The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours

Holger Moch a,*, Antonio L. Cubilla b, Peter A. Humphrey c, Victor E. Reuter d, Thomas M. Ulbright e

a Department of Pathology, University Hospital Zurich, Zurich, Switzerland; b Instituto de Patología e Investigación, Facultad de Ciencias Médicas, Universidad Nacional de Asunción, San Lorenzo, Paraguay; c Department of Pathology, Yale University School of Medicine, New Haven, CT, USA; d Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; e Department of Pathology and Laboratory Medicine, Indiana University Health Partners, Indiana University School of Medicine, Indianapolis, IN, USA

Abstract

The fourth edition of the World Health Organization (WHO) classification of urogenital tumours (WHO “blue book”), published in 2016, contains significant revisions. These revisions were performed after consideration by a large international group of pathologists with special expertise in this area. A subgroup of these persons met at the WHO Consensus Conference in Zurich, Switzerland, in 2015 to finalize the revisions. This review summarizes the most significant differences between the newly published classification and the prior version for renal, penile, and testicular tumours. Newly recognized epithelial renal tumours are hereditary leiomyomatosis and renal cell carcinoma (RCC) syndrome–associated RCC, succinate dehydrogenase–deficient RCC, tubulocystic RCC, acquired cystic disease–associated RCC, and clear cell papillary RCC. The WHO/International Society of Urological Pathology renal tumour grading system was recommended, and the definition of renal papillary adenoma was modified. The new WHO classification of penile squamous cell carcinomas is based on the presence of human papillomavirus and defines histologic subtypes accordingly. Germ cell neoplasia in situ (GCNIS) of the testis is the WHO-recommended term for precursor lesions of invasive germ cell tumours, and testicular germ cell tumours are now separated into two fundamentally different groups: those derived from GCNIS and those unrelated to GCNIS. Spermatocytic seminoma has been designated as a spermatocytic tumour and placed within the group of non–GCNIS-related tumours in the 2016 WHO classification.

Patient summary: The 2016 World Health Organization (WHO) classification contains new renal tumour entities. The classification of penile squamous cell carcinomas is based on the presence of human papillomavirus. Germ cell neoplasia in situ of the testis is the WHO-recommended term for precursor lesions of invasive germ cell tumours.

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* Corresponding author. Department of Pathology, University Hospital Zurich, Schmelzbergstrasse 12, CH-8091 Zurich, Switzerland. Tel. +41 442552500; Fax: +41 442553194. E-mail address: holger.moch@usz.ch (H. Moch).
1. The new renal tumour classification

The Vancouver consensus conference of the International Society of Urological Pathology (ISUP) provided the foundation for much of the 2016 World Health Organization (WHO) renal tumour classification [1,2] (Fig. 1). The revision of the 2004 WHO renal tumour classification was performed after consideration of new knowledge about pathology, epidemiology, and genetics [3–5].

2. Important changes from existing renal tumour types

First, the new 2016 WHO classification refers to subtypes that have been named on the basis of predominant cytoplasmic features (eg, clear cell and chromophobe renal cell carcinomas [RCCs]), architectural features (eg, papillary RCC), anatomic location of tumours (eg, collecting duct and renal medullary carcinomas), and correlation with a specific renal disease background (eg, acquired cystic disease–associated RCCs) as well as molecular alterations pathognomonic for RCC subtypes (eg, MIT family translocation carcinomas and succinate dehydrogenase [SDH]–deficient renal carcinomas) or familial predisposition syndromes (eg, hereditary leiomyomatosis and RCC [HLRCC] syndrome–associated RCC). In contrast to the 2004 WHO classification, familial forms of RCC, which also occur in sporadic form (eg, clear cell RCC [cCRCC] in patients with von Hippel-Lindau [VHL] syndrome or chromophobe RCC in patients with Birt-Hogg-Dubé syndrome) are now discussed with the corresponding sporadic tumour types in joint chapters.

Second, multiple publications report no recurrence or metastasis in patients with multilocular cystic RCC [6]. Consequently, multilocular cystic renal neoplasm of low

WHO classification of tumours of the kidney

<table>
<thead>
<tr>
<th>Renal cell tumours</th>
<th>Mesenchymal tumours occurring mainly in adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell renal cell carcinoma</td>
<td>Leiomysarcoma</td>
</tr>
<tr>
<td>Multilocular cystic renal neoplasm of low malignant</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>papillary renal cell carcinoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Papillary renal cell carcinoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and renal cell carcinoma</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>carcinoma–associated renal cell carcinoma</td>
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<td>Chromophobe renal cell carcinoma</td>
<td>Angiomyolipoma</td>
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<tr>
<td>Collecting duct carcinoma</td>
<td>Epithelioid angiomyolipoma</td>
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<tr>
<td>Renal medullary carcinoma</td>
<td>Leiomyosarcoma</td>
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<td>MIT family translocation renal cell carcinomas</td>
<td>Haemangioendothelioma</td>
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<td>Succinate dehydrogenase–deficient renal carcinoma</td>
<td>Lymphangiendothelioma</td>
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<td>Mucinous tubular and spindle cell carcinoma</td>
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<tr>
<td>Tubulocystic renal cell carcinoma</td>
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<tr>
<td>Acquired cystic disease-associated renal cell carcinoma</td>
<td>Renomedullary interstitial cell tumour</td>
</tr>
<tr>
<td>Clear cell papillary renal cell carcinoma</td>
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</tr>
<tr>
<td>Renal cell carcinoma, unclassified</td>
<td>Solitary fibrous tumour</td>
</tr>
<tr>
<td>Papillary adenoma</td>
<td></td>
</tr>
<tr>
<td>Oncocytoma</td>
<td></td>
</tr>
</tbody>
</table>

| Metanephrine tumours                                   |                                              |
| Metanephrine adenoma                                   |                                              |
| Metanephrine adenolipoma                               |                                              |
| Metanephrine stromal tumour                            |                                              |

<table>
<thead>
<tr>
<th>Nephroblastic and cystic tumours occurring mainly in children</th>
<th>Neuroendocrine tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrogenic rests</td>
<td>Well-differentiated neuroendocrine tumour</td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>Large cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>Cystic partially differentiated nephroblastoma</td>
<td>Small cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>Paediatric cystic nephroma</td>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td></td>
<td>8700/0</td>
</tr>
</tbody>
</table>

| Miscellaneous tumours                                       |                                              |
| Renal haematoepoietic neoplasms                            |                                              |

<table>
<thead>
<tr>
<th>Mesenchymal tumours occurring mainly in children</th>
<th>Metastatic tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell sarcoma</td>
<td></td>
</tr>
<tr>
<td>Rhabdoid tumour</td>
<td></td>
</tr>
<tr>
<td>Congenital mesoblastic nephroma</td>
<td></td>
</tr>
<tr>
<td>Ossifying renal tumour of infancy</td>
<td></td>
</tr>
</tbody>
</table>

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (9th ed.), Behaviour is coded 0 for benign tumours, 1 for unspecified, borderline, or uncertain behaviour, 2 for carcinoma in situ and grade 3 intrapathelial neoplasia; and 3 for malignant tumours. The classification is modified from the previous WHO classification (7th ed.), taking into account changes in our understanding of these lesions.

*New code approved by the WHO/WHO Committee for ICD-O.
malignant potential is now the WHO-recommended term for this lesion. Such tumours are defined as tumours composed entirely of numerous cysts with low-grade tumour cells (WHO/ISUP grade 1 or 2). The cysts are lined by a single layer of tumour cells with abundant clear cytoplasm. The septa contain, at the maximum, groups of clear cells but without expansile growth.

Third, the entity of papillary RCC has traditionally been subdivided into type 1 and type 2 papillary RCCs [7,8]. It has been accepted that a subset of tumours have mixed histology. Recent molecular studies suggest that type 2 papillary RCCs may constitute not a single well-defined entity but rather individual subgroups with different molecular backgrounds [9]. Papillary RCCs with eosinophilic (oncocytic) cytoplasm and oncocytoma-like low-grade nuclei have been called oncocytic papillary RCCs. Because tumours with this morphology have not yet been fully characterized, they are not considered a distinct WHO entity. The Vancouver consensus conference has recommended diagnosing such tumours as type 2 papillary RCC for the time being [2].

Fourth, papillary adenomas were defined until 2015 as tumours measuring ≤0.5 cm. The WHO 2016 classification defines papillary adenomas as unencapsulated tumours with papillary or tubular architecture, low WHO/ISUP grade, and a diameter ≤1.5 cm. The decision to increase the cut-off size was based on available data showing that unencapsulated grade 1–2 tumours have no capacity to metastasize [10]. It is emphasized, however, that a diagnosis of papillary adenoma based on needle biopsy should be made with extreme caution because the presence of any capsule or grade heterogeneity may not be visualized. Current protocols, which define papillary adenomas as ≤0.5 cm in size, state that the presence of papillary adenoma in a donor kidney is not a contraindication for renal transplantation. The new cut-off of ≤1.5 cm could have a significant impact on some clinical situations (e.g., small renal papillary tumours detected in transplanted kidneys).

Fifth, mixed epithelial and stromal tumours (MEST) encompass a spectrum of tumours including predominantly cystic tumours (adult cystic nephromas) and tumours that are more solid. Adult cystic nephroma was previously classified, along with paediatric cystic nephroma, as a separate entity from MEST. On the basis of similar age and sex distributions and a similar histochemical profile, adult cystic nephroma is now classified within this spectrum of MEST, and the WHO renal tumour subcommittee recommended using the term mixed epithelial and stromal tumour family for both entities. In contrast to adult cystic nephroma, paediatric cystic nephroma is a distinct entity with specific DICER1 mutations [11].

Sixth, most carcinoids of the kidney have a poor prognosis, with frequent occurrence of metastasis after nephrectomy. The renal tumour subcommittee recommended renal carcinoids should be newly designated as well-differentiated neuroendocrine tumours of the kidney and simultaneously placed within the group of endocrine tumours encompassing small cell neuroendocrine carcinomas, large cell neuroendocrine carcinomas, and paragangliomas (extrarenal pheochromocytoma). The term carcinoid of the kidney is obsolete.

3. **New renal tumour entities**

Over the past decade, several new tumour entities have emerged; therefore, the WHO working group was entrusted with the responsibility to decide whether enough molecular clinical follow-up data and pathologic data justify the recognition of any new distinct tumour entity within the classification system. The newly recognized epithelial renal tumours in the 2016 WHO classification are HLRCC-associated RCC, SDH-deficient RCC, tubulocystic RCC, acquired cystic RCC, and clear cell papillary RCC. Paediatric cystic nephroma represents a new entity in the group of nephroblastic and cystic tumours occurring mainly in children (as described under “Important changes”).

3.1. **Hereditary leiomyomatosis and renal cell carcinoma (RCC) syndrome–associated RCC**

HLRCC-associated RCCs are rare tumours occurring in the setting of nonrenal leiomyomatosis and demonstrate germline fumarate hydratase mutations [12]. The tumours have papillary architecture with abundant eosinophilic cytoplasm, large nuclei, and very prominent nucleoli with perinucleolar clearing. The prognosis of these tumours is poor [13].

3.2. **Succinate dehydrogenase–deficient renal cell carcinoma**

SDH-deficient RCC is composed of vacuolated eosinophilic or clear cells [14,15]. Immunohistochemistry is a useful tool for their diagnosis because there is a loss of expression of SDHB, a marker of dysfunction of mitochondrial complex II (Fig. 2). It presents mainly in young adults, and most patients have germline mutations in an SDH gene [15]. Most tumours are solid, with a brown, sometimes red, cut surface. The most distinctive feature is the presence of cytoplasmic vacuoles. There are sometimes flocculent inclusions. Most SDH-deficient RCC has good prognosis. In cases with sarcomatoid differentiation and necrosis, the prognosis is less favourable.

3.3. **Tubulocystic renal cell carcinoma**

Tubulocystic RCC is a dominantly cystic renal epithelial neoplasm. Macroscopically, it is composed of multiple small to medium-sized cysts and has a spongy cut surface. The nuclei are enlarged with WHO/ISUP grade 3 nucleioli. The cytoplasm has abundant eosinophilic and oncocytoma-like aspects. Only 4 of 70 reported cases showed metastasis to bone, liver, and lymph nodes [16–19].

3.4. **Acquired cystic disease–associated renal cell carcinoma**

Acquired cystic disease–associated RCC occurs in the kidneys of end-stage renal disease and acquired cystic kidney disease [20]. Histologically, these tumours show a
broad spectrum with a cribriform, microcystic, or sieve-like architecture. They have an eosinophilic and/or clear cytoplasm and prominent nucleoli. Calcium oxalate crystal deposition is common. CK7 is typically not expressed. Most tumours have indolent behaviour.

3.5. Clear cell papillary renal cell carcinoma

Clear cell papillary RCC is a renal epithelial neoplasm composed of low-grade clear epithelial cells arranged in tubules and papillae with a predominantly linear nuclear alignment away from the basement membrane [20]. They account for up to 5% of all resected renal tumours and arise sporadically in end-stage renal disease and VHL syndrome [21,22]. Some of these tumours were previously referred to as renal angioadenomatous tumours. The tumour cells have characteristic diffuse CK7 positivity and carbonic anhydrase IX positivity in a cuplike distribution. CD10 is negative or only focally positive (Fig. 3). According to current knowledge, these tumours have indolent behaviour.

4. Emerging or provisional renal tumour entities

The 2013 ISUP Vancouver classification identified a category of emerging or provisional new entities. Some of these emerging entities have been accepted by the WHO, and others were kept as emerging. The WHO classification noted that although these entities appear to be distinct, they are rare tumours that are not yet fully characterized by morphology, immunohistochemistry, and molecular studies. Consequently, further reports are needed to refine their diagnostic criteria and established clinical outcomes.

SDH-deficient RCC was regarded as an emerging entity in the Vancouver classification but now is considered to be an established entity. RCC in neuroblastoma survivors was included in the 2004 WHO classification [23]; however, it is now recognized that some of these tumours represent MiT
family translocation RCCs [24], and others are difficult to classify based on the published pathologic details. Consequently, it was decided to remove this entity from the 2016 WHO classification, although it may be distinct, and to continue to consider it as an emerging entity. Very few thyroid-like follicular RCCs have been described [25,26]. Most of these tumours have indolent behaviour. Fewer than 10 RCCs associated with ALK gene rearrangements have been reported in the literature [27–29]; some are medullary-based tumours. Recently, reports of RCC associated with prominent angioleiomyomatous stroma have been published. It is unclear if the renal angioleiomyomatous tumour represents a variant of ccRCC or clear cell papillary RCC [30]. Some tumours were sporadic, and others were associated with tuberous sclerosis [31]. A recent report identified TCEB1 gene mutations in tumours with this morphology [32].

5. Grading of renal tumours

Many grading systems have been proposed for renal cell neoplasia. The Fuhrman system was the most frequently used grading system in RCC but should not be applied for chromophobe RCC [33]. Furthermore, the Fuhrman system has not been validated for most of the new subtypes of renal carcinoma. For these reasons, the four-tiered WHO/ISUP grading system is recommended by the WHO [34]. For grade 1–3 tumours, the system defines tumour grade based on nucleolar prominence. Grade 4 is defined by the presence of pronounced nuclear pleomorphism, tumour giant cells, and/or rhabdoid and/or sarcomatoid differentiation (Fig. 4). This grading system has been validated for ccRCC and papillary RCC. It has not yet been validated for other tumour types because of the small numbers of reported cases.

6. Important future issues in renal tumour pathology

First, the VHL tumour suppressor protein pVHL functions as a tumour suppressor via HIF-dependent regulation in most ccRCC. The chromosome 3p locus, however, contains up to seven potential ccRCC tumour suppressor genes: VHL, PBRM1, BAP1, SETD2, RASSF1A, TUS3A, and DLEC1. The elucidation of the effects of different combinations of mutations on the initiation and progression of ccRCC will be an important future area of research [4].

Second, the identification of novel therapeutic agents that are effective against RCC cells that harbour specific genetic alterations is an important ongoing research topic [35]. This area includes emerging immunotherapies targeting immune checkpoints and tumour-associated antigens in patients with RCC [36]. In contrast to other solid tumours (eg, melanoma or lung cancer), there are presently no predictive molecular biomarkers suitable for routine use [37]. The use of such potential biomarkers must account for the considerable genetic intratumoural heterogeneity with the parallel evolution of multiple tumour clones [38,39].

Third, there has been a remarkable expansion of knowledge about the genetics of renal cancer in recent years. This has led to greater understanding of the molecular pathogenesis of renal cancer [40]. Such knowledge will be incorporated into a future WHO classification and will clarify the position of some emerging renal tumour entities (eg, TCEB1-mutated RCC and angiomyoadenomatous RCC) or the subgroups of papillary RCC [9,30,32].

Fourth, the novel WHO/ISUP grading system has been validated for ccRCC and papillary RCC but not for other tumour types [34]. Several grading schemes have been proposed for chromophobe RCC to predict its behavioural outcome [41–44]. It is important to have an internationally accepted chromophobe RCC grading system in the near future.

7. The new classification of penile 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. Most previous classification schemes were exclusively morphology based. The 2016 WHO classification presents a new classification based on clinicopathologic distinctiveness and relation to human papillomavirus (HPV) infection (Fig. 5).

7.1. Non–human papillomavirus–related subtypes

Non–HPV-related subtypes of SCC are mainly SCC of the usual type (Fig. 6A). Pseudohyperplastic carcinomas [45] and pseudoglandular carcinomas [46] are also non–HPV related. Pseudohyperplastic carcinomas [45] occur in patients in the seventh and eighth decades of life and are associated with lichen sclerosus. Pseudoglandular carcinomas [46] are aggressive tumours simulating adenoscarcinomas. verrucous carcinoma is a nonmetastasizing low-grade neoplasm with carcinoma cuniculatum as a variant [47]. Carcinoma cuniculatum is a rare low-grade tumour with a labyrinthine growth pattern with no metastatic potential. Other non–HPV-related subtypes of SCC are papillary [48], adenosquamous [49], and sarcomatoid SCC, the latter with the worst prognosis among all penile carcinomas.
7.2. Human papillomavirus–related carcinomas

HPV-related carcinomas are basaloid [50] (Fig. 6B) and warty (condylomatous) SCC [51]. Basaloid SCC has a high rate of nodal metastasis, whereas warty (condylomatous) carcinomas [51] are rarely associated with regional nodal metastasis. Other HPV-related SCCs include warty-basaloid [52] and the rare variants of papillary-basaloid [53] and clear cell carcinomas [54]. Very unusual HPV-related tumours are lymphoepithelioma-like [55] and medullary SCC [56].

Penile intraepithelial neoplasia (PeIN) is a precursor lesion of invasive SCC showing a penile squamous epithelium characterized by dysplastic changes with an intact basement membrane. Non–HPV-related PeIN is the so-called differentiated PeIN, whereas basaloid and warty (or mixed basaloid–warty) PeINs are usually associated with HPV (Fig. 7).
The three-tiered WHO/ISUP grading system is the recommended grading system for penile SCC. Well-differentiated carcinomas (grade 1) have cytologic aspects of normal squamous tissue. The tumour cells grow in an irregular nesting pattern with little intervening stroma. Poorly differentiated carcinomas (grade 3) have an irregular growth of small tumour cell nests, poor keratinization, polymorphic tumour cells with hyperchromatic nuclei, frequent mitoses, and marked stromal reaction. The cases that do not qualify as grade 1 or 3 are grade 2.

8. The new classification of testicular tumours

Some important changes have been made in the WHO classification of testicular tumours in 2016 compared with that adopted in 2004 [3]. These revisions were discussed over the course of several months in 2014 through e-mail communications and were finalized in Zurich, Switzerland, in March 2015. The most significant differences between the newly published classification and the prior version concern the germ cell tumours (Fig. 8), but other categories are also affected.

It has been recognized for several decades that the majority of germ cell tumours arise from progression of an intratubular malignant germ cell that has the morphologic and immunohistochemical features of a seminoma cell. Such cells were usually designated as either carcinoma in situ (CIS) [57] or intratubular germ cell neoplasia, unclassified (IGCNU) [58], with those terms receiving preferential use in Europe and North America, respectively. Some others, however, have been used, including testicular intraepithelial neoplasia [59] and gonocytoma in situ [60]. The use of different terms for the identical lesion has been a source of some confusion, and neither the two predominant terms nor any of the previously used alternatives were considered entirely satisfactory by the testis subcommittee. The main objection to CIS was that the malignant germ cells to which it referred were not epithelial (a similar objection applied to testicular intraepithelial neoplasia), whereas IGCNU, because it contained the word unclassified, was felt to falsely convey an element of doubt concerning the nature and clinical behaviour of the lesion. Germ cell neoplasia in situ (GCNIS) was proposed as an alternative term, retaining the in situ nomenclature that correctly conveys the fact that the lesion is a well-established precursor to an invasive germ cell tumour and simultaneously does away with both the misleading epithelial-based nomenclature and the use of the word unclassified. It was recognized that IGCNU, and specifically the unclassified designation, was originally adopted to distinguish it from differentiated forms of intratubular neoplasia [58], most commonly intratubular seminoma and intratubular embryonal carcinoma. There was concern that GCNIS did not make this distinction, but the testis subcommittee made the important point that GCNIS refers to malignant germ cells that develop in the spermatogonial niche (Fig. 9), which is the usual in situ location for germ cells in the early differentiated testis [61]. All other forms of intratubular neoplasia are no longer confined to this location but typically fully occupy the tubular diameter. GCNIS is now the WHO-recommended term for this precursor lesion, and other forms of intratubular neoplasia should be referred to by their differentiated phenotype with the prefix intratubular.

A new emphasis in WHO 2016 is the distinction of GCNIS from maturation-delayed germ cells, which are a relatively common feature in the gonads of patients with disorders of sex development [61–63]. It is believed that maturation-delayed germ cells likely give rise to GCNIS, but they should be distinguished from the latter because progression is not invariable. Unfortunately, both lesions express the usual markers used for the identification of GCNIS (eg, OCT3/4, placental alkaline phosphatase, AP-2γ). The differentiation of the two relies on the more diffuse distribution and central tubular location of maturation-delayed germ cells (Fig. 10) as well as the lack of expression of KIT ligand (stem cell factor) in the associated seminiferous tubules, which contrast with the findings in GCNIS [61,63,64].

The prior version of the WHO classification was purely morphologically based and divided the germ cell tumours into those of simple or more than one histologic type. In so doing, quite disparate tumours came to be placed under similar diagnostic terms. The new approach recognizes that there are significantly different pathogeneses for testicular germ cell tumours, despite only subtle or even—in the case of yolk sac tumour of paediatric and adult types—no perceptible morphologic differences. The germ cell tumours are now broadly separated into two fundamentally different groups: those derived from GCNIS and those unrelated to
GCNIS (Fig. 8). It is apparent, however, that the latter group is heterogeneous. In contrast, the former group shows a number of basic similarities despite varied morphologies and, to some extent, behaviours. The GCNIS-derived tumours have comparable epidemiologic associations and usually occur in a background of perturbed testicular development that has recognizable morphologic features: impaired spermatogenesis, tubular shrinkage, peritubular sclerosis, immature Sertoli cells, interstitial widening, hyalinized tubules, and microlithiasis [65,66]. They share the finding of amplification of genetic material from the short arm of chromosome 12, often in the form of isochromosome 12p, and represent progression from GCNIS, often through at least a transient stage of seminoma that may be intratubular.

In making this separation among the germ cell tumours, it was necessary to remove entities from the GCNIS-derived group and to introduce changes in nomenclature. The testis subcommittee recommended that the entity known as spermatocytic seminoma be newly designated as spermatocytic tumour and simultaneously placed within the non–GCNIS-related tumours (Fig. 8) because its lack of association with GCNIS and different molecular features are well established, and it shows no relationship with seminoma or any other neoplasm in the GCNIS-derived group [67–72]. Because teratomas and yolk sac tumours may develop from GCNIS or apart from it, it was recommended that the GCNIS-derived entities be designated as postpubertal type and the non–GCNIS-related ones be designated as prepubertal type (Fig. 8) because the former

### WHO classification of tumours of the testis

<table>
<thead>
<tr>
<th>Germ cell tumours derived from germ cell neoplasia in situ</th>
<th>Germ cell tumours unrelated to germ cell neoplasia in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive germ cell neoplasia</strong></td>
<td>Spermatocytic tumour</td>
</tr>
<tr>
<td>Germ cell neoplasia in situ</td>
<td>9063/3</td>
</tr>
<tr>
<td>Specific forms of intratubular germ cell neoplasia</td>
<td>Teratoma, prepubertal-type</td>
</tr>
<tr>
<td><strong>Tumours of a single histological type (pure forms)</strong></td>
<td>9084/0</td>
</tr>
<tr>
<td>Seminoma</td>
<td>Dermoid cyst</td>
</tr>
<tr>
<td>Seminoma with syncytiotrophoblast cells</td>
<td>Epidermoid cyst</td>
</tr>
<tr>
<td>Non-seminomatous germ cell tumours</td>
<td>Well-differentiated neuroendocrine tumour (monodermal teratoma)</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>8240/3</td>
</tr>
<tr>
<td>Yolk sac tumour, postpubertal-type</td>
<td>Mixed teratoma and yolk sac tumour, prepubertal-type</td>
</tr>
<tr>
<td>Trophoblastic tumours</td>
<td>9085/3</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Yolk sac tumour, prepubertal-type</td>
</tr>
<tr>
<td>Non-choriocarcinomatous trophoblastic tumours</td>
<td>9071/3</td>
</tr>
<tr>
<td>Placental site trophoblastic tumour</td>
<td>Germ cell tumours of unknown type</td>
</tr>
<tr>
<td>Epithelioid trophoblastic tumour</td>
<td>9080/1</td>
</tr>
<tr>
<td>Cystic trophoblastic tumour</td>
<td>Germ cell tumours unrelated to germ cell neoplasia in situ</td>
</tr>
<tr>
<td>Teratoma, postpubertal-type</td>
<td>Spermatocytic tumour</td>
</tr>
<tr>
<td>Teratoma with somatic-type malignancy</td>
<td>9063/3</td>
</tr>
<tr>
<td>Non-seminomatous germ cell tumours of more than one histological type</td>
<td>Teratoma, prepubertal-type</td>
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<td>Mixed germ cell tumours</td>
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<td>Germ cell tumours of unknown type</td>
<td>Yolk sac tumour, prepubertal-type</td>
</tr>
<tr>
<td>Regressed germ cell tumours</td>
<td>9080/1</td>
</tr>
</tbody>
</table>

**Sex cord–stromal tumours**

- Pure tumours
  - Leydig cell tumour: 8650/1
  - Malignant Leydig cell tumour: 8650/3
- Sertoli cell tumour: 8640/1
  - Malignant Sertoli cell tumour: 8640/3
  - Large cell calcifying Sertoli cell tumour: 8642/1
  - Intratubular large cell hyalinizing Sertoli cell neoplasia: 8643/1*

**Granulosa cell tumour**
- Adult granulosa cell tumour: 8620/1
- Juvenile granulosa cell tumour: 8622/1*
- Tumours in the fibroma-thercoma group: 8600/0
- Mixed and unclassified sex cord–stromal tumours: 8592/1
- Mixed sex cord–stromal tumour: 8592/1
- Unclassified sex cord–stromal tumour: 8591/1
- Tumour containing both germ cell and sex cord–stromal elements: 8580/0
- Gonadoblastoma: 9073/1

**Miscellaneous tumours of the testis**
- Ovarian epithelial-type tumours: 8441/0
  - Serous cystadenoma
  - Serous tumour of borderline malignancy: 8442/1
  - Serous cystadenocarcinoma: 8443/1
  - Mucinous cystadenoma: 8470/0
  - Mucinous borderline tumour: 8472/1
  - Mucinous cystadenocarcinoma: 8470/3
  - Endometrioid adenocarcinoma: 8380/0
  - Clear cell adenocarcinoma: 8310/3
  - Brenner tumour: 9000/0
  - Juvenile xanthogranuloma: 9120/0
  - Haemangioma: 9120/0

**Haematolymphoid tumours**
- Diffuse large B-cell lymphoma: 9680/3
  - Follicular lymphoma, NOS: 9690/3
  - Extramedullary NK/T-cell lymphoma, nasal-type: 9719/3
  - Plasmacytoma: 9734/3
  - Myeloid sarcoma: 9930/3
  - Rosai–Dorfman disease: 9930/3

**Tumours of collecting duct and rete testis**
- Adenoma: 8140/0
- Adenocarcinoma: 8140/3

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*Fig. 8 – World Health Organization classification of germ cell tumours of the testis. Reproduced with permission from the World Health Organization International Agency for Research on Cancer [1].

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O-3) [1]. Behaviours are coded 1 for benign tumours; 2 for unspecified, borderline, or uncertain behaviour; 3 for carcinoma in situ and grade III intratubular neoplasia; and 4 for malignant tumours. The classification is modified from the previous WHO classification (798A), taking into account changes in our understanding of these lesions.

*New code approved by the IARC/WHO Committee for ICD-O.
usually develops in adults and the latter in children. It is recognized, however, that the prepubertal-type tumours may, rarely, occur in postpubertal patients [73,74], and the postpubertal-type tumours may occur in paediatric patients who have disorders of sex development [75,76]. The evidence for making these changes is abundant. Spermatocytic tumour lacks not only association with GCNIS but also 12p amplification, shows a unique amplification of chromosome 9 corresponding to the DMRT1 gene, and is never associated with other forms of germ cell tumour. In addition to lacking GCNIS [77,78], prepubertal-type teratoma and yolk sac tumour also lack 12p amplification and do not occur in malformed testes [79]. The prepubertal-type teratomas show no genetic abnormalities, whereas the prepubertal-type yolk sac tumours show characteristic gains and losses of portions of several chromosomes that differ from those frequently occurring in the GCNIS-derived tumours [79]. Although there are no apparent differences in tumour morphology between the prepubertal and postpubertal forms of yolk sac tumour, the prepubertal teratomas—in contrast to the postpubertal ones—lack any cytologic atypia and are more frequently organoid with prominent components of smooth muscle and ciliated and squamous epithelium [73]. The benign behaviour of the prepubertal-type teratomas [73,80] contrasts with that of the postpubertal type [81,82], and the prepubertal-type yolk sac tumours behave less aggressively than the postpubertal-type tumours, with a significantly lower frequency of relapse on surveillance of clinical stage I patients and of lymphatic-based metastases [83–85].

An additional change that naturally follows the recognition of the prepubertal-type teratomas is placement of dermoid cyst, epidermoid cyst, and carcinoid tumour (well-differentiated neuroendocrine tumour) as specialized forms of prepubertal-type teratomas (Fig. 8). This is supported by the absence of GCNIS and 12p amplification in association with these entities, consistently so for the first two and in the majority of cases for carcinoid tumour [73,78,86,87], although some contradictory information in the literature suggests the possibility of a dual pathogenesis for carcinoid tumour [88,89]. Additional work is required to resolve this question.

In the prior WHO classification, the trophoblastic tumours were divided into choriocarcinoma and nonchoriocarcinomatous trophoblastic tumours, the latter represented by placental-site trophoblastic tumour (PSTT). So-called monophasic choriocarcinoma was also discussed in the nonchoriocarcinomatous trophoblastic tumours category. The current classification, however, does not separately recognize monophasic choriocarcinoma but considers it a morphologic variant of choriocarcinoma. In addition, the nonchoriocarcinomatous trophoblastic tumour group has been expanded, recognizing not only PSTT but also epithelioid trophoblastic tumour (ETT) and cystic trophoblastic...
tumour (CTT) [Figs. 8 and 11] [90,91]. Although these entities have most frequently been reported in metastatic sites after chemotherapy, their de novo development in the testis is now established. The PSTT consists of intermediate trophoblast cells that are positive for human placental lactogen (HPL) and negative for p63. They are usually loosely cohesive and tend to invade the walls of blood vessels, provoking a fibrinoid reaction. ETT has a more cohesive arrangement of squamoid cells, typically displaying apoptotic and fibrinoid material within cell nests, usually lacks vascular invasion, and is HPL negative and p63 positive. CTT consists of frequently vacuolated trophoblast cells that line gaping spaces that may contain eosinophilic material. Based on the available evidence, these lesions are less aggressive than choriocarcinoma, but the data are limited.

In the sex cord–stromal tumours, the sclerosing Sertoli cell tumour [92,93] is no longer separately classified. These tumours are now considered to be morphologic variants of Sertoli cell tumour, not otherwise specified (NOS), based on the occurrence of CTNNB1 gene mutations and nuclear β-catenin staining in a similar proportion of both [94–96]. Nonetheless, it is recommended to continue to use this term for those Sertoli cell tumours, NOS, that have a hypocellular fibrous stroma in excess of 50% of the tumour based on their overall better prognosis than more cellular tumours. Intratubular large cell hyalinizing Sertoli cell tumour [97] has been added to the classification as a distinct entity associated with the Peutz-Jeghers syndrome and as having a characteristic mutation of the STK11 gene. Myoid gonadal stromal tumour [98–100] is considered an emerging entity characterized by fusiform cells arranged in short fascicles that coexpress S-100 protein and smooth muscle actin.

Gonadoblastoma [101–103] is now recognized as the only entity in the mixed germ cell–sex cord–stromal category, with the unclassified form of germ cell–sex cord–stromal tumour considered not sufficiently established by the available evidence [104,105]. There is additional emphasis on the recognition of “undifferentiated gonadal tissue” as a frequent finding that accompanies gonadoblastoma and is its likely precursor [106,107].

In contrast to the prior classification, there is no recognized benign mesothelioma category. The well-differentiated papillary mesothelioma was considered by the testis subcommittee to be a variant of mesothelioma that tends to behave indolently, but the members noted that progression has been identified in other sites by morphologically identical tumours [108,109]. In addition, cystic mesothelioma, which had also been placed in the benign mesothelioma category, was regarded as either a non-neoplastic condition (mesothelial cysts) [110] or a variant of conventional mesothelioma.

Fig. 11 – (A) A focus of placental site trophoblastic tumour showing loose clusters of variably sized mononucleated and occasionally multinucleated cells in a hyalinized, nonhaemorrhagic background. (B) Epithelioid trophoblastic tumour shows cohesive nests of atypical squamoid cells with admixed apoptotic cells and deposits of fibrinoid material. (C) Cystic trophoblastic tumour in an untreated testis showing the characteristic vacuolated tumour cells lining a cystic space.

References


