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Review – Education

The 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours

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Abstract

The fifth edition of the World Health Organization (WHO) classification of urogenital tumours (WHO "Blue Book"), published in 2022, contains significant revisions. This review summarises the most relevant changes for renal, penile, and testicular tumours. In keeping with other volumes in the fifth edition series, the WHO classification of urogenital tumours follows a hierarchical classification and lists tumours by site, category, family, and type. The section "essential and desirable diagnostic criteria" included in the WHO fifth edition represents morphologic diagnostic criteria, combined with immunohistochemistry and relevant molecular tests. The global introduction of massive parallel sequencing will result in a diagnostic shift from morphology to molecular analyses. Therefore, a molecular-driven renal tumour classification has been introduced, taking recent discoveries in renal tumour genomics into account. Such novel molecularly defined epithelial renal tumours include SMARCB1-deficient medullary renal cell carcinoma (RCC), TFEB-altered RCC, Alk-rearranged RCC, and ELOC-mutated RCC. Eosinophilic solid and cystic RCC is a novel morphologically defined RCC entity. The

[1] Standing WHO fifth edition members who also served as expert members for the urinary and male genital tumour volume.

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diverse morphologic patterns of penile squamous cell carcinomas are grouped as human papillomavirus (HPV) associated and HPV independent, and there is an attempt to simplify the morphologic classification. A new chapter with tumours of the scrotum has been introduced. The main nomenclature of testicular tumours is retained, including the use of the term "germ cell neoplasia in situ" (GCNIS) for the preneoplastic lesion of most germ cell tumours and division from those not derived from GCNIS. Nomenclature changes include replacement of the term "primitive neuroectodermal tumour" by "embryonic neuroectodermal tumour" to separate these tumours clearly from Ewing sarcoma. The term "carcinoid" has been changed to "neuroendocrine tumour", with most examples in the testis now classified as "prepubertal type testicular neuroendocrine tumour".

1. Concept of molecularly defined renal tumour entities

Traditionally, renal tumour subtypes have been named on the basis of predominant cytoplasmic features (eg, clear cell and chromophobe renal cell carcinoma [RCC]), architectural features (eg, papillary RCC), anatomical location of tumours (eg, collecting duct and renal medullary carcinomas), and correlation with a specific renal disease background (eg, acquired cystic disease-associated RCC), but also by characteristic molecular alterations (eg, MIT family translocation carcinomas and succinate dehydrogenase-deficient renal carcinomas) or familial predisposition syndromes (eg, hereditary leiomyomatosis and RCC [HLRCC] syndrome–associated RCC) [1]. For decades, a relatively strong genotype-phenotype correlation was suggested by conventional cytogenetic and comparative genomic hybridisation analyses for renal tumour subtypes, with 3p loss and consecutive von Hippel-Lindau (VHL) inactivation in clear cell RCC (ccRCC) [2,3], gains of chromosome 7 and 17 in papillary RCC [4,5], and losses of multiple chromosomes in chromophobe RCC [6,7]. Although the third edition of the World Health Organization (WHO) classification of urogenital tumours named some renal tumour entities on the basis of molecular alterations (eg, MIT family translocation carcinomas) already in 2004 [8], a comprehensive molecular classification of renal tumours is premature at the moment [9]. This is in contrast to haematopathology [10], or central nervous system (CNS) tumour classification [11]. Looking back, the current WHO classification of haematolymphoid neoplasms evolved from a pure morphologic classification to a classification that integrates clinical, morphologic, immunophenotypical, and molecular features in the definition of almost all entities. Parallel to this, the current WHO classification for CNS tumours also combined histologic patterns with molecular diagnostics to form an integrated diagnosis [12].

In the next years, massive parallel sequencing will be used more and more to identify molecular alterations in renal tumours with unusual morphology [13]. Therefore, the new 2022 WHO classification introduced a molecular-driven renal tumour classification in addition to morphology-based renal tumours (Table 1) [14]. Molecular-defined renal tumours may show very heterogeneous morphologic aspects and cannot be diagnosed by morphology alone. Such molecularly defined epithelial renal tumours include SMARCB1-deficient medullary RCC [15], TFEB-altered RCC [16,17], Alk-rearranged RCC [18], and elongin C (ELOC)-mutated RCC (see below) [19]. It can be argued that ccRCC and metanephric adenomas are also molecular-defined entities, because VHL inactivation is present in most ccRCC cases [13] and BRAF p.V600E mutations in almost all metanephric tumours [20]. Importantly, VHL wild-type ccRCC probably presents a different clinical phenotype [21,22]. Admittedly, the current WHO classification represents a transition from a traditional morphology-based classification system to an integrated approach, comprising many newly recognised "molecular entities", but it should be taken into account that renal tumour diagnosis according to the WHO classification should be standardised as well as usable for local, national, and international communication. Therefore, a morphologic descriptive diagnosis based on LM and immunohistochemistry (IHC), and a comment of the possible underlying molecular alterations is needed for a precise diagnosis. In line with this, the subsection "essential and desirable diagnostic criteria" is included in the WHO fifth edition for each tumour type. This includes clinical, radiologic, molecular, and histologic criteria, and IHC, as well as molecular biomarkers. In the future, this may be complemented with novel technologies, for example, proteomics or parameters of the tumour microenvironment [9]. The integration of classic histologic diagnoses with advanced molecular techniques such as methylation profiling, RNA sequencing, whole-genome sequencing, or whole-exome sequencing, is a prerequisite for more personalised therapeutic strategies. Therefore, it is important to include a pathologist/molecular expert on each trial design team of future clinical trials [15]. Many laboratories do not have the capability or access to advanced molecular tools.

2. New names and renal tumour entities

2.1. *Eosinophilic solid and cystic RCC*

Eosinophilic solid and cystic (ESC) RCC (Fig. 1A) has been accepted as a separate entity, with a set of "classical" histologic features, a characteristic cytokeration (CK) 20 IHC profile, and alterations in the *TSC* genes [23]. Clinically, ESC RCC was first reported to show an indolent behaviour [24–26]. ESC RCC adds to the spectrum of renal neoplasms associated with alterations in the *TSC* genes and activation of the mTOR pathway, which may have consequences for the patient in

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Table 1 – ICD-O coding of tumours of the kidney

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Renal cell tumours	
Clear cell renal tumours	
8310/3	Clear cell renal cell carcinoma
8316/1	Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours	
8260/0	Papillary adenoma
8260/3	Papillary renal cell carcinoma [a]
Oncocytic and chromophobe renal tumours	
8290/0	Oncocytoma
8317/3	Chromophobe cell renal carcinoma
	Other oncocytic tumours of the kidney
Collecting duct tumours	
8319/3	Collecting duct carcinoma
Other renal tumours	
8323/1	Clear cell papillary renal cell tumour[a]
8480/3	Mucinous tubular and spindle cell carcinoma
8316/3	Tubulocystic renal cell carcinoma
8316/3	Acquired cystic disease–associated renal cell carcinoma
8311/3	Eosinophilic solid and cystic renal cell carcinoma
8312/3	Renal cell carcinoma, NOS
Molecularly defined renal carcinomas	
8311/3	*TFE3*-rearranged renal cell carcinomas
8311/3	*TFEB*-altered renal cell carcinomas
8311/3	*ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma
8311/3	Fumarate hydratase–deficient renal cell carcinoma
8311/3	Hereditary leiomyomatosis and renal cell carcinoma syndrome–associated renal cell carcinoma
8311/3	Succinate dehydrogenase–deficient renal cell carcinoma
8311/3	*ALK*-rearranged renal cell carcinomas
8510/3	Medullary carcinoma, NOS
8510/3	SMARCB1-deficient medullary-like renal cell carcinoma
8510/3	SMARCB1-deficient undifferentiated renal cell carcinoma, NOS
8510/3	SMARCB1-deficient dedifferentiated renal cell carcinomas of other specific subtypes
Metanephric tumours	
8325/0	Metanephric adenoma
9013/0	Metanephric adenofibroma
8935/1	Metanephric stromal tumour
Mixed epithelial and stromal renal tumours	
8959/0	Mixed epithelial and stromal tumour
8959/0	Adult cystic nephroma
8959/0	Paediatric cystic nephroma
Renal mesenchymal tumours	
Adult renal mesenchymal tumours	
8860/0	Angiomyolipoma
8860/0	Oncocytic angiomyolipoma
8860/0	Angiomyolipoma with epithelial cysts
8860/1	Angiomyolipoma, epithelioid
9161/1	Haemangioblastoma
8361/0	Juxtaglomerular tumour
8361/0	Functioning juxtaglomerular cell tumour
8361/0	Nonfunctioning juxtaglomerular cell tumour
8966/0	Renomedullary interstitial cell tumour
Paediatric renal mesenchymal tumours	
8967/0	Ossifying renal tumour of infancy
8960/1	Mesoblastic nephroma
8960/1	Classic congenital mesoblastic nephroma
8960/1	Cellular congenital mesoblastic nephroma
8960/1	Mixed congenital mesoblastic nephroma
8963/3	Malignant rhabdoid tumour of the kidney
8964/3	Clear cell sarcoma of kidney
Embryonal neoplasms of the kidney	
Nephroblastic tumours	
	Nephrogenic rests
	Perilobar nephrogenic rests
	Intralobar nephrogenic rests
	Nephroblastomatosis
8959/1	Cystic partially differentiated nephroblastoma
8960/3	Nephroblastoma

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Table 1 (continued)

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Miscellaneous renal tumours	
Germ cell tumours of the kidney	
9084/0	Prepubertal-type teratoma
9084/3	Teratoma with carcinoid (neuroendocrine tumour)
9071/3	Yolk sac tumour, NOS
9085/3	Mixed teratoma–yolk sac tumour

NOS = not otherwise specified; IARC = International Agency for Research on Cancer; WHO = World Health Organization.
Please note that the WHO classification of tumour types is more readily reflected in the table of contents.
These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2): International Association of Cancer Registries (IACR) [Internet]. Lyon (France): International Agency for Research on Cancer; 2021. International Classification of Diseases for Oncology (ICD-O)—ICD-O-3.2; updated January 25, 2021. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.
This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*Codes marked with an asterisk were approved by the IARC/WHO Committee for ICD-O at its meeting in February 2022.
[a] These labels have undergone a change in terminology of a previous code.

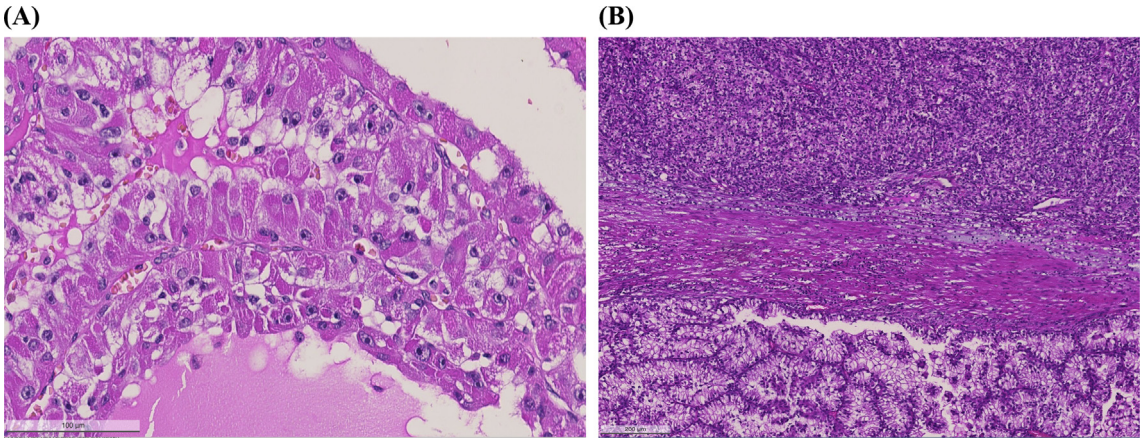

Fig. 1 – Novel renal tumour entities (H&E staining): (A) eosinophilic solid and cystic renal cell carcinoma. This tumour is diagnosed based on H&E morphology and immunohistochemistry. Tumour cells are frequently cytokeratin 20 positive. (B) *ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma as an example of a molecularly defined renal tumour type because identification of *ELOC* mutation is essential. Tumours frequently have a prominent leiomyomatous stroma within tumour cells with clear cytoplasm. H&E = haematoxylin and eosin.

terms of selection of specific targeted treatments (such as mTOR inhibitors) [23].

2.2. *ELOC (formerly TCEB1)-mutated RCC*

ELOC-mutated RCC (Fig. 1B) has a broad morphologic spectrum, but the main differential diagnosis is ccRCC or clear cell papillary RCC. Some of these cases have been reported in the past as tumours with angioleiomyomatous stroma [19,27]. ELOC-mutated RCC is a prototype of a molecularly based RCC subtype because the diagnosis cannot be made without molecular testing. Without molecular corroboration, one would rather diagnose such neoplasms as ccRCC with prominent fibromuscular septation and CK7 positivity, and give the differential diagnosis of an ELOC-mutated RCC. According to limited experience, the majority of these neoplasms have indolent behaviour after tumour resection [27].

2.3. *ALK-rearranged RCC*

ALK-rearranged RCC is a very rare RCC subtype [18,28,29]. This RCC has abundant eosinophilic cytoplasm, striking vacuolisation, but a very heterogeneous and broad morphologic spectrum, sometimes with mucinous deposits. It is a diagnosis of exclusion, and ALK IHC and/or fluorescence in situ hybridisation should be performed before rendering a case with an unusual mix of morphologies as "unclassified". Its clinical behaviour is very heterogeneous, but some patients had dramatic responses to targeted ALK inhibitors [30].

2.4. *SMARCB1-deficient medullary RCC*

This RCC type occurs within the renal medullary region including collecting duct carcinoma and medullary RCC. Whereas collecting duct carcinomas have retained SMARCB1 (also known as INI1), medullary RCC demonstrates loss of SMARCB1 [31–33]. Therefore, these neoplasms are named as SMARCB1-deficient medullary RCC. SMARCB1-deficient medullary RCC is highly aggressive and frequently occurs in young patients with sickle cell trait. Some unclassified RCC cases with medullary phenotype can show complete loss of SMARCB1, but no association with haemoglobinopathies, suggesting that sickle cell is not a prerequisite for this genetic lesion [34]. These tumours can be regarded as subtypes of SMARCB1-deficient medullary

RCC. Establishing the molecular profile is likely to have therapeutic implications as proteasome targeting therapies emerge [35]. It is important to realise that other renal cancer subtypes may have secondary SMARCB1 loss, for example, ccRCC with sarcomatoid transformation, translocation RCC, or fumarate hydratase (FH)-deficient RCC [36].

2.5. TFEB-altered RCC

In the fourth edition of the WHO classification of urogenital tumours, TFEB translocated RCC has been included in the family of MiTF translocation carcinomas [37]. In addition to TFEB translocations, TFEB amplification has also been reported in the last years, resulting in the designation of a novel TFEB-altered RCC category [17]. TFEB-altered RCC cases are less common than TFE3-rearranged RCC cases. Whereas TFEB-translocated RCC is more indolent than TFE3-translocated RCC, TFEB-amplified RCC represents highly aggressive tumours [17].

2.6. FH-deficient RCC (formerly HLRCC syndrome-associated RCC)

HLRCC syndrome-associated RCC with the diagnostic FH deficiency was a separate tumour entity in the 2016 WHO classification [38]. Post-2016 WHO classification studies have identified FH deficiency in many cases described as "unclassified high-grade renal carcinomas", "tubulocystic carcinomas with dedifferentiated foci", "type 2 papillary carcinomas", and "collecting duct carcinomas" [39–41]. Therefore, FH-deficient RCC is the preferred terminology for RCC with compatible morphology, negative FH IHC (which is highly specific but incompletely sensitive), positive 2SC IHC (which is highly sensitive but incompletely specific), and/or pathogenic FH mutation in the tumour, when the clinical and family history of skin and uterine leiomyomas is uncertain and the genetic status is unknown [42]. In familial cases, the term HLRCC syndrome-associated RCC is still acceptable. FH-deficient RCC has been targeted successfully in early-phase studies using erlotinib and bevacizumab [43].

3. Impact of the novel 2022 WHO classification on papillary RCC classification

Delahunt and Eble [44] proposed to distinguish papillary type 1 and type 2 RCC two decades ago. Morphology of these variants has been described in the 2004 WHO classification, and molecular differences were reported [45]. Recent molecular studies suggest that type 2 papillary RCC may not constitute a single well-defined entity, but rather individual subgroups with a different molecular background [46]. The spectrum of papillary RCC is evolving, and some entities are now regarded as independent tumours with specific clinical and molecular background, for example, sporadic FH-deficient RCC, tubulocystic RCC, ESC RCC, clear cell papillary RCC, SMARCB1-deficient RCC, and MiTF family RCC. This will lead to a new view on the "remaining" papillary RCC and may facilitate future research on this "cleaned up" tumour subtype. Although papillary RCC type 1 can be regarded as the classical papillary RCC morphology, there are "emerging entities" with papillary features, actually considered as variants of papillary RCC or emerging/provisional entities. These include papillary renal neoplasm with reversed polarity (PRNRP) [47], biphasic hyalinising psammomatous RCC (BHP RCC) [48], biphasic squamoid/alveolar RCC [49], or thyroid-like follicular RCC (TLF RCC) [50–52]. Importantly, some of them have a specific molecular driver alteration, for example, *KRAS* mutations in PRNRP [53], *NF2* mutations in BHP RCC [54], and *EWSR1-PATZ1* fusions in TLF RCC [55]. It can be foreseen that these tumours may become independent molecularly defined RCC entities in a future WHO classification.

4. Emerging oncocytoma- or chromophobe-like renal neoplasms

The WHO editorial board discussed several entities that have remarkably expanded the spectrum of oncocytoma- or chromophobe-like renal neoplasms. While some of these entities with eosinophilic or oncocytic cytoplasm are now well defined, such as SDH-deficient RCC [56], ESC RCC [23], and FH-deficient RCC [40,57], others are considered emerging entities for which detailed data are being gathered, such as eosinophilic vacuolated tumour (EVT) [58] and low-grade oncocytic tumour (LOT) [59–63]. TSC mutations are frequent in ESC RCC [23,64]. Interestingly, TSC1/2 mutations or activating mTOR mutations have also been identified in EVT and LOT. Importantly, unclassified RCC with oncocytic- or chromophobe-like features can also show somatic inactivating mutations of TSC2 or activating mutations of MTOR as the primary molecular alterations [65]. Therefore, it was decided to create a category of "other oncocytic/chromophobe RCC" for these tumours with a low metastatic potential, because the commonly found TSC mutations can be found in many other tumour types. The main advantage for creating this category is the potential of further clinical and molecular studies in these rare tumours. Oncocytic tumours with low malignant potential and EVTs should not be placed into the "RCC, not otherwise specified (NOS)" group, because the latter are mainly highly aggressive carcinomas. In contrast, a tumour category of TSC1/2 mutated RCC seems not to be appropriate because such a molecular-based subtype encompasses a category of tumours with an extremely broad histologic spectrum.

5. New classification of penile and scrotal tumours

The vast majority of malignant tumours of the penis are squamous cell carcinomas (SCCs) originating in the inner mucosal lining of the glans, coronal sulcus, or foreskin. In the 2022 WHO Blue Book, scrotal tumour classification finds a separate mention for the first time (Table 2). Whereas previous classification schemes of penile tumours were exclusively morphology based, the 2016 WHO classification introduced a classification based on the relation to human papillomavirus (HPV) infection [38]. The 2022 WHO classification followed this paradigm to subclassify tumours into HPV-associated and HPV-independent types (Table 2) [14]. This is consistent with the approach used for tumours of

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Table 2 – ICD-O coding of tumours of the penis and scrotum

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Benign and precursor squamous lesions	
	Condyloma acuminatum
Squamous cell carcinoma precursors, HPV associated	
8077/2	High-grade squamous intraepithelial lesion
Squamous cell carcinoma precursors, HPV independent	
8071/2	Differentiated penile intraepithelial neoplasia
Invasive epithelial tumours of the penis and scrotum	
Invasive squamous epithelial tumours	
8085/3	Squamous cell carcinoma, HPV associated
8083/3	Basaloid squamous cell carcinoma
8054/3	Warty carcinoma
8084/3	Clear cell squamous cell carcinoma
8082/3	Lymphoepithelial carcinoma
8086/3	Squamous cell carcinoma, HPV independent
8086/3	Squamous cell carcinoma, usual type
8051/3	Verrucous carcinoma (including carcinoma cuniculatum)
8052/3	Papillary squamous cell carcinoma
8074/3	Sarcomatoid squamous cell carcinoma
8070/3	Squamous cell carcinoma, NOS
Other epithelial tumours	
8560/3	Adenosquamous carcinoma
8430/3	Mucoepidermoid carcinoma
8542/3	Paget disease, extramammary
Other scrotal tumours	
8090/3	Basal cell carcinoma

HPV = human papillomavirus; IARC = International Agency for Research on Cancer; NOS = not otherwise specified; WHO = World Health Organization.
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Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.
This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*Codes marked with an asterisk were approved by the IARC/WHO Committee for ICD-O at its meeting in February 2022.
†Labels marked with a dagger have undergone a change in terminology of a previous code.

the female genital system [66]. Block-type p16 IHC is the most practical and reliable method to separate HPV-associated from HPV-independent penile SCC. It is recommended to report SCC as HPV associated or HPV independent in addition to the histologic diagnosis. If this is not possible, the designation SCC, NOS is acceptable.

The editorial board tried to simplify the histologic classification within HPV-associated and HPV-independent SCC categories. Previous HPV-independent SCC subtypes were grouped into an overarching SCC histology, for example, SCC of the usual type now includes pseudohyperplastic carcinomas and acantholytic/pseudoglandular carcinomas. Verrucous carcinoma is a separate nonmetastasising low-grade subtype including carcinoma cuniculatum as a pattern [67]. Other HPV-independent subtypes of SCC are papillary [68] and sarcomatoid SCC, the latter with the worst prognosis among all penile carcinomas. Combinations of subtypes and patterns should be designated as mixed SCC with specification of the subtypes. HPV-associated SCCs are basaloid [69], warty [70], clear cell [71], and lymphoepithelioma-like SCCs [72].

HPV-associated penile intraepithelial neoplasia (PeIN) is an HPV-associated precursor lesion of invasive SCC, whereas differentiated PeIN is an HPV-independent precursor lesion of SCC. The most common HPV-associated PeIN subtypes are the basaloid (undifferentiated, a term that should be avoided; Fig. 2A) and warty (Fig. 2B) subtypes. Differentiated PeIN (HPV independent) is characterised by a hyperplastic squamous epithelium with hyper- and parakeratosis, keratin pearl formation, prominent intercellular bridges, and atypical basal layer cells. Differentiated PeIN may be difficult to distinguish from reactive conditions such as squamous hyperplasia, pseudoepitheliomatous hyperplasia, lichen simplex chronicus, and lichen sclerosis with hyperplastic epithelium. Although some papers have advocated grading PeIN into grades 1–3, as per WHO 2022, fifth edition, all PeIN lesions are considered high grade irrespective of the degree of cytoarchitectural features within a lesion. The WHO 2022 editorial board discourages terms such as low-grade squamous intraepithelial lesion, low- and high-grade dysplasia, squamous carcinoma in situ,

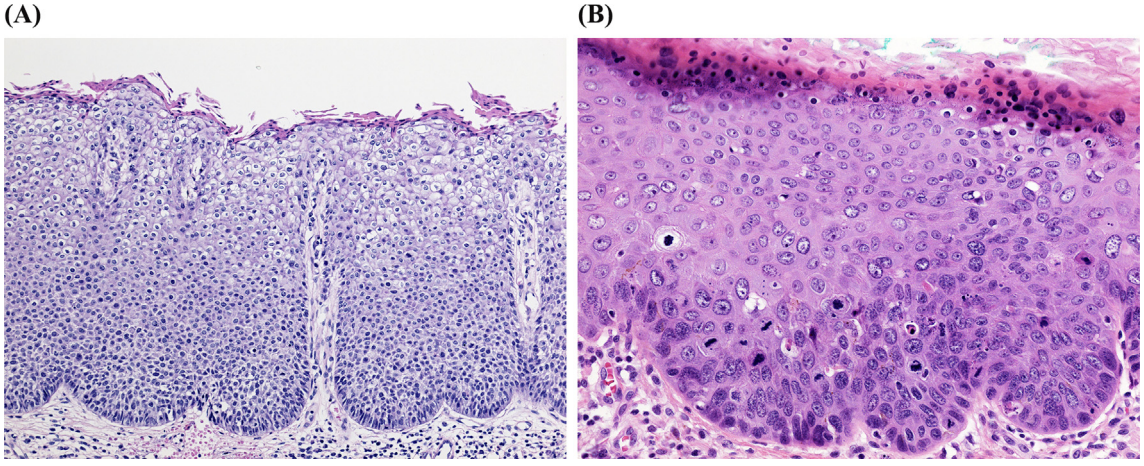

Fig. 2 – HPV-associated penile intraepithelial neoplasia (H&E staining): (A) basaloid subtype and (B) warty subtype. H&E = haematoxylin and eosin.

and simplex type of PeIN for differentiated PeIN. Condyloma accuminatum is regarded as a benign lesion caused by HPV.

6. New classification of testicular tumours

This 2022 WHO classification has been adapted to the new format of the fifth edition of the classification (Table 3) [14]. The testis tumour classification follows the definitions of "category", "family", then "type", and then "subtype" with a possibility of different patterns that do not fit neatly, especially in the diversity of germ cell tumours. The term "variants" is reserved for genomic variants and is no longer used as a histologic descriptor.

There was a radical revision in the 2016 WHO classification, especially to germ cell tumours [38]. The subdivision of germ cell tumours into the vast majority derived from germ cell neoplasia in situ (GCNIS) and those unrelated has been retained. Added to the noninvasive lesions derived from GCNIS is gonadoblastoma [73]. Although often defined as a mixed sex-cord stromal tumour, it is composed of neoplastic germ cells set in a matrix of immature sex cord cells.

Although the term "seminoma" remains unchanged, the issue of nomenclature, in the testis and in any other organ, was discussed by the editorial board [74]. The terms dysgerminoma, seminoma, and germinoma are used for the same tumour with a similar appearance throughout the body. To this end, seminoma was placed in the "germinoma" family of tumours in the classification, but greater unification of terminology would add to better consistency, especially for cancer researchers and for nonpathologists who have to treat this disease.

Nomenclature changes include replacement of the term "Primitive neuroectodermal tumour" by "embryonic neuroectodermal tumour" based on the redundancy of the former term and to separate these tumours clearly from Ewing sarcoma [75]. A teratoma with somatic-type malignancy is a teratoma that develops a distinct secondary component that resembles a somatic-type malignant neoplasm (Fig. 3A). Criteria for the diagnosis of "teratoma with somatic transformation" have been modified to move away from variable field size assessments. It is now recommended to make all measurements in millimetres [76]. While previously the diagnosis was established by using the definition

Table 3 – ICD-O coding of tumours of the testis

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Germ cell tumours derived from germ cell neoplasia in situ	
Noninvasive germ cell neoplasia	
9064/2	Germ cell neoplasia in situ
	Specific forms of intratubular germ cell neoplasia
9061/2	Intratubular seminoma
9070/2	Intratubular embryonal carcinoma
9061/2	Intratubular trophoblast
9071/2	Intratubular yolk sac tumour
9080/2	Intratubular teratoma
9073/1	Gonadoblastoma
Germinoma family of tumours	
9061/3	Seminoma
9061/3	Seminoma with syncytiotrophoblastic cells
Nonseminomatous germ cell tumours	
9070/3	Embryonal carcinoma
9071/3	Yolk sac tumour, postpubertal type
9100/3	Choriocarcinoma
9104/3[a]	Placental site trophoblastic tumour of the testis
9105/3	Epithelioid trophoblastic tumour
	Cystic trophoblastic tumour
9080/3	Teratoma, postpubertal type
9084/3	Teratoma with somatic-type malignancy
Mixed germ cell tumours of the testis	
9085/3	Mixed germ cell tumours
9085/3	Polyembryoma
9085/3	Diffuse embryoma
Germ cell tumours of unknown type	
9080/1	Regressed germ cell tumours
Germ cell tumours unrelated to germ cell neoplasia in situ	
9063/3	Spermatocytic tumour
9063/3	Spermatocytic tumour with sarcomatous differentiation
9084/0	Teratoma, prepubertal type
9084/0	Dermoid cyst
9084/0	Epidermoid cyst
9071/3	Yolk sac tumour, prepubertal type
8240/3	Well-differentiated neuroendocrine tumour (monodermal teratoma)
9085/3	Mixed teratoma and yolk sac tumour, prepubertal type
[b]**rs of the testis**	
Leydig cell tumour	
8650/1	Leydig cell tumour
8650/3	Malignant Leydig cell tumour
Sertoli cell tumours	
8640/1	Sertoli cell tumour

(*continued on next page*)

Table 3 (continued)

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
8640/3	Malignant Sertoli cell tumour
8642/1	Large cell calcifying Sertoli cell tumour
Granulosa cell tumours	
8620/1	Adult granulosa cell tumour
8622/0	Juvenile granulosa cell tumour
Fibroma thecoma family of tumours	
8600/0	Thecoma
8810/0	Fibroma
Mixed and other sex cord stromal tumours	
8592/1	Mixed sex cord-stromal tumour
8590/0	Signet ring stromal tumour
8590/0	Myoid gonadal stromal tumour[b]
8590/1	Sex cord stromal tumour, NOS

IARC = International Agency for Research on Cancer; NOS = not otherwise specified; WHO = World Health Organization.
Please note that the WHO classification of tumour types is more readily reflected in the table of contents.
These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2): International Association of Cancer Registries (IACR) [Internet]. Lyon (France): International Agency for Research on Cancer; 2021. International Classification of Diseases for Oncology (ICD-O)—ICD-O-3.2; updated January 25, 2021. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.
This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
[a] Codes were approved by the IARC/WHO Committee for ICD-O at its meeting in February 2022.
[b] Labels have undergone a change in terminology of a previous code.

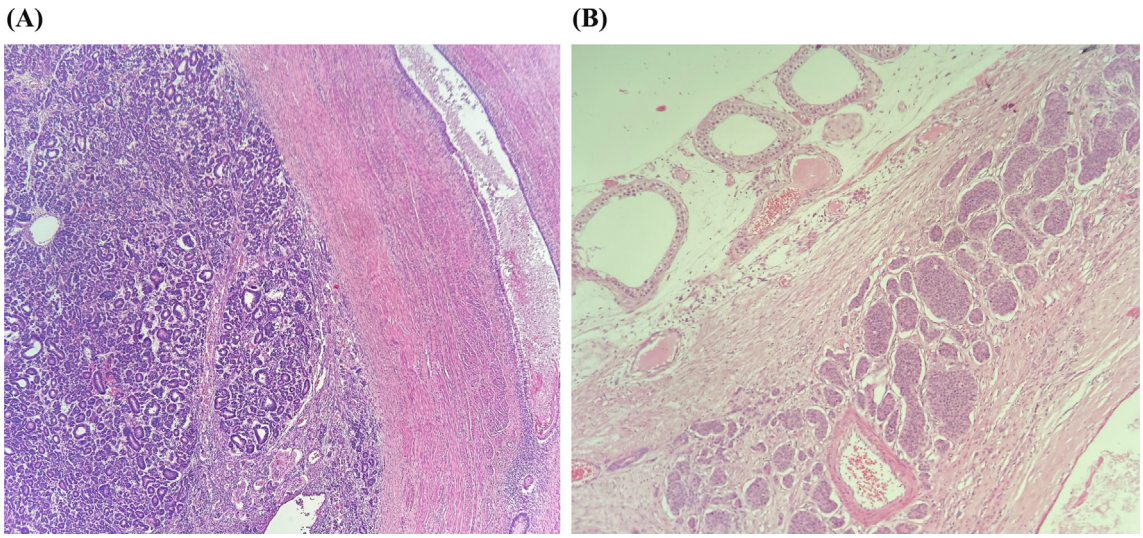

Fig. 3 – Germ cell tumours of the testis (H&E staining): (A) postpubertal teratoma with nephroblastoma-like somatic transformation (note adjacent residual teratoma) and (B) prepubertal-type teratoma with a low-grade neuroendocrine tumour (note absence of germ cell neoplasia in situ). H&E = haematoxylin and eosin.

"a nodule of malignant cells equivalent to area seen under 4× objective or expansile nodule overgrowing other GCT elements", the size criterion has been changed to a 5-mm diameter in the fifth edition. The term teratoma with a secondary malignant component or teratoma with malignant transformation should be avoided because it may lead to a misconception that teratomas lacking somatic-type malignancy are benign.

The word "carcinoid" has been changed to "neuroendocrine tumour", with most examples in the testis now classified as "prepubertal type testicular neuroendocrine tumour" (Fig. 3B) [77]. For sex cord stromal tumours, the use of mitotic counts per high-power field has been changed to per mm^2 for malignancy assessments [76], and the new entities "signet ring stromal tumour" [78] and "myoid gonadal stromal tumour" are defined [79].

Two changes are worth highlighting for adnexal tumours (Table 4). A well-differentiated papillary mesothelial tumour has now been defined as a tumour type with a favourable prognosis to emphasise its distinction from true diffuse mesothelioma [80]. Sertoliform cystadenoma has been removed as an entity from testicular adnexal tumours and placed with Sertoli cell tumours, because these may originate from cells at the junction of seminiferous tubules and rete testis that can differentiate towards sex cord stromal cells [81].

In conclusion, in the fifth edition of the WHO Blue Book, the spectrum of RCC is evolving with recognition of emerg-

Table 4 – ICD-O coding of tumours of the testicular adnexa

ICD-O-3.2	ICD-O label (subtypes are indicated in grey text, with the label indented)
Ovarian-type tumours of the collecting ducts and rete testis	
8441/0	Serous cystadenoma, NOS
8442/1	Serous borderline tumour, NOS
8441/3	Serous cystadenocarcinoma
8470/0	Mucinous cystadenoma
8472/1	Mucinous borderline tumour
8470/3	Mucinous cystadenocarcinoma
8380/1	Endometrioid tumour, borderline
8380/3	Endometrioid adenocarcinoma
8310/3	Clear cell adenocarcinoma
9000/0	Brenner tumour
Tumours of the collecting ducts and rete testis	
8140/0	Adenoma
8140/3	Adenocarcinoma
Paratesticular mesothelial tumours	
9054/0	Adenomatoid tumour
9052/0	Well-differentiated papillary mesothelial tumour
9050/3	Mesothelioma
9052/3	Epithelioid mesothelioma
9051/3	Sarcomatoid mesothelioma
9053/3	Biphasic mesothelioma
Tumours of the epididymis	
8440/0	Cystadenoma of the epididymis
8450/0	Papillary cystadenoma
8140/3	Adenocarcinoma of the epididymis
8070/3	Squamous cell carcinoma
9363/0	Melanotic neuroectodermal tumour

IARC = International Agency for Research on Cancer; NOS = not otherwise specified; WHO = World Health Organization.
Please note that the WHO classification of tumour types is more readily reflected in the table of contents.
These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2): International Association of Cancer Registries (IACR) [Internet]. Lyon (France): International Agency for Research on Cancer; 2021. International Classification of Diseases for Oncology (ICD-O)—ICD-O-3.2; updated January 25, 2021. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577.
Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.
This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*Codes marked with an asterisk were approved by the IARC/WHO Committee for ICD-O at its meeting in February 2022.
†Labels marked with a dagger have undergone a change in terminology of a previous code.

ing entities and molecularly defined renal tumour entities. The penile tumour classification has been simplified. In this review, we presented a summary of the important changes introduced in the WHO 2022 classification of renal, penile, and testicular tumours.

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Study concept and design: Moch, Cree, Netto.
Acquisition of data: Moch, Amin, Berney, Compérat, Gill, Hartmann, Menon, Raspollini, Rubin, Srigley, Tan, Tickoo, Tsuzuki, Turajlic, Cree, Netto.
Analysis and interpretation of data: Moch, Amin, Berney, Compérat, Gill, Hartmann, Menon, Raspollini, Rubin, Srigley, Tan, Tickoo, Tsuzuki, Turajlic, Cree, Netto.
Drafting of the manuscript: Moch.
Critical revision of the manuscript for important intellectual content: Moch, Amin, Berney, Compérat, Gill, Hartmann, Menon, Raspollini, Rubin, Srigley, Tan, Tickoo, Tsuzuki, Turajlic, Cree, Netto.
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