None.

Informed consent All co-authors have had and read the last version of the paper and agreed on it.

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