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Creating a Better Pathologist
The 2016 World Health Organization Classification of Testicular Tumors:
An Update

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The text of this handout is part of a summary/review on the 2016 WHO classification of urogenital tumors in European Urology (in press).
Some important changes have been made in the World Health Organization (WHO) classification of testicular tumors in 2016 compared to that adopted in 2004 [1]. These revisions were performed after consideration by a large group of pathologists with special interest and expertise in this area and who discussed them over the course of several months in 2014 through e-mail communications. A subgroup of these persons then met in Zurich, Switzerland in March 2015 to discuss and finalize the revisions. This paper will review the most significant differences between the newly published classification, including some changes in nomenclature, and the prior version. Most concern the germ cell tumors but other categories are also affected.

It has been recognized for several decades that the majority of germ cell tumors arise from progression of an intratubular malignant germ cell that has the morphological and immunohistochemical features of a seminoma cell. Such cells were usually designated either as “carcinoma in situ” (CIS) [2] or “intratubular germ cell neoplasia, unclassified” (IGCNU) [3], with those terms receiving preferential use in Europe and North America, respectively. Some others, however, have also been used, including testicular intraepithelial neoplasia [4] and gonocytoma-in-situ [5]. The use of different terms for the identical lesion has been a source of some confusion, and neither of the two predominant terms or any of the previously used alternatives was considered entirely satisfactory by the testis subcommittee. The main objection to CIS was that the malignant germ cells it referred to were not epithelial (a similar objection applies to testicular intraepithelial neoplasia), whereas IGCNU, because it contained “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 tumor and simultaneously does away with both the misleading epithelial-based nomenclature and the use of the word “unclassified.” It was recognized that the original adoption of IGCNU, and specifically the “unclassified” designation, was to distinguish it from
differentiated forms of intratubular neoplasia [3], 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,” which is the normal, “in situ” location for germ cells in the early differentiated testis [6]. All other forms of intratubular neoplasia are no longer confined to this location but typically fully occupy the tubular diameter. GCNIS, therefore, 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.”

One 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 (DSD) [6-8]. It is believed that maturation-delayed germ cells likely do give rise to GCNIS but they should be distinguished from the latter because progression is not invariable. Unfortunately, both lesions express the usual markers employed for the identification of GCNIS (e.g. – OCT3/4, placental alkaline phosphatase, AP-2γ, etc.) The differentiation of the two relies on the more diffuse distribution and central tubular location of maturation delayed germ cells, 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 [6, 8, 9].

The prior version of the WHO classification was purely morphologically based and divided the germ cell tumors into those of single and those of more than one histological type. In so doing quite disparate tumors came to be placed under similar diagnostic terms. The new approach recognizes that there are significantly different pathogeneses for testicular germ cell tumors, despite only subtle or even, in the case of yolk sac tumor of pediatric and adult types, no perceptible morphological differences. The germ cell tumors are now broadly separated into two fundamentally different groups – those derived from GCNIS and those unrelated to GCNIS (Table) - although it is even now apparent that
the latter group is heterogeneous. The former group, on the other hand, despite varied morphologies and, to some extent, behaviours, show a number of basic similarities. The GCNIS-derived tumors have comparable epidemiological 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 [10, 11]. They share the finding of amplification of genetic material from the short arm of chromosome 12, often, but not always, in the form of an isochromosome – i(12p) - and represent progression from GCNIS, often through at least a transient stage of seminoma, which may be intratubular.

In making this separation among the germ cell tumors, 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 tumor” and simultaneously placed within the non-GCNIS related tumors, as 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 group [12-17]. Because teratomas and yolk sac tumors 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,” since these usually develop in adults and children, respectively. It is recognized, however, that the prepubertal-type tumors may, rarely, occur in postpubertal patients [18, 19] and the postpubertal-type tumors in pediatric patients who have DSDs [20, 21]. The evidence for making these changes is abundant. Spermatocytic tumor not only lacks association with GCNIS, but it also lacks 12p amplification, shows a unique amplification of chromosome 9 corresponding to the DMRT1 gene and is never associated with other forms of germ cell tumor. In addition to lacking GCNIS [22, 23], prepubertal-type teratoma and yolk sac tumor also lack 12p amplification and do not occur in malformed testes [24].
The prepubertal-type teratomas show no genetic abnormalities whereas the prepubertal-type yolk sac tumors show characteristic gains and losses of portions of several chromosomes that differ from those frequently occurring in the GCNIS-derived tumors [24]. Although there are no apparent differences in tumor morphology between the prepubertal and postpubertal forms of yolk sac tumor, the prepubertal teratomas, in contrast to the postpubertal ones, lack any cytological atypia and are more frequently organoid with prominent components of smooth muscle and ciliated and squamous epithelium [18]. The benign behavior of the prepubertal-type teratomas [18, 25] contrasts with that of the postpubertal-type ones [26, 27], and the prepubertal-type yolk sac tumors behave less aggressively than the postpubertal-type tumors, with a significantly higher frequency of presentation with clinical stage I disease and less frequent occurrence of lymphatic-based metastases [28-30].

An additional change that follows naturally the recognition of the prepubertal-type teratomas is placement of dermoid cyst, epidermoid cyst and carcinoid tumor as specialized forms of prepubertal-type teratomas. 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 tumor [18, 23, 31, 32], although there is some contradictory information in the literature that suggests the possibility of a dual pathogenesis for carcinoid tumor [33, 34]. Additional work, however, is required to resolve this question.

In the prior WHO classification the trophoblastic tumors were divided into choriocarcinoma and non-choriocarcinomatous trophoblastic tumors, the latter represented by placental site trophoblastic tumor. So-called “monophasic choriocarcinoma” was also discussed in the non-choriocarcinomatous trophoblastic tumors category. The current classification, however, does not separately recognize “monophasic choriocarcinoma” but considers it a morphologic variant of choriocarcinoma. It has additionally expanded the non-choriocarcinomatous trophoblastic tumor group, recognizing not only placental site trophoblastic tumor (PSTT) but also epithelioid trophoblastic tumor (ETT) and cystic
trophoblastic tumor (CTT) [35, 36]. While 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 tumors the sclerosing Sertoli cell tumor [37, 38] is no longer separately classified. These tumors are now considered to be morphologic variants of Sertoli cell tumor, not otherwise specified (NOS) based on the occurrence of CTNNB1 gene mutations and nuclear β-catenin staining in a similar proportion of both [39-41]. Nonetheless, it is recommended to continue to use this term for those Sertoli cell tumors, NOS that have a hypocellular fibrous stroma in excess of 50% of the tumor based on their overall better prognosis than more cellular tumors. Intratubular large cell hyalinizing Sertoli cell tumor [42] has been added to the classification as a distinct entity associated with the Peutz-Jeghers syndrome and having a characteristic mutation of the STK11 gene. Myoid gonadal stromal tumor [43-45] is considered an emerging entity characterized by fusiform cells arranged in short fascicles that coexpress S-100 protein and smooth muscle actin.

Gonadoblastoma [46-48] 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 tumor not considered sufficiently established by the available evidence [49, 50]. There is additional emphasis on the recognition of “undifferentiated gonadal tissue” as a frequent finding that accompanies gonadoblastoma and is its likely precursor [51, 52].
In contrast to the prior classification, there is no recognized “benign mesothelioma” category. The well differentiated papillary mesothelioma was considered by the testis subcommittee as a variant of mesothelioma that tends to behave indolently, but the members noted that progression has been identified in other sites by morphologically identical tumors [53, 54]. Additionally “cystic mesothelioma,” which had also been placed in the “benign mesothelioma” category, was regarded as either a non-neoplastic condition (mesothelial cysts) [55] or a variant of conventional mesothelioma.
References


Table – Classification of germ cell tumors of the testis

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

Tumors of a single histological type (pure tumors)
  - Seminoma
  - Seminoma with syncytiotrophoblast cells

Non-seminomatous germ cell tumors
  - Embryonal carcinoma
  - Yolk sac tumor, postpubertal-type
  - Trophoblastic tumors
    - Choriocarcinoma
    - Non-choriocarcinomatous trophoblastic tumors
      - Placental site trophoblastic tumor
      - Epithelioid trophoblastic tumor
      - Cystic trophoblastic tumor
    - Teratoma, postpubertal-type
    - Teratoma with somatic-type malignancy

Non-seminomatous germ cell tumors of more than one histological type
  - 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
  - Dermoid cyst
  - Epidermoid cyst
  - Well-differentiated neuroendocrine tumor (monodermal teratoma)
  - Mixed teratoma and yolk sac tumor, prepubertal-type
  - Yolk sac tumor, prepubertal-type