



Review

The 2022 revision of the World Health Organization classification of tumors of the urinary system and male genital organs: advances and challenges[☆]

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Summary The fifth edition of the World Health Organization (WHO) classification of urinary and male genital organ tumors has been recently published in 2022. The application of molecular profiling has made a substantial impact on the classification of urologic tumors. The new WHO classification introduces a group of molecularly well-defined renal tumor subtypes. The significant changes include addition of a category of “other oncocytic tumors” with oncocytoma/chromophobe renal cell carcinoma (chRCC)-like features, elimination of the subcategorization of type 1/2 papillary RCC, and inclusion of eosinophilic solid and cystic RCC as an independent tumor entity. The WHO/ISUP grading now has been recommended for all RCCs. Major nomenclature changes include replacement of histologic “variants” by “subtypes,” “clear cell papillary renal cell carcinoma” to “clear cell renal cell tumor,” “TCEB1-mutated RCC” to “ELOC-mutated RCC,” “hereditary leiomyomatosis and renal cell carcinoma” to “fumarate hydratase-deficient RCC,” “RCC-Unclassified” to “RCC-NOS,” “primitive neuroectodermal tumor” to “embryonic neuroectodermal tumor,” “testicular carcinoid” to “testicular neuroendocrine tumor,” and “basal cell carcinoma of the prostate” to “adenoid-cystic (basal-cell) carcinoma of the prostate.” Metastatic, hematolymphoid, mesenchymal, melanocytic, soft tissue, and

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neuroendocrine tumors are collectively discussed in separate chapters. It has been suggested that the morphological classification of urothelial cancer be replaced with a new molecular taxonomic classification system.

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1. Introduction

Tumor classification is always a dynamic process, with continuous addition of significant new knowledge integrating novel molecular genomic discoveries and morphologic reappraisal of each disease entity. The fifth edition of the World Health Organization (WHO) classification of urinary and male genital organ tumors has been recently published in 2022 [1]. Building on the fourth edition published in 2016, there have been significant advances and emphasis on molecularly defined tumor entities as well as genetic tumor syndromes (Box 1). The application of molecular profiling has made a substantial impact on tumor classification, especially observed in renal cell carcinomas (RCCs), and with emerging promise for other urologic malignancies [2].

2. The new renal tumor classification

Despite considerable advances in the molecular characterization, morphology remains the foundation for this classification. The fifth edition of the WHO classification of renal tumors includes a new category of molecularly defined renal tumors (Table 1) [1]. It has stratified the renal tumors based on the predominant morphologic subtype, cytoplasmic and architectural alterations (eg, clear cell type, papillary type, oncocytic type), tumor location (eg, collecting duct carcinoma), correlations with the background renal disease (eg, acquired cystic disease-associated RCC), resemblance to embryological tissues (eg, metanephric adenoma) or a specific molecular profile (eg, hereditary leiomyomatosis and RCC (HLRCC) syndrome-associated RCC (Fig. 1), succinate dehydrogenase (SDH)-deficient RCC (Fig. 2).

The molecularly defined RCCs include *TFE3* rearranged RCC (Fig. 3), *anaplastic lymphoma kinase (ALK)*-rearranged RCC, *TFEB* rearranged and *TFEB* amplified RCC, *ELOC* (formerly *TCEB1*)-mutated RCC, *SMARCB1* (INI1)-deficient renal medullary carcinoma. The classification has evolved in the current iteration, with some new entities added, including eosinophilic, solid, and cystic renal cell carcinoma (ESC RCC); ELOC (formerly *TCEB1*)-mutated RCC; and *SMARCB1* (INI1)-deficient renal medullary carcinoma [1,2].

ALK-rearranged RCC, which was included in the emerging RCC category in the fourth edition, is now included as a distinct entity. These are usually solitary

tumors occurring in sporadic setting, with a slight male predominance, and have been described to occur in a wide age range, including adolescents. These tumors exhibit variable morphology, mimicking renal medullary carcinoma and collecting duct carcinoma. Therefore, immunohistochemical (IHC) expression for ALK antibody and FISH analysis for *ALK* rearrangement are mandatory for diagnosis. Thus, ALK IHC screening has been suggested for unclassifiable RCCs with heterogeneous features as well [3–5]. Targeted therapy using ALK inhibitors such as Alectinib and Crizotinib has proven efficacy and tolerability. In children and adolescents, these tumors frequently harbor *VCL-ALK* and *TPM3-ALK* fusion.

Hereditary leiomyomatosis and RCC syndrome-associated RCC is incorporated under the fumarate hydratase-deficient RCC category, which now includes some sporadic tumors (Fig. 1). HLRCC syndrome-associated RCC/fumarate hydratase (FH)-deficient RCC and HLRCC-associated RCC are highly aggressive tumors. Even a small size tumor can metastasize early, frequently to the regional lymph nodes [5–10]. They usually occur in people affected by an autosomal-dominant tumor syndrome associated with germline mutations in the *FH* gene located at the chromosome 1q42. Patients with HLRCC syndrome commonly exhibit cutaneous leiomyomas, uterine leiomyomas in females, and seldom leiomyosarcomas. Thirty percent of the patients can also present with a type 2 papillary RCC morphology, characterized by large nucleus with prominent eosinophilic nucleolus, surrounded by a clear halo, reminiscent of a viral (cytomegalic) inclusion [5,10].

Another new tumor subgroup included in the current WHO is the oncocytic tumors of the kidney. These are a heterogeneous group of low-grade oncocytic tumors currently not classifiable as either oncocytoma or chromophobe RCC. This tumor category includes low-grade oncocytic tumor, eosinophilic and vacuolated tumor, hybrid oncocytic tumor (Birt-Hogg-Dube syndrome-related tumor), and oncocytic renal neoplasms of low malignant potential [1,2]. Low-grade oncocytic tumor is composed of tumor cells with bland nuclei, diffuse strong cytokeratin 7 immunoreactivity, and negative KIT (CD117) labeling (Fig. 4).

Eosinophilic, solid, and cystic RCC, an emerging renal tumor entity of the 2016 WHO classification of genitourinary tumors, has now been included in the current classification [11–14]. Usually described as a sporadic, solitary, and small neoplasm with an indolent course, these tumors

Box 1. TAKE HOME MESSAGES**KIDNEY**

- Changes in nomenclature from “clear cell papillary renal cell carcinoma (RCC)” to “clear cell renal cell tumor,” “*TCEB1*-mutated RCC” to “*ELOC*-mutated RCC,” “hereditary leiomyomatosis and renal cell carcinoma” to “fumarate hydratase-deficient RCC,” “RCC-unclassified” to “RCC-NOS.”
- Type 1/2 papillary RCC subcategorization has been eliminated.
- A category of “other oncocytic tumors,” including LOT, eosinophilic vacuolated tumor, and hybrid oncocytic tumor, has been introduced.
- Eosinophilic solid and cystic RCC is accepted as a new and independent tumor entity.
- WHO/ISUP grading now has been validated for clear cell and papillary RCCs.

PROSTATE GLAND

- PIN-like carcinoma has been reclassified as a subtype of acinar rather than ductal adenocarcinoma
- Change in nomenclature from “basal cell carcinoma of the prostate” to “adenoid-cystic (basal cell) carcinoma of the prostate.”
- Treatment-related neuroendocrine carcinoma of the prostate has been described in a separate dedicated chapter because of its high mortality.

URINARY TRACT

- Special attention has been given to grading, heterogeneous lesions, inverted tumors, substaging, and new molecular taxonomy based on a 4-gene panel consisting of *GATA3*, *KRT20*, *KRT14*, and *KRT5*.
- Flat urothelial hyperplasia is now considered benign.
- “Papillary urothelial hyperplasia” or “urothelial proliferation with undetermined malignant potential” is no longer recognized as distinct entities in the current edition.
- Urachal carcinomas have been updated in their molecular profiling.
- Littre gland carcinoma of the urethra, Skene gland carcinoma of the urethra, and Cowper gland adenocarcinoma of the urethra have been newly included in the current edition.

TESTIS

- Change in nomenclature from “primitive neuroectodermal tumor” to “embryonic-type neuroectodermal tumor” and “testicular carcinoid” to “testicular neuroendocrine tumor.”
- Seminoma is included in the “germinoma” family of tumors.
- Gonadoblastoma is included under the noninvasive lesions derived from the non-GCNIS.

- New entities like signet ring stromal tumor and myoid gonadal stromal tumor are described in the SCST of the testis.
- Mixed/undifferentiated SCST have been separated into individual entities as mixed SCST and “SCST, NOS.”

PENIS & SCROTUM

- Change in nomenclature from “Paget disease” to “extra-mammary Paget disease.”
- Current recommendation of reporting tumors as HPV-associated or HPV-independent along with their histological subtype.
- In cases where this distinction is not possible, a designation of SCC NOS is considered perfectly acceptable.
- The authors also encourage reporting and quantification of subtypes and provision of percentages in case of mixed tumors.

Abbreviations: GCNIS, germ cell carcinoma in situ; HPV, human papillomavirus; LOT, low-grade oncocytic tumor; RCC, renal cell carcinoma; NOS, not otherwise specified; SCC, squamous cell carcinoma; SCST, sex cord-stromal tumors.

commonly occur in young females. Few cases have also been described in males. A subset of patients with tuberous sclerosis complex (TSC) can harbor this tumor [15–17]. Characteristic morphological features of this tumor include a solid and cystic architecture, voluminous eosinophilic cytoplasm, granular cytoplasmic stippling, and cytokeratin (CK) 20 positivity (Fig. 5). These tumors often harbor somatic tuberous sclerosis gene mutations (*TSC1* and *TSC2*) with recurring chromosomal copy number gains and losses [18,19]. Ongoing clinical trials targeting the mTOR pathway are promising.

ELOC-mutated RCC, formerly *TCEB1* RCC, is a subset of clear cell RCC, expressing CAIX and displaying thick fibromuscular bands transecting across the tumor with clear cell cytology with voluminous cytoplasm. These neoplasms harbor hotspot mutations in the *ELOC* gene. Although initial data suggested these tumors to be nonaggressive, there have been a few published recent reports of aggressive tumor behavior [20–22].

A significant change in the fifth edition has been the change in terminology from “Clear Cell Papillary Renal Cell Carcinoma” to “Clear Cell Papillary Renal Cell Tumor,” the name change suggested as there are only rare reports of metastatic events for this indolent tumor entity [23,24,24a,24b] (Fig. 6). Although the definition of type 1 Papillary Renal Cell Carcinoma (PRCC) is now considered as the prototype PRCC, the diagnostic criteria as well as the need to include the entity type 2 PRCC because of its variable morphological types needs to be further evaluated. Subclassification of PRCCs into type 1 and type 2 is no longer recommended in the current edition, given the

Table 1 WHO classification of tumors of the kidney, fifth edition, 2022.**Renal cell tumors***Clear cell renal tumors*

Clear cell renal cell carcinoma

Multilocular cystic renal neoplasm of low malignant potential

Papillary renal tumors

Renal papillary adenoma

Papillary renal cell carcinoma

Oncocytic and chromophobe renal tumors

Oncocytoma of the kidney

Chromophobe renal cell carcinoma

Other oncocytic tumors of the kidney

Collecting duct tumors

Collecting duct carcinoma

Other renal tumors

Clear cell papillary renal cell tumor

Mucinous tubular and spindle cell carcinoma

Tubulocystic renal cell carcinoma

Acquired cystic disease-associated renal cell carcinoma

Eosinophilic solid and cystic renal cell carcinoma

Renal cell carcinoma NOS

Molecularly defined renal carcinomas

TFE3-rearranged renal cell carcinomas

TFEB-rearranged renal cell carcinomas

ELOC (formerly TCEB1)-mutated renal cell carcinoma

Fumarate hydratase-deficient renal cell carcinoma

Succinate dehydrogenase-deficient renal cell carcinoma

ALK-rearranged renal cell carcinomas

SMARCB1-deficient renal medullary carcinoma

Metanephric tumors

Metanephric adenoma

Metanephric adenofibroma

Metanephric stromal tumor

Mixed epithelial and stromal renal tumors

Mixed epithelial and stromal tumor of the kidney

Pediatric cystic nephroma

Renal mesenchymal tumors*Adult renal mesenchymal tumors*

Classic angiomyolipoma/Perivascular epithelioid cell tumor (PECOMA) of the kidney

Epithelioid angiomyolipoma/epithelioid PECOMA of the kidney

Renal hemangioblastoma

Juxtaglomerular cell tumor

Renomedullary interstitial cell tumor

Pediatric renal mesenchymal tumors

Ossifying renal tumor of infancy

Congenital mesoblastic nephroma

Rhabdoid tumor of the kidney

Clear cell sarcoma of the kidney

Embryonal neoplasms of the kidney*Nephroblastomatous tumors*

Nephrogenic nest

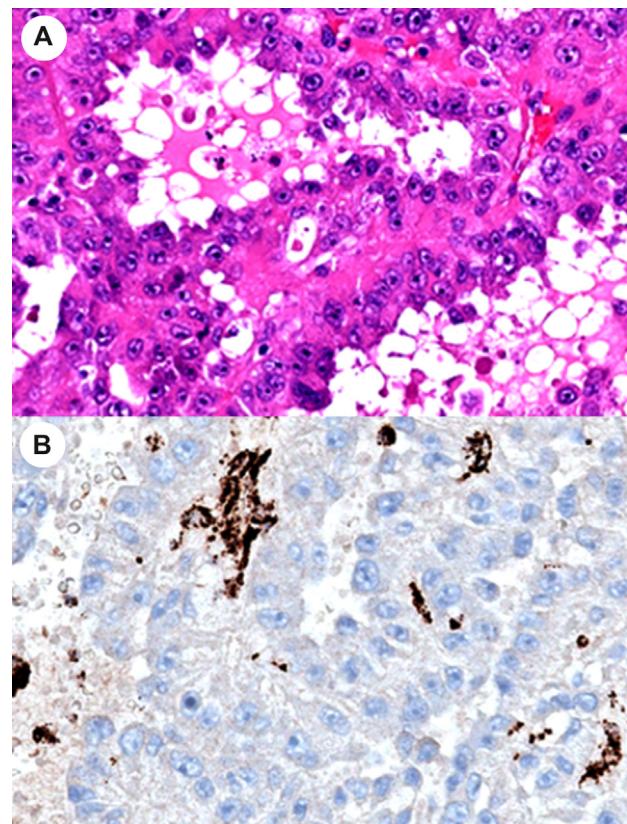
Cystic partially differentiated nephroblastoma

Nephroblastoma

Miscellaneous renal tumors

Germ cell tumors of the kidney

Abbreviations: WHO, World Health Organization; NOS, not otherwise specified; ALK, anaplastic lymphoma kinase.

**Fig. 1** Hereditary leiomyomatosis and renal cell carcinoma. A, The tumor cells with large (inclusion-like) nucleoli surrounded by clear halos. B, Loss of fumarate hydratase immunostaining.

recognition of frequent mixed tumor phenotypes and the existence of entities with different molecular background within the type 2 PRCC category. Many evolving entities such as biphasic squamoid alveolar RCC, Warthin-like PRCC, and biphasic hyalinizing psammomatous RCC are included as part of the PRCC continuum.

Papillary renal neoplasm with reverse polarity is a new distinct category recognized and described as papillary tumors with thin branching papillae and low-grade oncocytic nuclei and reversed nuclear polarity [25] (Fig. 7). The consistent GATA3 and L1CAM positivity and negative vimentin staining pattern and frequent *KRAS* mutations are hallmarks of these tumors [25–27]. There is a high likelihood that papillary renal neoplasm with reverse polarity will be included as a new distinct entity in the next edition of WHO classification. However, the GUPS update suggests that although GATA3 expression and *KRAS* mutations make this tumor a unique entity, the predominant papillary architecture, documented gains of chromosomes 7 and 17, and loss of Y in some reports also argue for the inclusion of this tumor as a subtype of PRCC [27a].

There are other emerging new entities, such as biphasic hyalinising psammomatous RCC (BHP RCC) [28], biphasic squamoid/alveolar RCC [29], or thyroid-like follicular RCC (TLF RCC) [30–32], some of them have

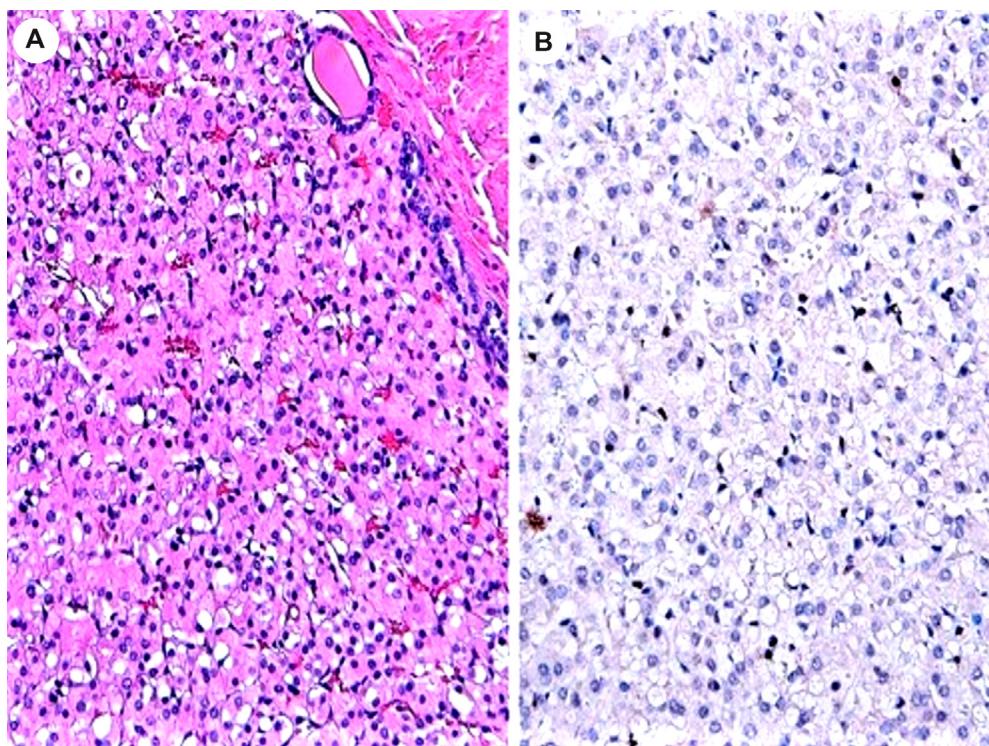


Fig. 2 Succinate dehydrogenase-deficient renal cell carcinoma. A, Sheets of polygonal tumor cells with eosinophilic and vacuolated cytoplasm. B, Loss of succinate dehydrogenase staining by immunohistochemistry.

a specific molecular driver alteration, for example, NF2 mutations in BHP RCC [33], and EWSR1-PATZ1 fusions in TLF RCC [34]. It is anticipated that several of these newly defined tumors will become independent RCC entities in the future WHO classification.

The category “renal cell carcinoma, unclassified” has now been renamed as “renal cell carcinoma, not otherwise specified (NOS)” — for those tumors that do not fulfill the diagnostic criteria for other well-defined entities, either low-grade or high-grade. There are no defined diagnostic criteria for these tumors and tumors in the following scenarios may be placed in the unclassified category (or RCC, NOS): tumors that show features of >1 different subtype; low- or high-grade unclassified oncocytic/eosinophilic neoplasms; or tumors with pure sarcomatoid morphology [11,12,20]. The category of unclassifiable RCC should be reserved to only those renal tumors, wherein all modalities of investigation have been exhausted [35]. As a group, these tumors carry a mortality rate higher than clear cell RCC. The correct use of this category (RCC, NOS) is important. Continuous re-evaluation of this category of tumors with the emerging molecular markers is critically important for future renal tumor classification [12].

The category of renal hematolymphoid neoplasms, neuroendocrine neoplasms (NEN) of the kidney, melanocytic tumors, and metastatic tumors of the kidney have all been addressed in dedicated chapters where these tumors are described for all the organs of the genitourinary system.

Thus, instead of having multiple separate sections in the kidney, bladder, and prostate, there is a single section devoted to NEN, with the exception of treatment-related neuroendocrine prostatic carcinoma which has been only included in the prostate chapter, because of its unique molecular and clinical characteristics specific to that anatomical site [36–39].

Adult cystic nephroma, which was previously listed as a separate entity from mixed epithelial and stromal tumor (MEST), is now considered as a subtype of MEST. Pediatric cystic nephroma, harboring DICER1 mutation in approximately 90% of cases, is now listed as a separate entity under the MEST. Pediatric cystic nephroma was discussed in the 2016 WHO classification under the broad heading of nephroblastic and cystic tumors occurring mainly in children. The category of nephroblastic tumors previously described is now included as embryonal neoplasms of the kidney (Table 1).

While in the previous edition, the WHO Classification of Tumors/International Society of Urological Pathology (WHO/ISUP) histological grading of renal cell tumor types was recommended specifically for clear cell RCC and PRCC, as grading was not validated for the other subtypes of RCC. However, it has been proposed as potentially useful for SDH-deficient RCC, mucinous tubular and spindle cell carcinoma, *ELOC*-mutated RCC, *TFEB*-rearranged RCC, RCC NOS, FH-deficient RCC including HLRCC-RCC, Collecting duct carcinoma and *SMARCB1*-

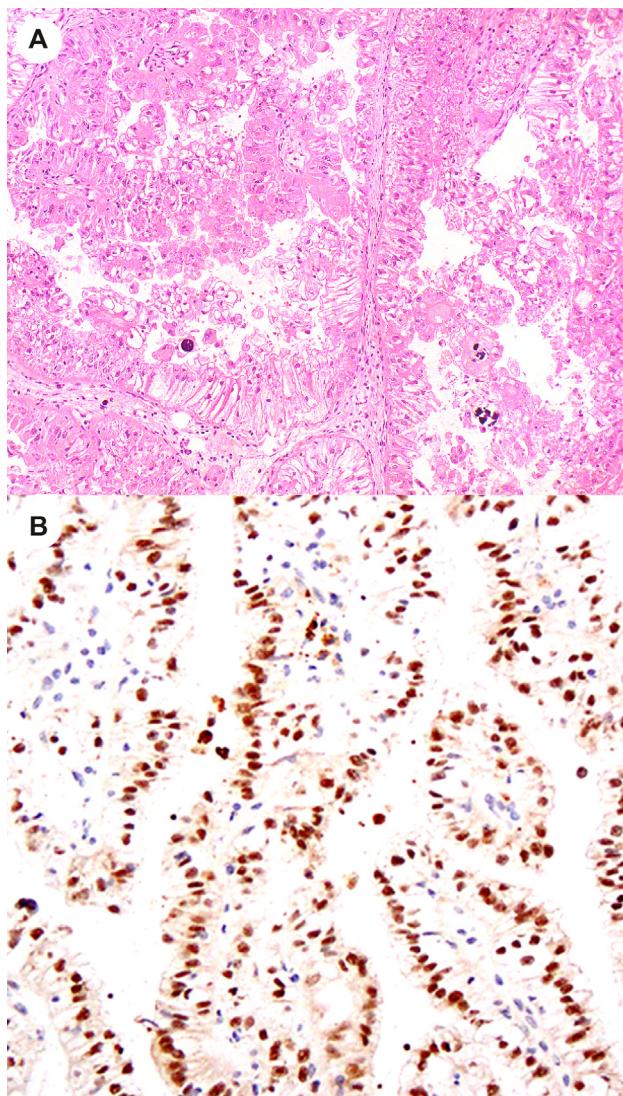


Fig. 3 TFE3 rearranged renal cell carcinoma (RCC). A, Tumor cells with abundant clear to eosinophilic cytoplasm forming papillae with scattered psammoma bodies. B, Strong and diffuse immunohistochemical expression of TFE3 is seen in the tumor cells.

deficient renal medullary carcinoma are considered as inherently aggressive RCCs, irrespective of their WHO/ISUP grading. WHO/ISUP grading can be potentially misleading in tubulocystic RCC, acquired cystic disease-associated RCC, ESC RCC, and eosinophilic and vacuolated tumor because despite their higher nuclear grade, the overall biologic behavior of these tumors is rather indolent. Limited data are available on nuclear grading and its correlation with disease outcome in *ALK*-rearranged RCC and RCC NOS, while WHO/ISUP grading is not clearly applicable or may not be useful in chRCC and *TFE3*-rearranged RCC. Clinicians rely on nuclear grade and sarcomatoid differentiation which is considered as a feature of aggressiveness, allows the selection of immune checkpoint inhibitors as the first-line treatment in such cases.

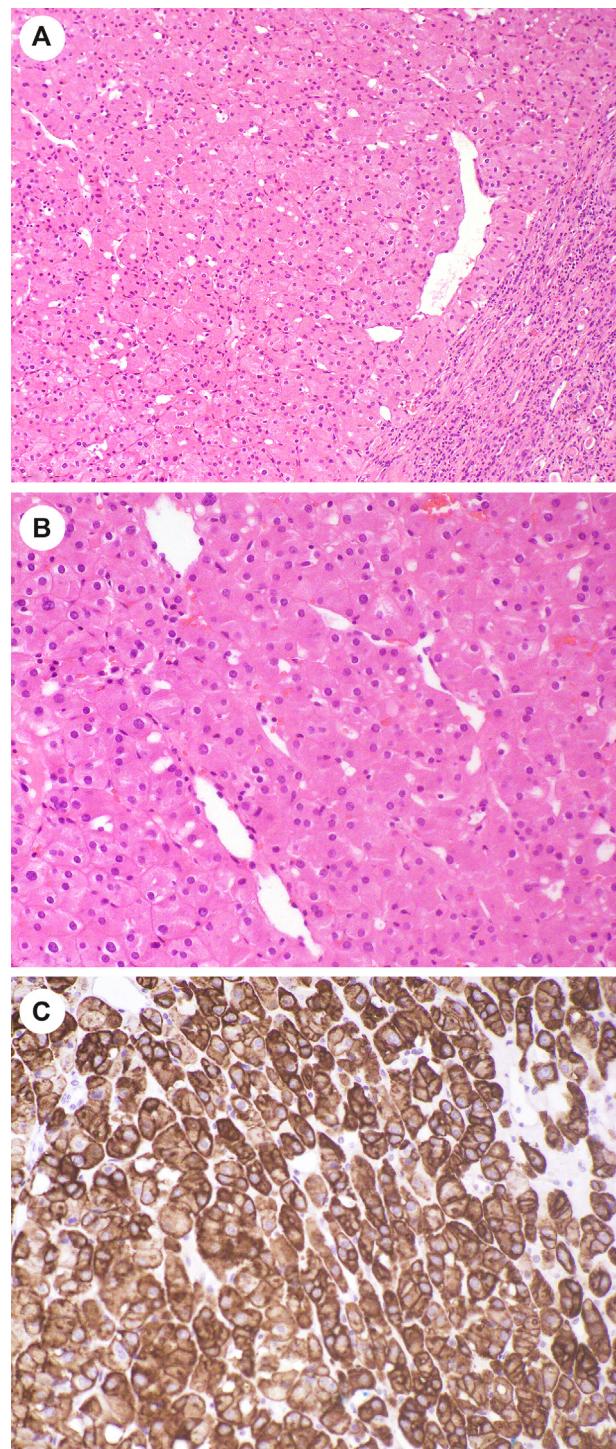


Fig. 4 Low-grade oncocytic tumor. A, Predominantly solid growth. B, Perinuclear clearing ("halo") is noticeable. C, The tumor cells with diffuse and strong cytokeratin 7 (CK7) expression.

Advanced and high-quality IHC and molecular assays have become crucial for accurate cancer diagnosis, prognosis, and treatment response prediction. This has important implications for low- and middle-income countries. As

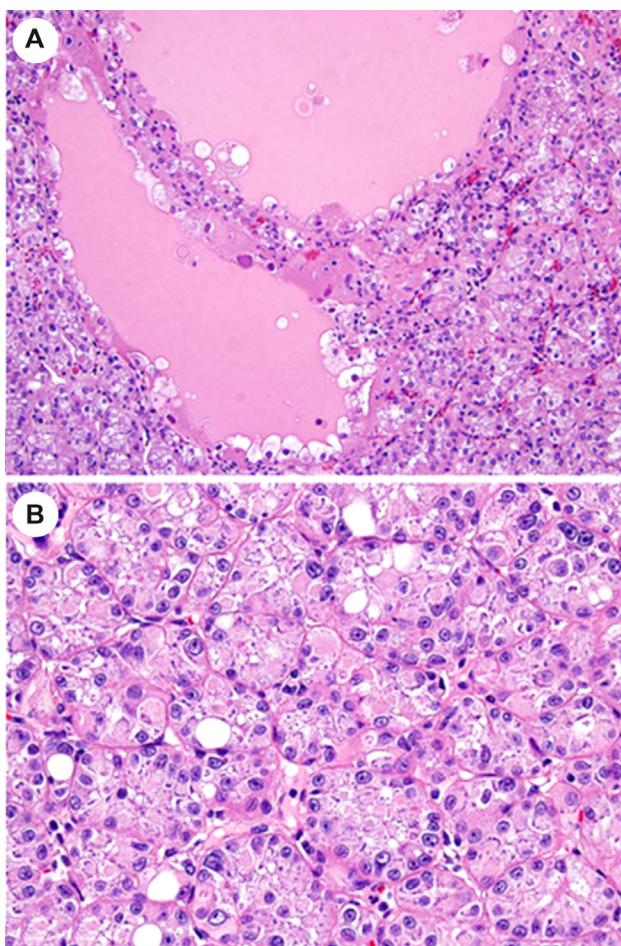


Fig. 5 Eosinophilic solid and cystic renal cell carcinoma. A, Solid areas admixed with cysts. B, The tumor cells showing eosinophilic cytoplasm with granular cytoplasmic basophilic stippling and round-to-oval nuclei.

there is a growing effort to transform the morphological classification to one based on molecular profiles, many pathologists worldwide may encounter difficulties in standardizing an optimal diagnostic algorithm to categorize RCCs [12]. These limitations not only pertain to fiscal issues, but also to proper availability of diagnostic genetic tests as well as skilled and trained manpower and resources. Therefore, the value of histomorphology as the first and foremost diagnostic tool can never be outshone.

3. The new prostate tumor classification

The term “variants” is replaced by “subtypes” for distinct clinical and morphological categories within a tumor type. The authors preferred to reserve the term “variant” for genomic rather than morphological alterations. The various histological subtypes of acinar adenocarcinoma as mentioned in the previous classification are retained in this new edition. The various subtypes have no special prognostic or therapeutic significance, besides their associated Gleason

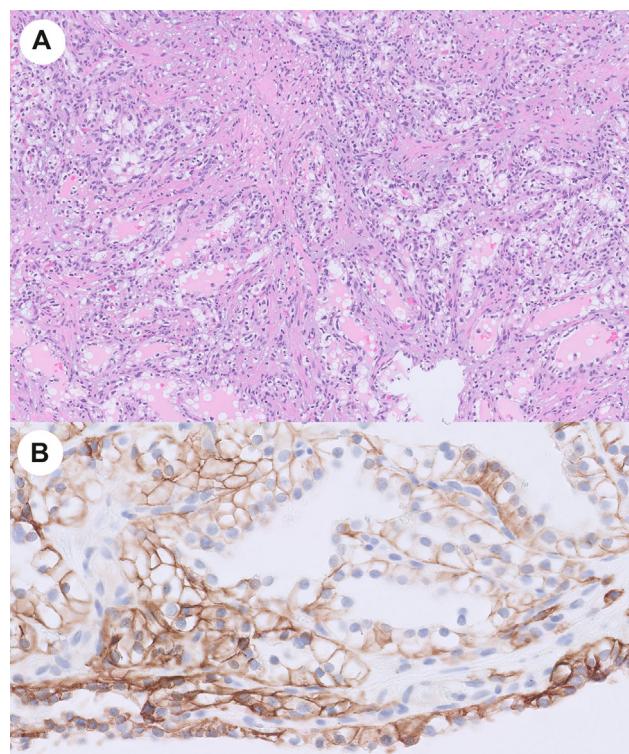


Fig. 6 Clear cell papillary renal cell tumor. A, The tumor has an admixture of branched tubular, solid, and papillary components, lined by clear cells; the nuclei are aligned away from the basement membrane (resembling secretory pattern endometrium with inverted polarity) and variable amounts of sclerotic stroma. B, CAIX immunohistochemistry showing characteristic “cup-shaped” pattern with absence of staining along luminal aspect.

grade; their importance lies in the fact that many can simulate a benign histological pattern (Table 2A).

Gleason grading system is an essential and independent prognostic factor that correlates well with the serum prostate-specific antigen level, clinical recurrence, and survival; however, because of the reproducibility issues, special mention has been made in the current edition of artificial intelligence and computational pathology, which holds great promise for improving both the efficacy and reproducibility of grading (Tables 2B and 2C) [39–41].

The authors also contemplated the notion of transitioning ductal adenocarcinoma into a subtype of acinar adenocarcinoma rather than maintaining it as a separate entity. This discussion was steered by the fact that most ductal adenocarcinoma cases usually coexist with acinar adenocarcinoma as well as the fact that both these entities were clonally related due to shared *ERG* rearrangements with only occasional studies indicating a discordant molecular origin [42,43]. Only future studies and data would determine the further integration of both these lesions. In the current edition of WHO classification, the term “ductal adenocarcinoma” is now retained for only those cases with more than 50% ductal morphology in radical

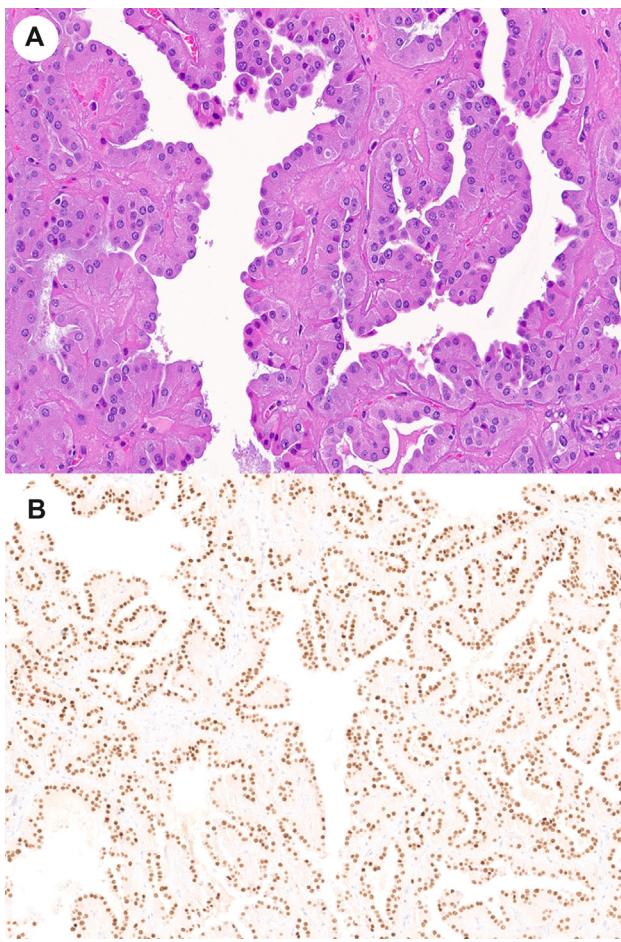


Fig. 7 Papillary renal neoplasm with reverse polarity. A, Classic morphology of the tumor with papillary architecture and oncocytic appearance and apically located, low-grade nuclei. B, Diffuse nuclear immunoreactivity for GATA3 in the tumor cells.

Table 2A WHO classification of tumors of the prostate gland, fifth edition, 2022.

Epithelial tumors of the prostate

Glandular neoplasms of the prostate

Prostatic cystadenoma

High-grade prostatic intraepithelial neoplasia

Intraductal carcinoma of the prostate

Prostatic acinar adenocarcinoma

Prostatic ductal adenocarcinoma

Treatment-related neuroendocrine prostatic carcinoma

Squamous neoplasms of the prostate

Squamous cell carcinoma of the prostate

Adenosquamous carcinoma of the prostate

Adenoid cystic (basal cell) carcinoma of the prostate

Mesenchymal tumors unique to the prostate

Stromal tumors of the prostate

Prostate stromal tumor of uncertain malignant potential

Prostatic stromal sarcoma

Abbreviation: WHO, World Health Organization.

Table 2B The new Gleason grade group system with the histological definitions.

Gleason Grade	Gleason Score	Histological Definitions
Group		
1	Less than or equal to 6	Only individual discrete well-formed glands
*2	$3 + 4 = 7$	Predominantly well-formed glands with lesser component of poorly formed/fused/**cribriform glands
*3	$4 + 3 = 7$	Predominantly poorly formed/fused/**cribriform glands with lesser component of well-formed glands
4	$4 + 4 = 8$	Only poorly formed/fused/cribriform glands
	$3 + 5 = 8$	Predominantly well-formed glands and lesser component lacking glands (or with necrosis)
	$5 + 3 = 8$	Predominantly lacking glands (or with necrosis) and lesser component of well-formed glands
5	9-10 ($4 + 5$ or $5 + 4$ or $5 + 5$)	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

* Exact quantification of Gleason grade 4 tumor is necessary because of its independent prognostic implication (NCCN Guidelines Version 4.2022 Prostate Cancer).

** Acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate, or ductal adenocarcinoma component have increased genomic instability, and germline testing may be considered (NCCN Guidelines Version 4.2022 Prostate Cancer).

prostatectomy, whereas the term “adenocarcinoma with ductal features” is recommended in needle biopsy cases for those lesions exhibiting both pure ductal and mixed ductal and acinar features [1].

The decision to rename “Basal Cell Carcinoma” to “Adenoid Cystic (Basal Cell) Carcinoma of the prostate” was agreed upon to avoid confusion with the skin tumor [1]. The term “adenoid cystic” is synonymous with the prototype salivary gland neoplasm having cribriform morphology, and prostate basal cell carcinoma can show a cribriform, anastomosing cords, and tubules as well as solid nested appearance with/without central necrosis [44] (Fig. 8).

Intraductal carcinoma of the prostate (IDC-P), a newly described entity in the 2016 WHO classification, is an expansive proliferation of neoplastic cells within the native ducts and acini; predominantly a solid or dense cribriform growth involving >50% of the glandular lumen [45]. Comedonecrosis is strongly associated with IDC-P and may be used as a diagnostic criterion. The inclusion of loose cribriform and/or micropapillary architecture as IDC-P is still a matter of debate and whether cytological atypia is required is also controversial (Table 2D). The most important differential diagnosis from a morphological

2022 WHO classification of genitourinary tumors

Table 2C The 2019 ISUP and GUPS conference on grading of the prostate cancer.

1. Report in biopsies the percentage Gleason pattern (GP) 4 for all Gleason score (GS) 7 (ISUP GG 2 and 3).
2. Preferred method of reporting percentage GP 4: either $\leq 5\%$ or $\leq 10\%$ or 10% increment thereafter for GG 2 and 3.
3. Report percentage GP 4 in needle biopsy in other part of lower grade in cases with at least one part showing GS $4 + 4 = 8$ (GG4).
4. For radical prostatectomies, include the presence of tertiary/minor GP 4 or 5 in the GS, if constituting $>5\%$ of the tumor volume.
5. Report in radical prostatectomies, the presence of tertiary/minor GP 4 or 5.
6. Replace “tertiary grade pattern” in radical prostatectomy specimen with the term “minor tertiary pattern 5.”
7. Only use “minor tertiary pattern 5” in radical prostatectomy specimen with GG 2 or 3.
8. Minor tertiary pattern 5 is noted along with the GS, with GG based on the GS.
9. Do not grade intraductal carcinoma without invasive cancer.
10. Incorporate the grade of intraductal carcinoma into GS only when invasive cancer is present (ISUP). However, GUPS recommends not to include IDC in the final GS on biopsy or radical prostatectomy specimen.
11. Comment on the presence and significance of intraductal carcinoma in biopsies and radical prostatectomy specimens.
12. Comment on the presence and significance of invasive cribriform cancers in biopsies and radical prostatectomy specimens.
13. Report in systematic biopsies a separate GS (ISUP GG) for each individual biopsy site.
14. Report in multiparametric magnetic resonance imaging (MRI)-targeted biopsies a global (aggregate) GS (ISUP GG) for each suspicious MRI lesion.
15. Report specific benign histologic findings in suspicious (Prostate Imaging Reporting and Data System, PIRADS 4–5) MRI-targeted biopsies without cancer.
16. When multiple undesignated cores are taken from a single MRI-targeted lesion, an overall grade for that lesion is given as if all the involved cores were one long core.
17. If providing a global score, when different cores are found in the standard and the MRI-targeted biopsies give a single global score (factoring both the systematic standard and the MRI-targeted positive cores).

Abbreviations: ISUP, International Society of Urological Pathology; GUPS, Genitourinary Pathology Society Consensus; MRI, magnetic resonance imaging.

standpoint, particularly in needle biopsies include high-grade prostatic intraepithelial neoplasia and cribriform Gleason pattern 4 acinar adenocarcinoma [2,45–47]. For atypical lesions that do not meet the criterion of IDC-P, the term “atypical intraductal proliferation” (AIP) is preferred. The lesions which have been previously described as cribriform patterns of HGPIN are currently included in the AIP category. Basal cell markers are recommended for prostate biopsies displaying isolated IDC-P without

concomitant invasive prostate cancer and prostate-specific and urothelial markers are also mandatory in solid patterns of IDC-P which may mimic intraductal spread of urothelial carcinoma or metastasis from other organ sites. Ductal prostatic adenocarcinoma can also grow in an intraductal fashion; hence, the definition of IDC-P needs to be more stringent with definite morphological and IHC criteria. It is recommended that IDC-P should not be assigned a Gleason grade and reporting of an isolated IDC-P in needle biopsies should be followed by a comment stating that therapy may be warranted considering its usual association with high-grade and high-volume prostate carcinoma. However, whether need to include the architecture of IDC-P into the current Gleason grading system and the Gleason Grade Group, is still a matter of further investigation due to insufficient data.

As aligned with the entire organization of the fifth edition series, metastatic, hematolymphoid, mesenchymal, neuroendocrine, and genetic syndrome-related tumors are each discussed in separate chapters across various genitourinary organs. The only exceptions are mesenchymal tumors that are thought to originate from the prostate stromal cell proper, and treatment-related neuroendocrine prostatic carcinoma, given their distinct features at the biological and clinical level [1,48] (Fig. 9).

The current classification of neuroendocrine neoplasm for the various genitourinary organs stratifies them into 4 subtypes: well-differentiated neuroendocrine tumors, small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, and mixed neuroendocrine carcinoma. However, the previous edition [37,38] included 2 additional categories of neuroendocrine cells in the usual prostate cancer and adenocarcinoma with Paneth cell-like differentiation. The current WHO does not mention the status of the latter 2 definite entities; probably as the latter 2 mentioned entities do not seem to originate from the neuroendocrine cells.

Adenocarcinoma with Paneth cell-like differentiation”, excluded from the current WHO prostate neuroendocrine tumor classification, is biologically distinct from neuroendocrine carcinomas and should not be confused as a high-grade neuroendocrine carcinoma. The tumor contains a varying proportion of cells with prominent eosinophilic granules that expresses neuroendocrine markers and PSA. Paneth cell-like change is technically a misnomer, as these cells are in fact more similar to gastrointestinal neuroendocrine cells with small eosinophilic granules (usually basally located) rather than true Paneth cells (usually apically located and larger granules). Nonetheless, this change may be seen across the spectrum of Gleason grades, regardless of treatment status. From a prognostic standpoint, it appears that solid nests and single cells with this pattern are not as unfavorable as Gleason pattern 5. Therefore, solid nests of these eosinophilic cells should be excluded from grading, and grading should be based on other associated conventional prostatic adenocarcinoma. A

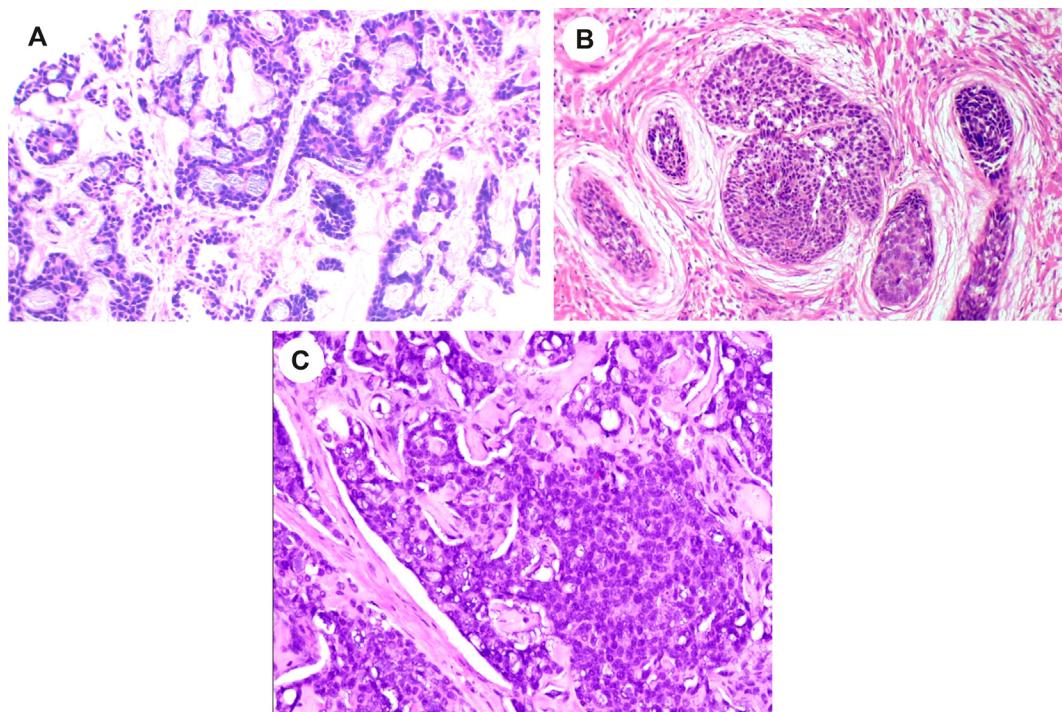


Fig. 8 Adenoid-cystic (basal cell) carcinoma of the prostate. Low-power magnification showing cribriform (A) and solid architectures (B). C, Basaloid neoplastic cells in cribriform architecture with extracellular hyaline-like material.

comment may be provided on the favorable prognosis of this unique morphologic feature.

Treatment-related neuroendocrine carcinomas of the prostate continue to present management challenges and exert a heavy mortality toll in castration-resistant prostate cancer (CRPC) [38]. In addition, the ISUP Working Group recommends specific criteria for the usage of neuroendocrine markers in prostate cancer, which include the following: (1) for clinically localized prostate cancer, immunostaining for neuroendocrine markers (e.g., synaptophysin, chromogranin, or CD56) are not recommended, unless there are clear morphologic features of neuroendocrine differentiation; (2) given its clinical implications, the term neuroendocrine differentiation is best reserved for high-grade cancers and not usual-type adenocarcinomas or well-differentiated neuroendocrine tumors; and (3) advanced metastatic CRPC may manifest a range of morphologic features of neuroendocrine differentiation and a combination of molecular evaluation and morphologic features may be required in future definitions of CRPC, guided by biomarker-driven clinical trials.

The entity prostatic intraepithelial neoplasia-like adenocarcinoma has been included under acinar adenocarcinoma in the current edition because of its behavior and recently described genetic changes, which are different from those of ductal adenocarcinoma. PIN-like carcinoma has been described morphologically by large discrete glands, crowded and often cystically dilated, lined by flat or tufted epithelium of tall columnar cells, lacking the

papillary or cribriform architecture characteristic of ductal adenocarcinoma. PIN-like carcinoma has been reported to have a more favorable prognosis, similar to low-grade acinar adenocarcinoma, and has thus been assigned a GS of 6 only [49,50].

4. The new urinary tract tumor classification

In the fifth edition of the WHO classification of urinary and male genital tumors, histomorphology still remains the gold standard in the diagnosis and classification of urinary tract tumors [1,51] (Table 3). The morphological grading system of papillary neoplasms into urothelial papillomas, papillary urothelial neoplasm of low malignant potential, low-grade urothelial carcinoma, and high-grade urothelial carcinoma is still retained. Two benign entities, namely, urothelial papilla and inverted papilla, have been included in the noninvasive urothelial neoplasm section with their individual subchapters. Although some pathologists prefer to report papillary urothelial neoplasm of low malignant potential (PUNLMP) as a stage pTa lesion, the current WHO does not recommend the name “carcinoma” with this entity, as these lesions have lower rates of recurrence and progression when compared with actual pTa low-grade carcinomas.

Neuroendocrine (NE) carcinomas of the bladder encompass small-cell NE carcinoma, large-cell NE carcinoma, and mixed NE neoplasms. Mixed NE neoplasms include a combination of any NE component with a

Table 2D Diagnostic criteria for the intraductal carcinoma of the prostate gland (WHO, 2022).

1. Complex, generally expansile proliferation of the neoplastic cells within native ducts and acini, which displays at least partial preservation of the basal cell layer.
2. Solid or dense cribriform growth pattern: A dense cribriform pattern has been defined as one with more solid than luminal areas, ie, > 50% of the gland comprising epithelial cells relative to the luminal spaces.
3. Comedo necrosis is strongly associated with intraductal carcinoma of the prostate; may be used as a diagnostic criterion.
4. Loose cribriform/micropapillary architecture is included only if associated with marked cytological atypia.
5. The term “atypical intraductal proliferation” can be used for atypical lesions that do not meet the criteria for intraductal carcinoma of the prostate. Lesion formerly labeled as cribriform high-grade prostatic intraepithelial neoplasia is also included in this category.
6. Cribriform architecture, occasionally encountered in the normal prostatic glands, especially from the central zone and in benign hyperplastic nodules, lack the cytological atypia and should not be unnecessarily labeled as intraductal carcinoma.
7. Basal cell marker immunohistochemistry is recommended for prostate biopsies displaying isolated IDC-P without concomitant invasive prostate cancer.
8. Immunohistochemistry is not considered necessary in cases where the distinction between IDC-P and invasive prostate cancer will not change the assigned prostate cancer grade.
9. **Germline BRCA2 testing has been recommended formally by the National Comprehensive Cancer Network and the Philadelphia Prostate Cancer Consensus Conference.

* According to the NCCN Guidelines Version 4.2022 Prostate Cancer, germline genetic testing should be considered in patients with a personal history of prostate cancer and (1) intermediate-risk prostate cancer and intraductal/cribriform histology or (2) a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.

*Germline testing, when performed, should include **MLH1**, **MSH2**, **MSH6**, and **PMS2** (for Lynch syndrome) and the homologous recombination genes **BRCA1**, **BRCA2**, **ATM**, **PALB2**, and **CHEK2**. Additional genes may be appropriate depending on clinical context. For example, HOXB13 is a prostate cancer risk gene and, whereas there are not currently clear therapeutic implications in the advanced disease setting, testing may have utility for family counseling.

Abbreviations: WHO, World Health Organization; IDC-P, intraductal carcinoma of the prostate.

significant portion of non-NE component. It is critical, especially therapeutically, to report the histologic type and percentage of NE carcinoma component in the mixed forms. As this diagnostic nomenclature informs the clinician that there is an aggressive tumor component with a differing therapeutic modality, it provides important prognostic and predictive information and has a major impact

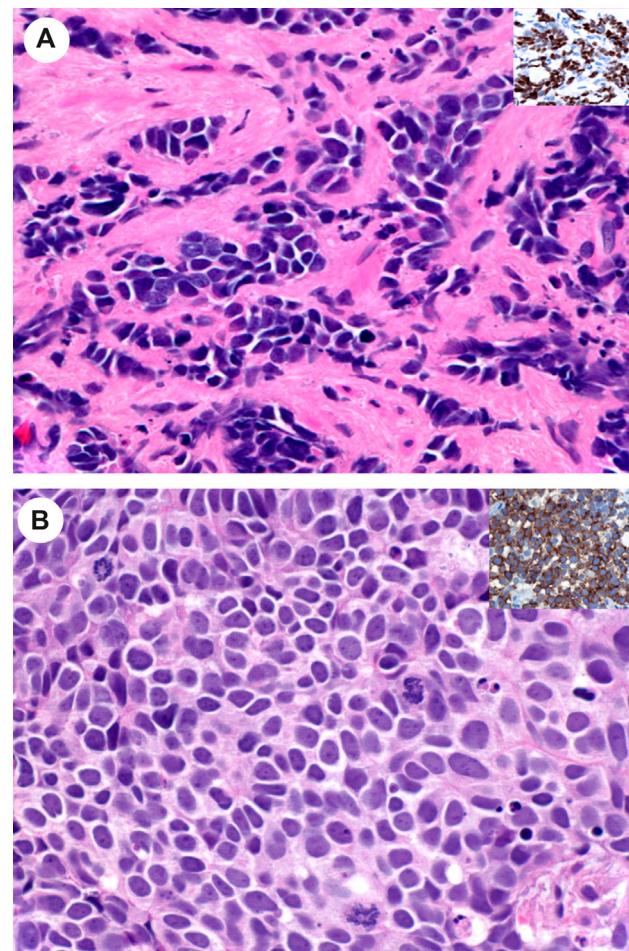


Fig. 9 A, Small cell neuroendocrine carcinoma of the prostate with thyroid transcription factor (**inset**) positivity. B, Small cell neuroendocrine carcinoma of the urinary bladder with synaptophysin (**inset**) expression.

on management, especially regarding potential neoadjuvant/adjuvant chemotherapy [1,52].

The issue of intratumoral heterogeneity and lack of clearly delineated criteria continues to be a major diagnostic challenge [53–56]. As tumor heterogeneity in grade is noted in as many as one-third of noninvasive papillary urothelial carcinomas, and the presence of a high-grade component influences the outcome, the proposed criterion is of reporting papillary tumors as high-grade if the high-grade component represents ≥5% of the tumor [2,51,56]. Conversely, if the high-grade component is <5%, the report should be stated as “low-grade with <5% high-grade component” [48]. Thus, maintaining such uniformity and consistency in reporting tumors with grade heterogeneity, could facilitate data acquisition to formulate more consistent evidence-based criteria. Multidisciplinary collaboration is essential.

The current edition has advocated the use of The Paris System for Reporting Urine Cytology for cytological diagnosis and has been described with each entity, as it has

Table 3 WHO classification of tumors of the urinary tract, fifth edition, 2022.**Urothelial tumors****Non-invasive urothelial neoplasms**

Urothelial papilloma

Inverted urothelial papilloma

Papillary urothelial neoplasm of low malignant potential

Non-invasive papillary urothelial carcinoma, low-grade

Non-invasive papillary urothelial carcinoma, high-grade

Urothelial carcinoma in situ

Invasive urothelial neoplasms

Invasive urothelial carcinoma

Squamous cell neoplasms of the urinary tract**Squamous cell papilloma of the urinary tract****Squamous cell carcinomas of the urinary tract**

Verrucous carcinoma of the bladder

Pure urothelial squamous cell carcinoma

Glandular neoplasms**Adenomas**

Villous adenoma

Adenocarcinomas

Adenocarcinoma NOS

Urachal and diverticular neoplasms

Urachal carcinoma

Diverticular carcinoma

Urethral neoplasms**Urethral accessory gland carcinomas**

Littré gland carcinoma of the urethra

Skene gland carcinoma of the urethra

Cowper gland adenocarcinoma of the urethra

Tumors of Müllerian type

Clear cell adenocarcinoma of the urinary tract

Endometrioid carcinoma of the urinary tract

Abbreviations: WHO, World Health Organization; NOS, not otherwise specified.

been widely adopted because of its easy technique, wide availability, and high clinical relevance [1,57]. However, the cytology cannot determine tumor stage or distinguish between papillary or flat lesions. Although accurate pathological staging of bladder cancer is critical, the combined use of transurethral resection of the bladder tumor and vesical imaging reporting and data system in conjunction is expected to improve bladder cancer staging [58–61].

The new WHO 2022 does not include the terms “hyperplasia” or “urothelial proliferation of unknown malignant potential” described previously in the 3rd and 4th editions. The potential usage of the term “urothelial dysplasia” is a matter of debate, and continues to be a lack of agreement and poor reproducibility in the diagnosis of urothelial dysplasia. The definition of dysplasia is not synonymous to “intraepithelial neoplasia” and is defined as a lesion that is considered to be preneoplastic in nature, but falls short of the diagnosis of “carcinoma in situ”. In patients with a prior history of urothelial carcinoma associated with changes that could have been induced by prior instrumentation and intravesical therapy, a diagnosis of

dysplasia can be quite challenging. The previously described lesions designated as “papillary urothelial hyperplasia” or “urothelial proliferation with undetermined malignant potential” are no longer recognized as unique entities in the current edition.

Paner et al. recently reviewed the literature, criteria and definitions of hyperplasia, dysplasia and atypia of unknown significance [62]. The authors have attempted to refine the definition of dysplasia as a lesion thought to be clearly neoplastic, but with morphologic features that do not quite make the threshold of urothelial carcinoma in situ, and that of urothelial atypia of unknown significance as a descriptive term in case of diagnostic uncertainty of a lesion of whether it is clearly reactive or neoplastic [62].

Flat urothelial hyperplasia is observed in a variety of conditions and is considered to be a putative precursor [62–64]. According to the current edition, in the presence of early tufting without a fibrovascular core, urothelial thickening might be considered to be shoulder lesions for pTa tumors in patients with papillary tumors and chromosome 9 alterations such as loss of 9p21 (CDKN2A), playing a role in tumor suppressor genes, have been described in this context. It is suggested that these flat lesions be named “atypical urothelial proliferation” (AUP), with the additional qualifier of “flat,” or “tent” if some papillary formations without a fibrovascular core are present.

The morphological classification of urothelial cancer is suggested to be replaced with a new molecular taxonomy. Two main pathways of the existence of bladder cancer have been established: non-muscle-invasive and muscle-invasive carcinoma. Non-muscle-invasive carcinoma comprises up to 80% of urothelial cancers, and includes low- and high-grade papillary noninvasive and superficially invasive tumors (pTa, pT1). This category of tumors, most commonly show modifications in the *fibroblast growth factor receptor 3* (*FGFR3*), *PI3-kinase catalytic subunit a* (*PIK3CA*), and *GTPaseHRas* (*HRAS*) while also carrying mutations in the genes for chromatin-modifying enzymes (*H3K27*, *KDM6A*) as well (Fig. 10) [65,66]. Advanced muscle-invasive urothelial carcinomas usually develop from flat urothelial lesions (ie, carcinoma in situ) and express either a papillary or a nonpapillary phenotype. This subset of tumors usually reveal *p53*, *RBL*, and *cyclin-dependent kinase inhibitor 2A* (*CDKN2A*) modifications and genomic instability, as well as high mitotic and proliferation activity (high Ki-67/MIB-1 index), and harboring mutations in the genes for chromatin-modifying enzymes as well, but mostly for *H3K4* and *KMT2D*.

The discovery of the molecular pathways in urothelial carcinogenesis may allow for better classification, prognosis, and development of novel noninvasive detection and surveillance strategies as well as selection of efficacious therapeutic targets in a neoadjuvant to adjuvant setting. However, owing to lack of sufficient data, there has been a delay in the consistent application of these prognostic and

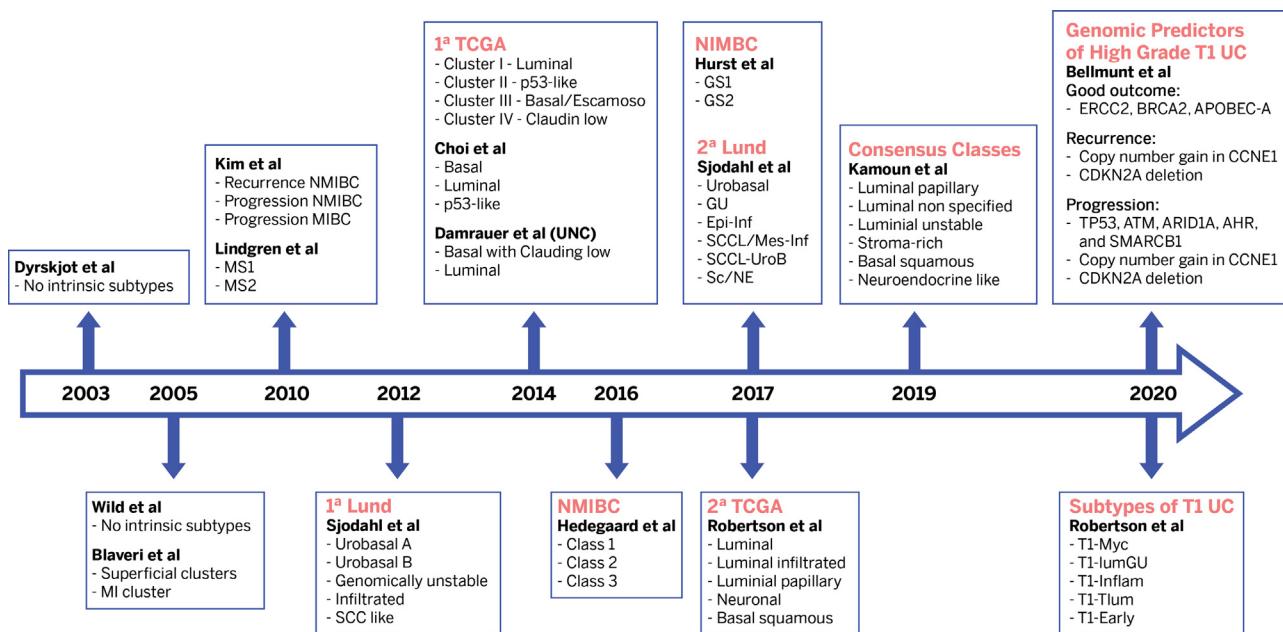


Fig. 10 Evolving schemes of molecular classification of urothelial carcinoma of the bladder. Modified from Lopez-Beltran A, Cimadamore A, Montironi R, Cheng L.: Molecular pathology of urothelial carcinoma. *Hum Pathol* 2021; 113:67–83.

predictive markers in routine pathology and clinical use. More recently, Lopez-Beltran and colleagues evaluated the molecular taxonomy of urothelial carcinoma; as luminal, basal, and null/double negative categories with regard to a 4-gene expression panel comprising *GATA3*, *KRT20*, *KRT14*, and *KRT5* [67]. These 3 molecular categories were corroborated in terms of overall cancer-specific survival as well as programmed death ligand-1 (PD-L1) expression. The luminal subtype (*GATA3*+/*KRT20*+) denoted a more favorable cancer-specific survival in contrast to the basal (*KRT14*+/*KRT5*+/*GATA3*low/-/*KRT20*low/-) and null subtypes (*GATA3*-/*KRT20*-/*KRT14*-/*KRT5*-). Furthermore, a high PD-L1 expression was mostly seen in basal and null subtypes and in carcinomas with variant histology [67].

Urachal carcinomas have been updated in their molecular profiling to aid in the differential diagnosis. Noncystic urachal adenocarcinoma shows a distinct molecular phenotype that is more similar to colorectal adenocarcinomas than urothelial carcinoma of the bladder. Urachal adenocarcinomas often harbor *TP53* mutations with activation of the *MAPK* and *PI3K* pathways and molecular alterations, mostly in *RAS* (*KRAS* > *NRAS*), gene(s), followed by *PIK3CA*, *BRAF*, and *NF1* genes. Microsatellite instability, DNA mismatch repair deficiency, and *TERT* promoter and *POLE* mutations are less frequent in urachal adenocarcinomas and they are associated with higher tumor mutation burden [65–69].

Littre gland carcinoma of the urethra, Skene gland carcinoma of the urethra, and Cowper gland adenocarcinoma of the urethra have been newly included in the current edition [1].

5. The new testicular tumor classification

The 2016 modifications of testicular tumors continue to be retained with the use of the term “germ cell neoplasia in situ (GCNIS)” for the range of preneoplastic lesions as well as the classification of testicular tumors derived from GCNIS or non-GCNIS-derived germ cell tumors (GCTs) such as some teratomas and spermatocytic tumors [70–74] (Table 4). The current WHO edition on the testicular neoplasms has also placed seminoma in the “germinoma” family of tumors, thus leading to a more unified classification since these tumors (dysgerminoma, seminoma, and germinoma) share almost identical morphological, molecular, and immunoprofiles [1].

Neuroectodermal differentiation is frequently encountered in postpubertal-type teratomas, and primitive neuroectodermal tumors (PNET) may arise as a secondary somatic type of malignancy in nonseminomatous germ cell tumors (NSGCTs) [75]. In keeping with the fifth edition of the WHO classification of CNS tumors, the term “PNET” has been substituted with “embryonic-type neuroectodermal tumor” to circumvent the ill-defined nature of the former term and to separate these tumors from Ewing’s sarcoma. Similarly, “primitive ectoderm” noted frequently as a component in postpubertal teratomas has been replaced by “embryonic-type neuroectoderm” [1].

The entity “testicular carcinoid” has been renamed to “testicular neuroendocrine tumor (NET).” As most of the NETs in the testis arise from prepubertal teratomas and most prepubertal teratomas are not associated with GCNIS [76,77], the current WHO classification has added

Table 4 WHO classification of the testicular tumors, fifth edition, 2022.

Germ cell tumors derived from germ cell neoplasia in situ

Non-invasive germ cell neoplasia

Germ cell neoplasia in situ

Specific forms of intratubular germ cell neoplasia

Gonadoblastoma

Germinoma family of tumors

Seminoma

Non-seminomatous germ cell tumors

Embryonal carcinoma

Yolk sac tumor, postpubertal-type

Choriocarcinoma

Placental site trophoblastic tumor

Epithelioid trophoblastic tumor

Cystic trophoblastic tumor

Teratoma, postpubertal-type

Teratoma with somatic-type malignancy

Mixed germ cell tumors of the testis

Mixed germ cell tumors

Germ cell tumors of unknown type

Regressed germ cell tumors

Germ cell tumors unrelated to germ cell neoplasia in situ

Spermatocytic tumor

Teratoma, prepubertal-type

Yolk sac tumor, prepubertal-type

Testicular neuroendocrine tumor, prepubertal-type

Mixed teratoma and yolk sac tumor, prepubertal-type

Sex cord-stromal tumors of the testis

Leydig cell tumor

Leydig cell tumor

Sertoli cell tumors

Sertoli cell tumor

Large cell calcifying Sertoli cell tumor

Granulosa cell tumors

Adult granulosa cell tumor

Juvenile granulosa cell tumor

Fibroma thecoma family of tumors

Tumors in the fibroma thecoma group

Mixed and other sex cord stromal tumors

Mixed sex cord stromal tumor

Signet ring stromal tumor

Myoid gonadal stromal tumor

Sex cord stromal tumor NOS

Abbreviations: WHO, World Health Organization; NOS, not otherwise specified.

prepubertal NET to the list of non-GCNIS-associated tumors, although GCNIS-associated NET can arise under the category of “teratoma with somatic-type malignancy” [1].

The fifth edition WHO has defined the following 2 entities in sex cord-stromal tumors of the testis: signet ring stromal tumor and myoid gonadal stromal tumor. Both entities have distinct morphological and immunoprofiles, different from other sex cord tumors, thus warrant inclusion as separate entities.

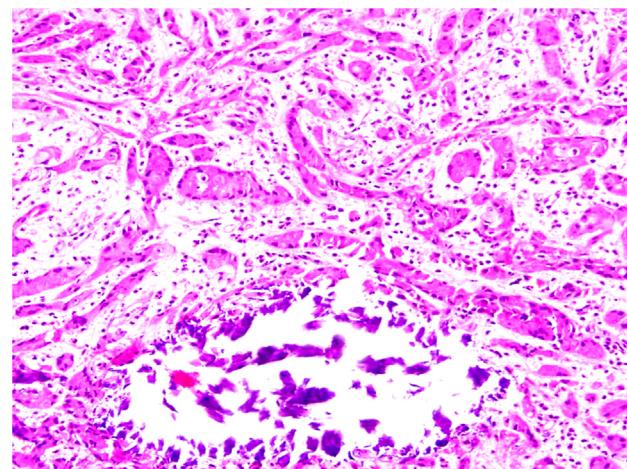


Fig. 11 Large cell calcifying Sertoli cell tumor. Irregular cords of large epithelioid-looking neoplastic cells with eosinophilic cytoplasm, prominent nucleoli, and minimal cytologic atypia present in a variably myxoid stroma. Mulberry calcification is seen.

Another important change in the current edition is the inclusion of sertoliform cystadenoma under Sertoli cell tumors. Although this tumor is exclusively located in the rete testis tubules, the rationale behind the classification under sex cord-stromal (SCS, Sertoli cell) tumor is the close histological and IHC similarities among these tumors [78]. Well-differentiated papillary mesothelial tumor has now been defined as a testicular adnexal tumor type with a favorable prognosis. This is a solitary papillary neoplasm lined by a single row of cuboidal cells with bland nuclear features, positivity for mesothelial markers, retained BAP1 expression, and absence of homozygous deletion of *CDKN2A* and *BRAF V600E* mutation [78a].

Intratubular large cell hyalinizing Sertoli cell tumor is exclusively seen in patients with Peutz-Jeghers syndrome, thus this tumor is included in the chapter on genetic tumor syndromes. Conversely, as large cell calcifying Sertoli cell tumor is seen both sporadically as well as in the setting of Carney complex; it is included in both the sections on sex cord tumors as well as genetic tumor syndromes (Fig. 11).

The fifth edition WHO also further separates mixed/un-differentiated sex cord-stromal tumors into separate categories of “mixed SCST” and “SCST, NOS,” as the individual components of Sertoli cell, Leydig cell, and granulosa cell components are readily recognizable in the former entity, whereas in the latter, they are not morphologically clear. The clinical behavior of testicular SCST is relatively unpredictable, with the occurrence of metastasis in relatively bland tumors, resulting in adverse outcomes and death [79]. Owing to lack of effective chemoradiation treatment option in SCST, several histopathological criteria, including tumor size, necrosis, nuclear atypia, angiolympathic invasion, invasive/infiltrative margins, and mitotic count, have been proposed as predictors of aggressive clinical behavior. The use of high-

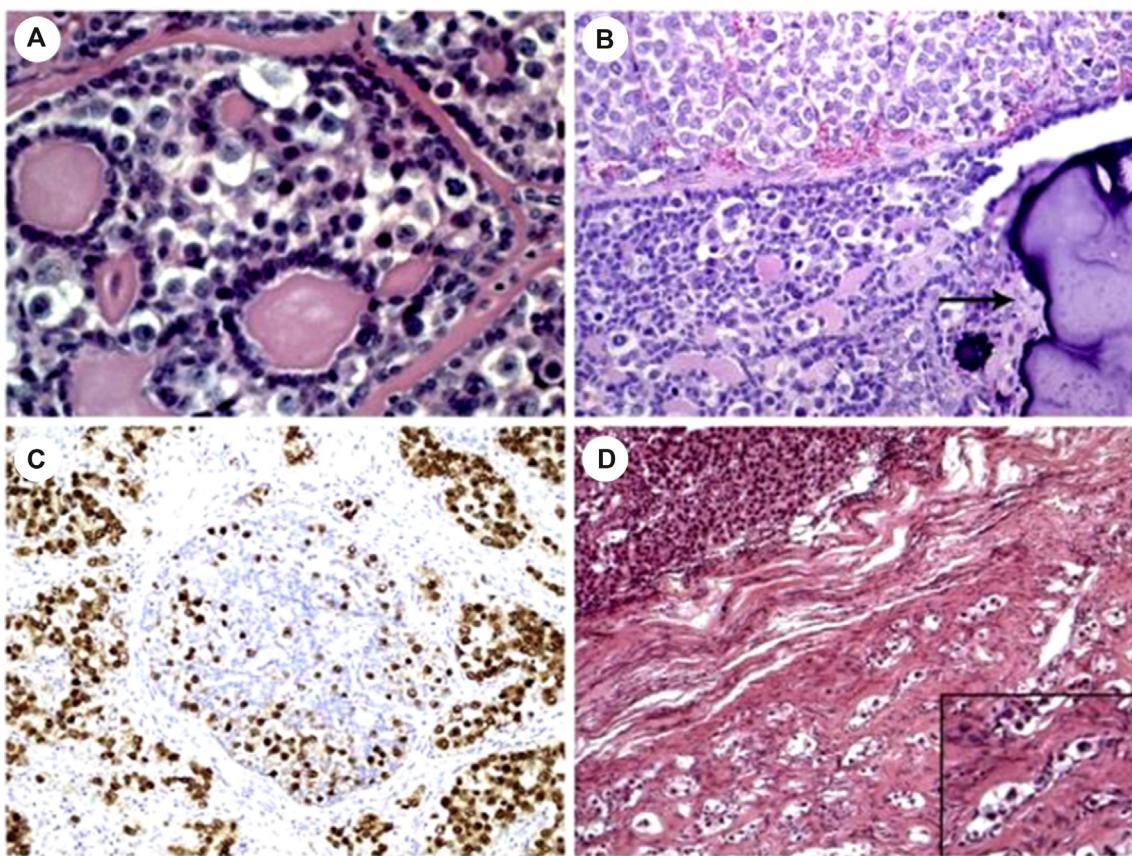


Fig. 12 Gonadoblastoma and related neoplasms. A, Classical gonadoblastoma is composed of cellular islands separated by hyaline basement membrane material. The islands are made up of germ cells and sex cord elements. Two types of germ cells are identified. Some germ cells have uniform bland nuclei with small nucleoli and abundant cytoplasm resembling spermatogonia, whereas others have larger nuclei with a prominent nucleolus resembling those of germinoma. The sex cord elements sometimes surround hyaline bodies composed of basement membrane material. B, A thin fibrous band separates classical gonadoblastoma containing a mulberry calcification (arrow) in the lower portion of the field from germinoma composed of primitive malignant germ cells with enlarged nuclei and clear cytoplasm in the upper third. C, An island of classical gonadoblastoma in the center of the field is surrounded by germinoma. The germ cell nuclei in both neoplasms express SALL4. D, Dissecting gonadoblastoma composed of small cords of cells in a fibrous stroma in the lower and right portion of the field is separated from germinoma in the upper left by a thick wavy fibrous band. Inset, the cords of dissecting gonadoblastoma are composed predominantly of germ cells, but a few residual sex cord derivatives can be identified mostly at their periphery. Modified from Roth LM, Lyu B, Cheng L: Perspectives on testicular sex cord-stromal tumors and those composed of both germ cells and sex cord-stromal derivatives with a comparison to corresponding ovarian neoplasms. Hum Pathol 2017; 65:1–14.

power fields for mitotic counts has been removed in the fifth edition and replaced by square millimeters, due to differences in field diameters from different manufacturers [80]. Further investigation is needed to establish accurate risk stratification schemes based on these morphologic characteristics, including mitotic counts using specified field diameter.

Gonadoblastoma, a mixed sex cord-stromal tumor, often described as occurring in dysgenetic gonads, has now been added to the noninvasive lesions derived from GCNIS. Many variants of gonadoblastoma as well as cases of mixed germ cell/sex cord tumors have been recently described [79,81–85] (Fig. 12). However, owing to the unusual and uncertain nature of these tumors, and lack of sufficient publications, their inclusion in the formal classification will still be awaited.

6. The new classification for tumors of the penis and scrotum

The current model of classifying tumors of the penis and scrotum essentially follows the previous editions, further stratifying the lesions into human papillomavirus (HPV)-dependent and HPV-independent tumors because of its prognostic implications [1]. Evaluation of block-type p16 IHC is a practical method in cases of ambiguous morphology or where molecular methods are not available. The current recommendation also includes reporting tumors as HPV-associated or HPV-independent along with their histological subtype; in cases where this distinction is not possible, a designation of squamous cell carcinoma (SCC) NOS is considered perfectly acceptable [1] (Table 5). In addition, the

Table 5 WHO classification of tumors of the penis and scrotum, fifth Edition, 2022.**Benign and precursor squamous lesions**

Condyloma acuminatum

Squamous cell carcinoma precursors, HPV-associated

Penile intraepithelial neoplasia, HPV-associated

- Common patterns: Basaloid (undifferentiated), warty (condylomatous, bowenoid)
- Other (less frequent) patterns: Clear cell, spindle cell, and pagetoid

Squamous cell tumors and precursors, HPV-independent

Differentiated penile intraepithelial neoplasia, HPV-independent

Invasive epithelial tumors of the penis and scrotum**Invasive squamous epithelial tumors**

HPV-associated squamous cell carcinoma

- Subtypes: Basaloid, warty, clear cell, lymphoepithelioma-like, mixed, and NOS

HPV-independent squamous cell carcinoma

- Subtypes: Usual type, verrucous carcinoma, papillary, sarcomatoid, and mixed

Squamous cell carcinoma NOS

- Invasive keratinizing carcinoma without special features, for which evaluation of p16 is not available

Other epithelial tumors

Penile adenosquamous carcinomas

Penile mucoepidermoid carcinomas

Extramammary Paget disease

Other scrotal tumors

Basal cell carcinoma of the scrotum

Abbreviations: WHO, World Health Organization; HPV, human papillomavirus; NOS, not otherwise specified.

current edition has further outlined a simplified histological classification of the precursor and invasive lesions (Table 5). In addition, the authors also encourage reporting and quantification of subtypes and provision of percentages, although the prognostic significance and justification of this practice is not yet established. Consistent and uniform practice and approach would only provide a more precise and definite framework for further refinement of the classification and grading schemes and recommendations.

Besides the histological subtype and HPV associated, the pathological stage continues to be the most important prognostic factor of penile SCC, and the 3-tiered grading scheme introduced by WHO/ISUP based on the degree of differentiation, pleomorphism and keratin production, is still of paramount importance.

Although scrotal malignancies have not been a prime subject in the prior classifications, owing to their rarity, the current edition has described scrotal cancers in the same classification as that for the penile carcinomas, based on their association with HPV status [1].

7. Perspectives and conclusions

There has been immense progress and innovations in the field of cancer immunology, which has unveiled many a complexity involving mechanisms regulating cellular immune responses. These advances have led to the successful targeting of immune checkpoints while attempting to

enhance antitumor T cell responses [86–91]. Immunotherapy is now among the first-line treatment for multiple cancer types, including urologic malignancies. In addition to companion diagnostic kit-based PD-L1 IHC assays, biomarkers including tumor mutational burden, mismatch repair deficiency/microsatellite instability, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APO-BEC) mutational signature, and immune gene expression profiling are being evaluated in various clinical trials with promising results. Inclusion of immune checkpoint molecules and their blockers would be of immense importance in future editions.

All classifications are dynamic and a continuously evolving imperfect representation, reflecting the current state of understanding in a particular field, at a particular time as well as the current interpretations based on available data. The current WHO fifth edition, like its antecedents, should be seen as an evolving work in progress, as a progressing stage in the advancement of urinary system and male genital organ tumor classification (Tables 6 and 7). The current edition has fervently attempted to establish and usher in new knowledge into the existing classification systems in a stepwise and meticulous manner, by including newly recognized entities, phasing out seemingly outdated tumor types, and integrating the molecular taxonomic structure. It is hoped that such changes and their explanations provide practical guidance to the surgical pathologists and specialists in genitourinary pathology

Table 6 Summary of changes between the fourth and fifth WHO classifications of the urinary and male genital organ tumors.**General Changes**

1. The term “variants” is replaced by “subtypes.”
2. Metastatic, hematolymphoid, mesenchymal, melanocytic, neuroendocrine, and genetic syndrome-related tumors for all the organs are collectively discussed in separate chapters. Only exceptions are mesenchymal tumors that are thought to originate from the prostate stromal cell proper and treatment-related neuroendocrine prostatic carcinoma, given their distinct features at the biological and clinical levels.
3. WHO/ISUP grading previously applied only to CCRCC and PRCC now has been recommended for all RCCs.

ORGAN	Fourth Edition, 2016	Fifth Edition, 2022
KIDNEY	<p><i>TCEB1</i>-mutated RCC</p> <p>HLRCC</p> <p>Clear cell papillary renal cell Carcinoma</p> <p>RCC Unclassified</p> <p>Nephroblastic and cystic tumors occurring mainly in children</p> <p><i>ALK</i>-rearranged RCC (provisional entity)</p> <p>Eosinophilic solid and cystic RCC (provisional entity)</p>	<p><i>ELOC</i>-mutated RCC</p> <p>Fumarate hydratase-deficient RCC</p> <p>Clear cell papillary renal cell tumor</p> <p>RCC-NOS</p> <p>Embryonal neoplasms of the kidney</p> <p><i>ALK</i>-rearranged RCC</p> <p>Eosinophilic solid and cystic RCC</p>
PROSTATE	Neuroendocrine tumors of prostate	Molecularly defined renal carcinomas
	<ol style="list-style-type: none"> 1. Neuroendocrine cells in usual prostate cancer 2. Adenocarcinoma with Paneth cell-like neuroendocrine differentiation 3. Well-differentiated neuroendocrine tumor (carcinoïd) 4. Small cell neuroendocrine carcinoma 5. Large cell neuroendocrine carcinoma <p>Basal cell carcinoma of prostate</p> <p>Primitive neuroectodermal tumor</p> <p>Primitive ectoderm</p> <p>Testicular carcinoid</p> <p>Added entities in sex cord-stromal tumors</p> <p>Mixed/undifferentiated sex cord-stromal tumor</p>	<p><i>TFE3</i>-rearranged renal cell carcinomas</p> <p><i>TFEB</i>-rearranged renal cell carcinomas</p> <p><i>ELOC</i> (formerly <i>TCEB1</i>)-mutated renal cell carcinoma</p> <p>Fumarate hydratase-deficient renal cell carcinoma</p> <p>Succinate dehydrogenase-deficient renal cell carcinoma</p> <p><i>ALK</i>-rearranged renal cell carcinomas</p> <p><i>SMARCB1</i>-deficient renal medullary carcinoma</p>
TESTIS		Neuroendocrine tumors of prostate
		<ol style="list-style-type: none"> 1. Well-differentiated neuroendocrine tumor (carcinoïd) 2. Small cell neuroendocrine carcinoma 3. Large cell neuroendocrine carcinoma 4. Mixed neuroendocrine carcinoma 5. Treatment-related neuroendocrine carcinoma <p>Adenoid-cystic (basal cell) carcinoma of prostate</p> <p>Embryonic-type neuroectodermal tumor</p> <p>Embryonic-type neuroectoderm</p> <p>Testicular neuroendocrine tumor</p> <ol style="list-style-type: none"> 1. Signet ring stromal tumor 2. Myoid gonadal stromal tumor 1. Mixed sex cord-stromal tumor 2. Sex cord-stromal tumor NOS <p>Squamous cell carcinoma NOS</p> <p>HPV-independent squamous cell carcinoma</p> <p>HPV-associated squamous cell carcinoma</p> <p>Penile intraepithelial neoplasia HPV-associated</p>
PENIS AND SCROTUM	<p>Squamous cell carcinoma</p> <p>Non-HPV-related squamous cell carcinoma</p> <p>HPV-related squamous cell carcinoma</p> <p>Penile intraepithelial neoplasia, warty/basaloid/warty-basaloid</p> <p>Differentiated penile intraepithelial neoplasia</p> <p>Paget disease</p> <p>Non-HPV-related squamous cell carcinoma:</p> <p>Adenosquamous carcinoma</p>	<p>Differentiated penile intraepithelial neoplasia, HPV-independent</p> <p>Extramammary Paget disease</p> <p>Other epithelial tumors:</p> <p>Adenosquamous carcinoma</p>

Abbreviations: RCC, renal cell carcinoma; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; ALK, anaplastic lymphoma kinase; HPV, human papilloma virus; NOS, not otherwise specified; WHO, World Health Organization; ISUP, International Society of Urological Pathology; CCRCC, clear cell renal cell carcinoma; PRCC, papillary renal cell carcinoma; HLRCC, hereditary leiomyomatosis and RCC.

Table 7 A summary of modifications made in the WHO 2022, fifth edition.

1. Emphasis on molecularly defined tumor entities as well as genetic tumor syndromes such as molecularly defined renal tumor subtypes and molecular classification of urothelial carcinomas.
2. Major nomenclature changes include replacement of the term “variants” by the term “subtypes”, “clear cell papillary renal cell carcinoma (RCC)” to “clear cell renal cell tumor”; “*TCEB1*-mutated RCC” to “*ELOC*-mutated RCC”, “hereditary leiomyomatosis and renal cell carcinoma” to “fumarate hydratase-deficient RCC”, “RCC-unclassified” to “RCC-NOS”, “primitive neuroectodermal tumor” to “embryonic-type neuroectodermal tumor”, “testicular carcinoïd” to “testicular neuroendocrine tumor”, “Paget Disease” to “extramammary Paget disease” and “basal cell carcinoma of the prostate” to “adenoid-cystic (basal cell) carcinoma of the prostate”.
3. The WHO 2022 classification eliminated the type 1/2 papillary renal cell carcinoma (PRCC) subcategorization.
4. A category of “other oncocytic tumors with oncocyтома/ chromophobe RCC-like features” has been introduced.
5. Eosinophilic solid and cystic RCC is accepted as a new and independent tumor entity.
6. WHO/ISUP grading now has been recommended for all RCCs.
7. Adult cystic nephroma, which was previously considered as a separate entity from mixed epithelial and stromal tumor (MEST), is now regarded as a subtype of MEST.
8. PIN-like carcinoma has been reclassified as a subtype of acinar rather than ductal adenocarcinoma
9. The category of nephroblastoid tumors previously described is now included as embryonal neoplasms of the kidney.
10. Treatment-related neuroendocrine carcinoma of the prostate has been described in a separate dedicated chapter because of its high mortality.
11. In the bladder section, special attention has been given to grading, heterogeneous lesions, inverted tumors, substaging, and new molecular taxonomy.
12. Flat urothelial hyperplasia is believed to be benign. “Papillary urothelial hyperplasia” or “urothelial proliferation with undetermined malignant potential” are no longer recognized as distinct entities in the current edition.
13. The urothelial carcinomas are categorized into three distinct luminal, basal, and null/double negative subtypes based on a four gene expression panel comprising of *GATA3*, *KRT20*, *KRT14*, and *KRT5*. These categories were corroborated in terms of overall cancer-specific survival as well as programmed death ligand-1 expression.
14. Seminoma is included in the “germinoma” family of tumors in order to create a more unified classification for the tumors like dysgerminoma, seminoma, and germinoma as they all represent similar appearing tumors with identical immunohistochemistry (IHC) and molecular characteristics.
15. Gonadoblastoma is included under the noninvasive lesions derived from the germ cell carcinoma in situ (GCNIS).
16. Prepubertal neuroendocrine tumors are included in the non-GCNIS-associated tumors.

Table 7 (continued)

17. Sertoliform cystadenoma is included under Sertoli cell tumors because of its close histological and IHC similarity.
18. Signet ring stromal tumor and myoid gonadal stromal tumor are described in the sex cord stromal tumors (SCST) of the testis. Both these entities show distinct morphological and IHC differences from other sex cord tumors, and thus warrant inclusion as separate entities.
19. Mixed/undifferentiated SCST are categorized into mixed SCST and “SCST, NOS,” as the individual components of Sertoli cell, Leydig cell, and granulosa cell components are readily recognizable in the former entity, whereas in the latter, they are not morphologically clear.
20. Metastatic, hematolymphoid, mesenchymal, melanocytic, neuroendocrine, and genetic syndrome-related tumors for all the organs are collectively discussed in separate chapters.
21. Well-differentiated papillary mesothelial tumor has now been defined as a testicular adnexal tumor type with a favorable prognosis.

Abbreviations: WHO, World Health Organization; NOS, not otherwise specified; ISUP, International Society of Urological Pathology.

across the globe, and that such progress would only eventually improve risk stratification and treatment selection that will have an impact on clinical outcome.

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