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REVIEW

The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel

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The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel

Since the last World Health Organization (WHO) classification scheme for tumours of the urinary tract and male genital organs, there have been a number of advances in the understanding, classification, immunohistochemistry and genetics of testicular germ cell tumours. The updated 2016 draft classification was discussed at an International Society of Urological Pathology Consultation on Testicular and Penile Cancer. This review addresses the main updates to germ cell tumour classification. Major changes include a pathogenetically derived classification using germ cell neoplasia *in situ* (GCNIS) as a new name for the precursor lesion, and the distinction of prepubertal tumours (non-GCNIS-derived) from postpubertal-type tumours (GCNIS-derived), acknowledging the existence of rare benign prepubertal-type teratomas in the postpubertal testis. Spermatocytic tumour is adopted as a replacement for spermatocytic seminoma, to avoid potential confusion with the unrelated usual seminoma. The spectrum of trophoblastic tumours arising in the setting of testicular germ cell tumour continues to expand, to include epithelioid and placental site trophoblastic tumours analogous to those of the gynaecological tract. Currently, reporting of anaplasia (seminoma or spermatocytic tumour) or immaturity (teratoma) is

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not required, as these do not have demonstrable prognostic importance. In contrast, overgrowth of a teratomatous component (somatic-type malignancy) and sarcomatous change in spermatocytic tumour indicate more aggressive behaviour, and should be reported.

Keywords: germ cell neoplasia *in situ*, germ cell tumour, postpubertal-type teratoma, spermatocytic tumour

Introduction

Since the publication of the last World Health Organization (WHO) Classification of Tumours of the Urinary System and Male Genital Organs in 2004,[1] there have been a number of advances in our knowledge of the diagnosis, classification and genetics of testicular germ cell tumours, including novel immunohistochemical markers, improved understanding of underlying molecular changes, and refinements to the relationships of tumour types. To reflect current thinking on the classification of germ cell tumours, the WHO draft classification system for the genitourinary organs[2] was discussed by the International Society of Urological Pathology (ISUP) at an International Consultation on Testicular and Penile Cancer in Boston, Massachusetts, USA in 2015. Areas of controversy not encompassed by the WHO classification were debated, and consensus practice recommendations were proposed. As part of the ISUP Consultation, a survey was distributed to the ISUP membership to assess current practice patterns in testicular tumour classification, microscopy, and staging.

Classification system

With regard to an overall classification scheme, the vast majority of participants in the ISUP survey reported their current status as using the 2004 WHO classification for reporting of testicular germ cell tumours (226/232, 97%), with only a small minority using alternative systems, including: the British Testicular Tumour Panel[3] (BTTP) in tandem with the WHO classification (4/232, 2%), the BTTP alone (1/232, <1%), or an earlier version of the WHO classification (1/232, <1%).

Precursor lesions

GERM CELL NEOPLASIA *IN SITU* (GCNIS)

The lesion that is most widely accepted as the precursor of adult malignant testicular germ cell tumours is composed of seminoma-like cells with enlarged hyperchromatic nuclei, clumped chromatin, and often prominent nucleoli, aligned along the basement membrane of seminiferous tubules (within the spermatogonial niche; Figure 1A,B).[4–7] Similarly to what is seen in seminoma and embryonal carcinoma, these cells are uniformly positive for the embryonic stem cell marker OCT3/4 (POU5F1).[8] This lesion has been historically referred to by a number of names, and was officially regarded as intratubular germ cell neoplasia, unclassified type (IGCNU) in the 2004 WHO system.[9] As has been discussed recently in detail,[10] GCNIS was accepted as an abbreviated but precise replacement for these terms in the 2016 WHO system, as it combines elements from the two most widely used terms, IGCNU and carcinoma *in situ*.[11]

OTHER INTRATUBULAR NEOPLASMS

The significance of other forms of intratubular neoplasia in the testis is less clearly understood than that of GCNIS. Intratubular seminoma (Figure 1C,D), for example, refers to complete filling of seminiferous tubules by cells with a similar appearance and immunohistochemical staining profile as seminoma. In contrast to GCNIS, the tubular architecture is lost (absent Sertoli cells), and sometimes the tubules are expanded in diameter.[12–14] Similarly, intratubular embryonal carcinoma refers to filling of pre-existing seminiferous tubules by embryonal carcinoma cells, often accompanied by intratubular necrosis and calcification (Figure 1E,F).[13–15] This tendency for there to be intratubular necrosis and calcification also has implications for the recognition of germ cell tumour regression,[16] as discussed additionally in later sections.

It remains incompletely understood whether these intratubular tumours represent an advanced precursor state or retrograde colonization of pre-existing seminiferous tubules by already invasive cancer.[12,14,15] Intratubular seminoma intuitively seems likely to represent a more advanced degree of GCNIS, as it can be found adjacent to both seminoma and non-seminomatous germ cell tumours, similarly to GCNIS.[12] In contrast, as intratubular embryonal carcinoma is rarely encountered as a sole lesion[17] without associated invasive non-seminomatous germ cell

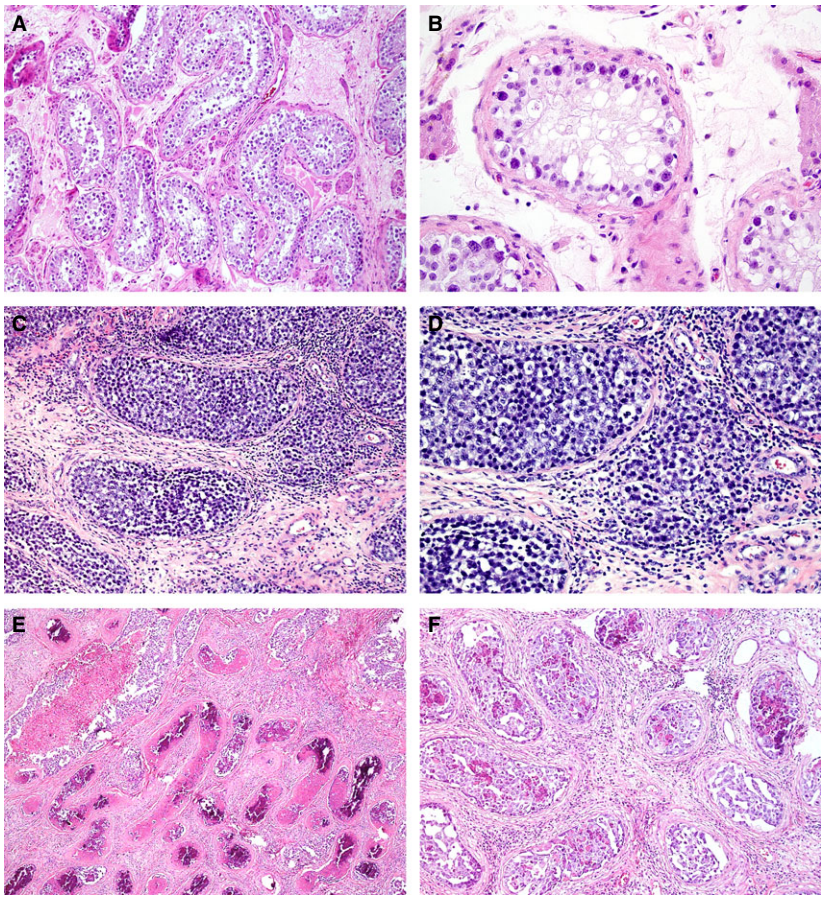

Figure 1. Germ cell neoplasia *in situ* typically shows an absence of maturing spermatogenesis (**A**) and a conspicuous layer of atypical cells resembling seminoma cells aligned along the basement membrane [the spermatogonial niche (**B**)]. Intratubular seminoma (**C**) often results in complete filling of seminiferous tubules by seminoma cells, in this example showing both intratubular and invasive components (**D**). Intratubular embryonal carcinoma is characteristically associated with intratubular necrosis and calcification (**E,F**).

tumour components,[14] it could be hypothesized that it represents already invasive cancer with retrograde colonization of seminiferous tubules. Conversely, if indeed it represents a precursor lesion, it is possible that it progresses very rapidly to invasion, accounting for its rarity as an isolated finding.

Intratubular trophoblastic cells can also be occasionally identified adjacent to germ cell tumours.[18] Although this phenomenon has gained relatively little attention and is probably often overlooked, one study using beta-human chorionic gonadotropin (hCG) immunohistochemistry found that intratubular trophoblastic cells can be seen adjacent to a considerable fraction of seminomas (5/29), particularly (or perhaps exclusively) when trophoblastic cells are also present in the invasive tumour.[18] Less frequently, hCG-positive intratubular cells can also be found adjacent to non-seminomatous and mixed germ cell tumours, again particularly when similar cells are also present in the invasive component.[18] This finding raises the question of whether this represents divergent differentiation within GCNIS or whether it develops through another mechanism.

In addition to these, spermatocytic tumour (formerly known as spermatocytic seminoma; discussed below) also frequently contains an intratubular component,[19] possibly representing its precursor lesion.[11] Like embryonal carcinoma, intratubular spermatocytic tumour has been very rarely found to occur without an infiltrative component,[19] which could similarly reflect rapid progression to invasion or perhaps that such early lesions rarely come to clinical attention.

Restructuring of classification

A major change to the structure of the WHO classification system for testicular germ cell tumours[11] is the division into two main groups (Figure 2): (i) tumours predominantly (but not exclusively) occurring in prepubertal patients, considered not to be derived from GCNIS; and (ii) tumours derived from GCNIS. The terms 'type I and type II' germ cell tumours' were previously suggested for his division,[20] but this typing has not been specifically adopted by

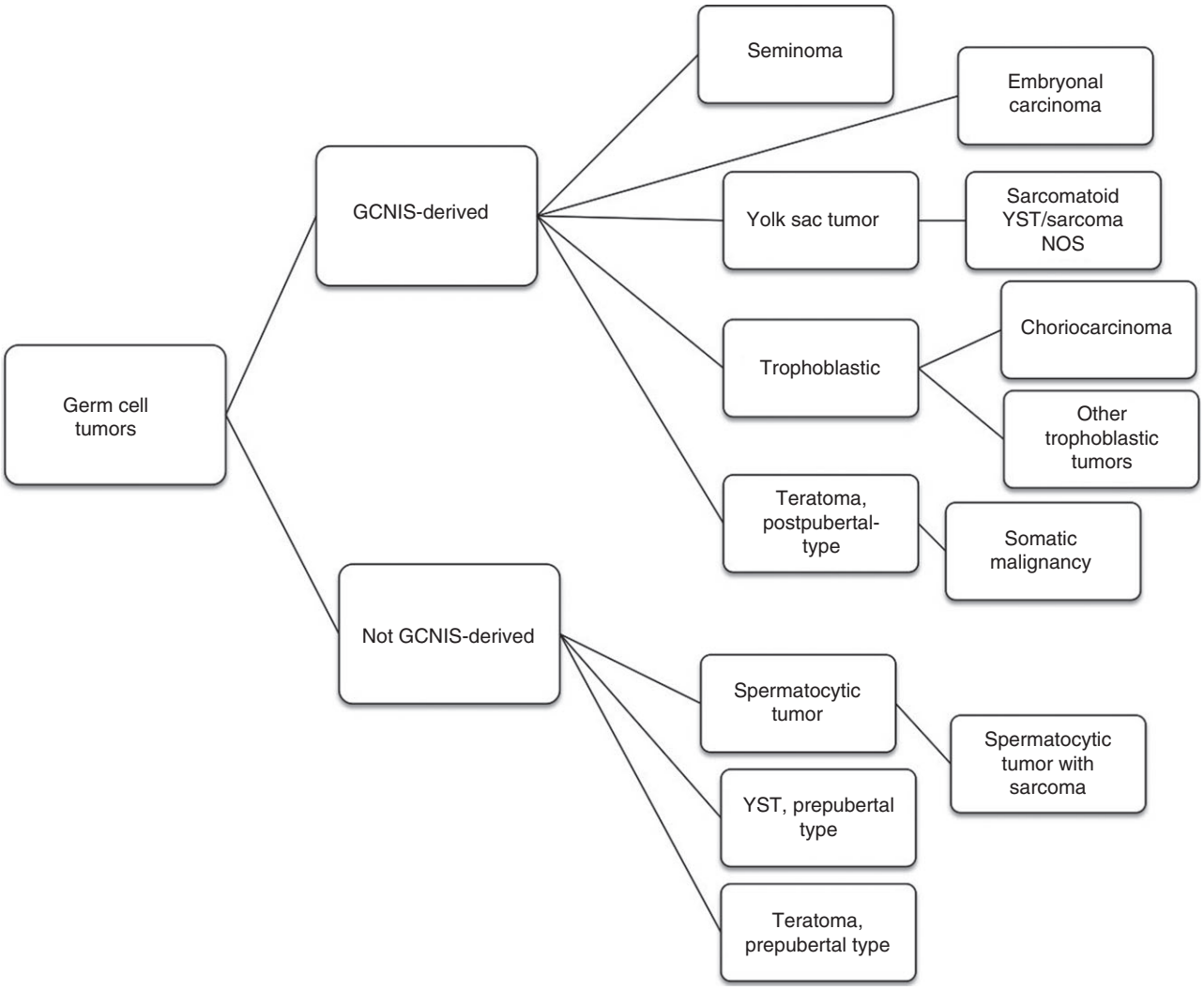

Figure 2. In the 2016 edition of the World Health Organization classification, germ cell tumour classification is restructured into tumours derived from germ cell neoplasia *in situ* (GCNIS) and those not derived from GCNIS. NOS, not otherwise specified; YST, yolk sac tumour.

the WHO. In the same schema, spermatocytic tumour was considered separately as a type III tumour. This change reflects the different behaviour, pathogenesis and tumour biology of similar histological patterns occurring in different contexts.

Seminoma

Although seminoma has been recognized to show a variety of histological patterns that may cause diagnostic challenges, there is currently no established clinical significance for these, apart from pathologists' ability to recognize them as seminoma and discriminate them from other tumours that would necessitate different clinical management. Syncytiotrophoblastic cells are occasionally present in seminoma, and this may be associated with typically modest elevations in serum beta-hCG levels.[21] When especially prominent, their presence may lead to potential diagnostic confusion with choriocarcinoma. Although these cells may form aggregates associated with cystic spaces or erythrocyte accumulation, they lack the association with a mononuclear trophoblastic component that is required for the diagnosis of choriocarcinoma. Other variations of seminoma morphology include subtle interstitial or intertubular infiltration (rarely occurring as a sole pattern without gross mass formation),[22] corded growth, microcystic or tubular structures,[23,24] a signet ring-like appearance,[25] and predominantly eosinophilic cytoplasm. The importance of most of

these patterns lies in their recognition as seminoma and distinction from potential mimics, such as sex cord–stromal tumours or carcinoma metastatic to the testis. In challenging cases, this can be facilitated by immunohistochemical staining for the highly associated germ cell tumour markers, such as OCT3/4, and markers of other lineages, such as inhibin, steroidogenic factor-1 (for sex cord–stromal tumours), or organ-specific carcinoma markers.[26]

An area that has received some attention in seminoma classification is assessment of differentiation or anaplasia.[27–29] Features that have been specifically assessed in this setting include larger, more vesicular nuclei and increased mitotic activity.[29] However, evidence that such histological features correlate with behaviour and outcome in pure seminoma is currently largely mixed and inconclusive. It is possible that these atypical cytological features represent an early stage in the transition from seminoma to another tumour type, particularly embryonal carcinoma. However, studies that have assessed ancillary markers of an embryonal carcinoma phenotype, such as CD30 immunohistochemistry in tumours morphologically appearing to be seminomas, have generally found an imperfect correlation with behaviour and staging.[30,31] The majority of respondents to the ISUP survey (204/232, 88%) indicated that they do not attempt to assess for differentiation or anaplasia in seminoma, and likewise the recommendation of this working group is that this should not be specifically reported, unless institutional or research protocols require it.

Trophoblastic tumours

Since the last WHO classification system was published,[9] there has been additional attention paid to testicular trophoblastic tumours other than the most widely recognized: choriocarcinoma. This group of lesions remains incompletely understood, and the rarity of some variant trophoblastic lesions precludes full analysis at present.

Cystic trophoblastic tumour[32] refers to a unique lesion that, to date, has shown non-aggressive behaviour, and is composed of cystic spaces lined by trophoblastic cells with smudged nuclei, often containing luminal fibrin (Figure 3A,B). Because of the eosinophilic cytoplasm of the cells and their low nuclear to cytoplasmic ratio, this may, in some cases, remain unrecognized and be interpreted as squamous epithelium or another type of teratomatous epithelium. This phenomenon is most often encountered in post-chemotherapy lymph node dissection specimens,

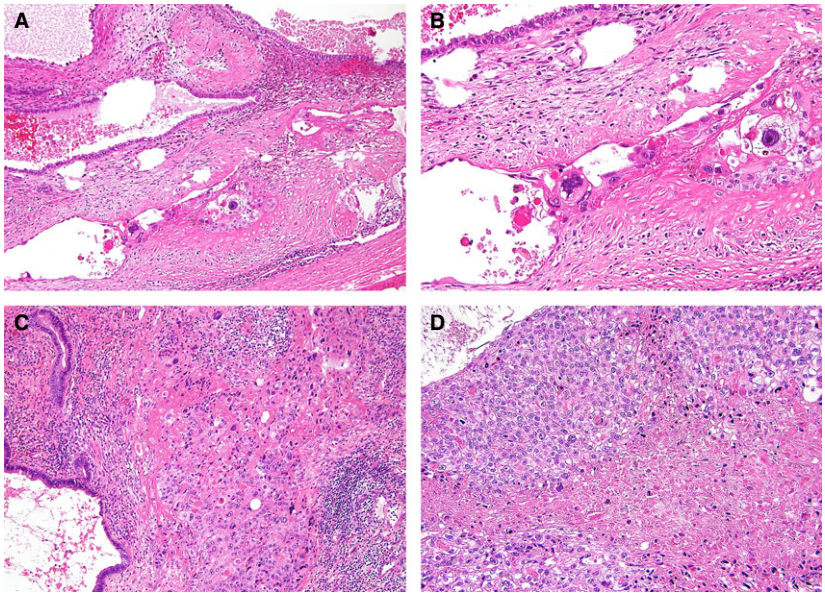

Figure 3. Discussion of trophoblastic tumours has been expanded in the 2016 World Health Organization classification of testicular tumours. Cystic trophoblastic tumour (**A,B**) is often associated with teratoma, composed of cystic spaces lined by trophoblastic cells with enlarged, hyperchromatic or smudged nuclei (B) and fibrinoid luminal contents. Despite the trophoblastic differentiation of this lesion, it appears to have similar behaviour to teratoma. Other forms of trophoblastic tumours, such as epithelioid trophoblastic tumour (**C,D**), have been rarely reported to arise in a primary testicular germ cell tumour. This example is composed of a solid arrangement of epithelioid trophoblastic cells arising in association with teratoma [(**C**) left and lower left].

usually as scattered foci admixed with teratoma. Despite the trophoblastic appearance of these cells and occasional reactivity for beta-hCG, the lesions are not infiltrative, lack the biphasic growth pattern of choriocarcinoma, and have low mitotic activity. Patients typically have only modest, if any, elevation of serum beta-hCG.[32] As patients with this finding do not appear to have the high rate of disease progression observed in patients with residual post-chemotherapy non-teratomatous tumours, current thinking is that cystic trophoblastic tumour should be clinically managed similarly to residual teratoma (not necessitating additional germ cell tumour-directed chemotherapy apart from surgical resection of persistent disease).[32] An initial hypothesis for this occurrence was that it represents choriocarcinoma with treatment response and 'maturation'; however, less frequently, this pattern may be found in the primary testicular tumour from untreated patients, suggesting that it may develop spontaneously as well. This raises the possibility that it might still evolve from choriocarcinoma, with spontaneous regression of the more highly proliferative elements.[33,34]

In addition to cystic trophoblastic tumour, other trophoblastic tumours analogous to their counterparts in the female genital tract have been recently and increasingly recognized both as primary testicular tumours and post-chemotherapy metastatic lesions, including epithelioid trophoblastic tumour, placental site trophoblastic tumour, regressing choriocarcinoma, and rare unclassified and hybrid trophoblastic tumours.[34–38] As for trophoblastic neoplasia in general,[39] GATA3 has emerged as a useful immunohistochemical marker of these various trophoblastic cell lineages, and this appears to also hold true if they have a testicular origin.[34] This, in combination with other trophoblastic lineage markers such as human placental lactogen (HPL), beta-hCG, placental alkaline phosphatase, and inhibin, may be helpful both in confirming a trophoblastic lineage and in cases where differential diagnostic considerations include a carcinoma arising from germ cell tumour (such as squamous cell carcinoma).[34] On the basis of work on the gynaecological counterparts, epithelioid trophoblastic tumours have been characterized as typically showing diffuse immunoreactivity for p63 and being negative for HPL, whereas placental site trophoblastic tumour shows the opposite pattern.[40] Although these non-choriocarcinomatous trophoblastic tumours appear to be rare in the testis, one recent series found epithelioid trophoblastic tumour to be the most common type (four of eight examples in the series; Figure 3C,D).[34] The behaviour of these tumours is not entirely understood; however, currently, distinguishing them from choriocarcinoma appears to be warranted, because of their less aggressive behaviour.[34]

Teratoma, postpubertal type

One of the key changes in the 2016 WHO classification system is the discrimination of postpubertal-type teratoma from prepubertal-type teratoma (Figure 4).[11] The former is regarded as differentiation from other germ cell tumour types. Therefore, patients with apparently pure testicular teratomas often have GCNIS in the testis, and may develop metastases consisting of teratoma or other germ cell tumours, with the former being theorized to derive from non-teratomatous germ cell tumours at the metastatic site.[41] Therefore, the vast majority of apparently pure adult testicular teratomas are still regarded as malignant germ cell tumours.

IMMATURITY AND PRIMITIVE NEUROECTODERMAL ELEMENTS

No established prognostic value for discriminating mature from immature elements in postpubertal testicular teratomas, unlike those of the ovaries, has been documented. Nonetheless, responses in the ISUP survey with regard to reporting of immaturity were mixed, with 48% of respondents (112/232) indicating that they do comment on maturity in teratoma. The recommendation of this working group is that such reporting is not necessary, in light of the lack of known prognostic value and the fact that even pure mature teratomas of the postpubertal testis are overwhelmingly derived from a malignant germ cell tumour precursor. Therfore, patients may have metastases composed of either teratomatous or non-teratomatous elements. Neither the 2004 nor the 2016 WHO classification systems distinguish mature from immature teratoma of the postpubertal testis.[9,11]

A majority of respondents (182/231, 79%) to the ISUP survey, in contrast, indicated that they do report the presence of primitive neuroectodermal elements in testicular germ cell tumours. Similarly to immaturity (for which primitive neuroectodermal elements would be the prototypical form of immaturity), it is not clear that the presence of minor foci of such elements has prognostic value when they are intermingled with usual teratoma. However, overgrowth of primitive neuroectodermal elements to the exclusion of other teratoma is the principal criterion for

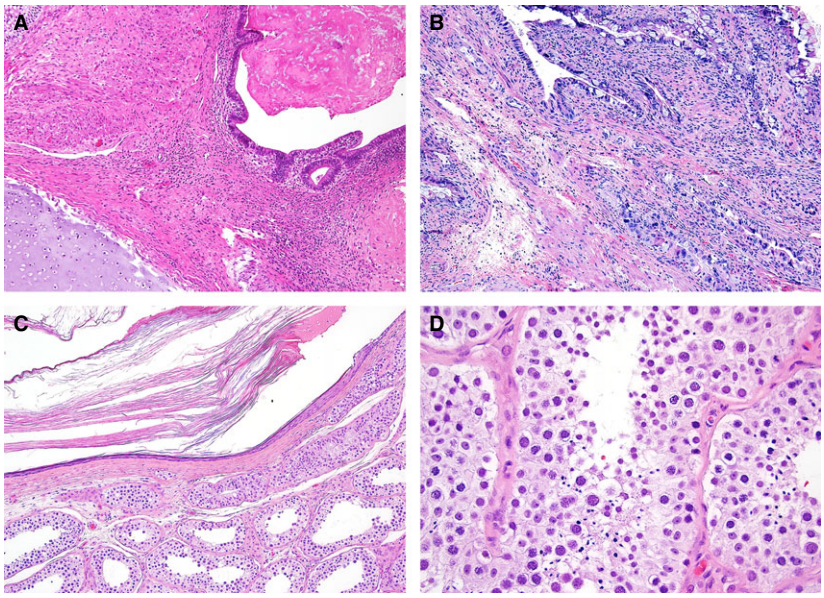

Figure 4. Postpubertal-type teratoma (**A**) is composed of a haphazard arrangement of varying amounts of ectodermal, mesodermal or endodermal elements, sometimes with substantial cytological atypia (**B**). In the absence of overgrowth or destructive invasion by a single element, cytological atypia alone does not warrant interpretation as secondary somatic-type malignancy. Epidermoid cyst (**C**) is one form of prepubertal-type teratoma. Prepubertal teratomas are not associated with germ cell neoplasia *in situ*, and should show normal spermatogenesis in adjacent tubules (**D**).

the diagnosis of primitive neuroectodermal tumour (PNET) arising from germ cell tumour (discussed in the next section).[42] It is of note that a recent investigation into PNET of germ cell tumour origin has found that such tumours typically resemble paediatric-type central nervous system PNET rather than peripheral PNET (Ewing sarcoma), in that rearrangements of the *EWSR1* gene on chromosome 22 are lacking.[43]

SOMATIC-TYPE MALIGNANCY ARISING FROM TERATOMA

A variety of malignancies have been reported to occur as secondary, somatic-type neoplasms arising from germ cell tumours (Figure 5), including: sarcoma (commonly embryonal rhabdomyosarcoma, more often than leiomyosarcoma or angiosarcoma), PNET, carcinoma, glial and meningeal neoplasms, haematological neoplasms, and nephroblastoma-like (Wilms) tumour.[42,44–54] As many of these tissue types make up components of teratoma, it is thought that many of these secondary somatic-type malignancies arise via overgrowth of a particular component of teratoma.[54] However, there is also recent evidence that some 'sarcomas', especially myxoid or not otherwise classifiable sarcomas, may represent sarcomatoid yolk sac tumour; this is supported by subtle morphological clues, including basement membrane deposition (parietal differentiation), and immunohistochemical positivity for keratin and glypican 3.[55] The phenomenon of secondary somatic-type malignancy has been described under a variety of names, including secondary malignancy and teratoma with 'malignant transformation'. The latter ('malignant transformation') is not recommended, for the reasons discussed previously, as it falsely implies that teratoma is not malignant. In general, the main diagnostic criterion for distinguishing a secondary malignancy from teratoma has been overgrowth of a particular element, to the extent that others are excluded (a low-power magnification or ×4 field, 5 mm in diameter).[42] In the case of carcinoma, destructive overgrowth with associated desmoplastic reaction may also be a helpful distinguishing feature. However, owing to the relative rarity of this phenomenon, it remains incompletely understood whether a single low-magnification field inherently implies more aggressive behaviour when it is found within the testicular primary tumour[44,53] rather than at metastatic sites (retroperitoneal lymph nodes), where this is typically encountered.

Cytological atypia, in contrast, is not inherently indicative of a somatic-type neoplasm. Postpubertal-type teratomas often show some degree of cytological atypia, reflecting their origin from a malignant cell type (Figure 4B). For example, cartilage within a teratoma often shows increased cellularity and cytological atypia that would be regarded as indicating chondrosarcoma if found in a primary bone tumour. Similarly, epithelial elements of teratoma may have cytological atypia that would be considered to indicate dysplasia or carcinoma *in situ* in another organ; however, there is no evidence that this implies a

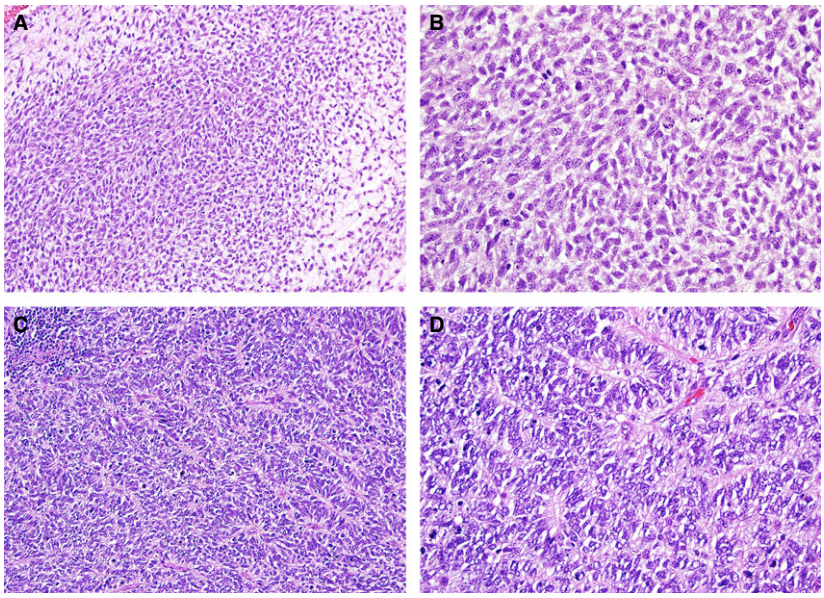

Figure 5. Secondary, somatic-type malignancy arising from germ cell tumour may assume various histologies. Sarcomas are common, including embryonal rhabdomyosarcoma (**A,B**), here forming a primitive small-cell neoplasm with spindle-shaped cells and brisk mitotic activity. Immunohistochemical staining in this case demonstrated patchy positivity for myogenin (not shown), supporting an embryonal rhabdomyosarcoma phenotype. Another common form of secondary somatic-type malignancy is primitive neuroectodermal tumour (**C,D**), here forming rosettes.

worse outcome than dictated by the germ cell tumour itself.

Prepubertal-type tumours (including dermoid and epidermoid cyst)

PREPUBERTAL-TYPE TERATOMA

A major shift in the restructuring of germ cell tumour classification as introduced above is the discrimination of prepubertal-type from postpubertal-type germ cell tumours of the testis.[11,56] Adult testicular teratomas, even when unmixed with other elements, are overwhelmingly considered to be derived from malignant germ cell tumour components, and are thought to occur through a pathway of differentiation of seminoma, or possibly GCNIS, to other tumour types (yolk sac tumour, embryonal carcinoma, and choriocarcinoma) and subsequent differentiation into teratoma.[41,57] In contrast, teratomas occurring in prepubertal patients lack association with GCNIS,[58] have a more organoid architecture, lack significant cytological atypia,[59] and largely lack 12p amplification,[60,61] and have not been reported to metastasize[62,63] (except in perhaps rare scenarios of carcinoid tumour or other secondary somatic-type tumours that may arise from teratoma).[11,56] Although distinguishing these two groups by the prepubertal or postpubertal status of the patient is helpful, there is increasingly accumulating evidence that prepubertal-type tumours can nonetheless be found in postpubertal patients,[59] possibly representing a rarer manifestation of the same process in an older age group or late presentation of a tumour that had been present since childhood.

Examples of 'benign' testicular teratomas have been recognized for some time, including dermoid[58] and epidermoid[64] cysts (Figure 4C,D), which are now grouped in this overall category of prepubertal-type teratomas. Whereas epidermoid cysts are relatively simply characterized by their squamous epithelium-lined cystic cavity containing keratin material (lacking associated skin adnexal elements or other tissues), the definition of dermoid cyst has historically been more controversial, including debate as to whether other, non-cutaneous elements, such as cartilage, bone, and pancreatic tissue, are allowable for diagnosis.[58] In a recent study, Zhang *et al.*[59] confirmed the existence of benign teratomas in the postpubertal testis, supported by the absence of a number of features, including: cytological atypia, GCNIS, tubular atrophy or scarring, impaired spermatogenesis (Figure 4D), microlithiasis, and chromosome 12p gain (isochromosome 12p or other over-representation). Such teratomas may have an increased representation of certain histological elements, including ciliated respiratory epithelium, sometimes encircled by smooth muscle, creating an organoid bronchus-like structure. Intestinal-type epithelium, conversely, may be underrepresented as compared with postpubertal-type teratoma. In contrast to dermoid cysts, a subset of these benign prepubertal-type teratomas occurring in postpubertal patients did not include cutaneous adnexal elements, instead often being composed of squamous-lined cysts and glands with ciliated or seromucinous epithelium with encircling smooth muscle.[59]

Conversely and unexpectedly, however, a recent study reported isochromosome 12p in two of 11 prepubertal teratomas, despite the absence of GCNIS in these cases[61] and in contrast to the entirely negative findings in prior cytogenetic studies.[60] This finding calls into question the accuracy of fluorescence *in-situ* hybridization for the detection of isochromosome 12p, making its corroboration by other laboratories crucial. Nonetheless, accumulating evidence is in support of rare teratomas in postpubertal patients being benign, although their recognition demands that a specific set of restrictive diagnostic criteria are met.[59]

Rare examples of testicular well-differentiated neuroendocrine tumour (carcinoid tumour) have been reported; in the 2016 WHO classification, these are considered under prepubertal-type teratoma as a form of monodermal teratoma. Some have been associated with prepubertal-type teratomas, including dermoid cysts and epidermoid cysts, whereas others are pure primary testicular carcinoid tumours.[65] The pathogenesis of such neoplasms remains debated and incompletely understood. Although one study found testicular carcinoid tumours to have isochromosome 12p,[66] other studies have reported negative results for this alteration.[11,65]

PREPUBERTAL-TYPE YOLK SAC TUMOUR

Prepubertal-type yolk sac tumour also appears to be biologically and pathogenetically different from postpubertal-type yolk sac tumour, despite having a generally similar range of histological features and patterns as yolk sac tumour in the postpubertal setting.[56] In children, yolk sac tumour occurs primarily in pure form rather than as a component of a mixed germ cell tumour (the opposite of what occurs in postpubertal patients), and, in the uncommon mixed examples, yolk sac tumour is only associated with teratoma and not with other germ cell tumour types.[56] Associations with GCNIS and cryptorchidism are lacking, supporting the unique derivation of these tumours, in spite of their overlapping morphology.[11] In prepubertal yolk sac tumour, there is a low incidence of extratesticular involvement (non-clinical stage I) as compared with postpubertal germ cell tumours in general,[56,67] and, in cases of advanced disease, chemotherapy is very effective,[11] indicating differences in aggressiveness as well.

Regression of germ cell tumour

An addition to the 2016 WHO classification is expanded discussion of germ cell tumour regression (also known as 'burnt-out' germ cell tumour).[11] Although in the past some germ cell tumours have been labelled as 'primary' retroperitoneal tumours, current thinking is that these uniformly represent metastases from an occult or regressed testicular primary tumour. Findings in the testes of such patients typically include a scar, reduced spermatogenesis, and microlithiasis. However, findings that have been proposed as specific for germ cell tumour regression rather than non-neoplastic scarring are limited to: (i) GCNIS in the adjacent parenchyma; and (ii) coarse, large intratubular calcifications. The latter are thought to result from intratubular growth, necrosis, and calcification of embryonal carcinoma.[16] However, these coarse calcifications must be distinguished from microlithiasis (small, rounded calcifications), which may be found in the adjacent parenchyma of germ cell tumour patients but are not specific for the presence of tumour. Overall, pathologists must be aware in the setting of scarring that, even if careful search does not reveal these highly specific lesions (GCNIS or coarse calcifications), the possibility of germ cell tumour regression remains a consideration for any testicular 'scar', and this must be communicated to clinical colleagues to ensure appropriate follow-up.

Spermatocytic tumour

A substantive change to the 2016 WHO classification is the reclassification of spermatocytic seminoma as spermatocytic tumour.[11] This change improves the nomenclature for this tumour in several ways: First, labelling this entity as a tumour rather than as an unequivocal malignancy emphasizes that the behaviour of usual spermatocytic tumour is non-aggressive, with only very rare examples of metastases.[19] Treatment with orchiectomy is typically curative, and additional therapy apart from surveillance is generally not required, as only a handful of well-characterized metastases from usual spermatocytic tumour have been reported.[68] An exception to this is that occasional examples of spermatocytic tumour with progression or dedifferentiation into sarcoma have been described, in which case the behaviour is considerably more aggressive, with a high metastatic rate, typically warranting consideration of additional therapeutic approaches. In such tumours, rhabdomyosarcomatous differentiation has been most commonly described, in addition to non-specific spindle-cell and pleomorphic sarcoma patterns.[11,68] Second, removing the term seminoma from the name of

this tumour stresses that it has no true relationship to usual seminoma, apart from the potential for diagnostic confusion histologically. Spermatocytic tumour has shown no evidence of derivation from GCNIS, occurs in an older patient population (mean age in the sixth decade), does not possess chromosome 12p abnormality, is negative for OCT3/4, and has no extragonadal counterpart.[11,19,68] Third, this terminology reduces the possibility of confusion and miscommunication, as both seminoma and spermatocytic tumour can occur at a wide range of ages.

As in seminoma, an area that has also received some attention for spermatocytic tumour is the presence of 'anaplasia', characterized by increased cytological atypia and giant tumour cells.[68,69] As in seminoma, and in contrast to spermatocytic tumour with sarcoma, this finding has not been clearly shown to have an adverse impact on behaviour.[68]

Summary

In summary, the 2016 update to the WHO Classification of Tumours of the Urinary Tract and Male Genital Organs brings a number of changes and refinements to the classification of germ cell tumours. The most notable changes include GCNIS as an abbreviated but precise replacement for IGCNU and carcinoma *in situ*, restructuring of the overall classification into GCNIS-derived and non-GCNIS-derived tumours (largely but not exclusively correlating with postpubertal and prepubertal age groups, respectively), and reclassification of spermatocytic seminoma as spermatocytic tumour to emphasize its typically non-aggressive behaviour and lack of relationship to usual seminoma. The category of non-choriocarcinoma trophoblastic tumours has continued to gain attention in recent years, and has been expanded to include several entities analogous to their counterparts in the gynaecological tract. There is growing evidence for the existence of benign teratomas of the postpubertal testis (termed prepubertal-type teratomas), supported by their organoid growth pattern and absence of cytological atypia, lack of association with germ cell tumour regressive changes or testicular dysgenetic changes, and absence of GCNIS. Although the ISUP survey indicates that practice remains variable for reporting the presence of minor primitive elements and immaturity in teratomas, this has no known prognostic value unless overgrowth with exclusion of other teratoma elements is present (somatic-type malignancy arising from germ cell tumour).

Author contributions

S. R. Williamson: drafting of the article. D. M. Berney: conception, design, and oversight. All authors: critical revision and final approval of the article.

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References

1. Eble JN, Sauter G, Epstein JI, Sesterhenn IA eds. *World Health Organization classification of tumours: pathology and genetics of tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2004.
2. Moch H, Humphrey PA, Ulbright TM, Reuter VE eds. *World Health Organization classification of tumours of the urinary system and male genital organs*. 4th ed. Lyon: IARC Press, 2016.
3. Berney DM. Staging and classification of testicular tumours: pitfalls from macroscopy to diagnosis. *J. Clin. Pathol.* 2008; **61**; 20–24.
4. Skakkebaek NE. Possible carcinoma-*in-situ* of the testis. *Lancet* 1972; **2**; 7.
5. Skakkebaek NE. Atypical germ cells in the adjacent 'normal' tissue of testicular tumours. *Acta Pathol. Microbiol. Scand. A* 1975; **83**; 127–130.
6. Skakkebaek NE. Carcinoma *in situ* of the testis: frequency and relationship to invasive germ cell tumours in infertile men. *Histopathology* 1978; **2**; 157–170.
7. Emerson RE, Cheng L. Premalignancy of the testis and paratestis. *Pathology* 2013; **45**; 264–272.
8. Jones TD, Ulbright TM, Eble JN, Cheng L. OCT4: a sensitive and specific biomarker for intratubular germ cell neoplasia of the testis. *Clin. Cancer Res.* 2004; **10**; 8544–8547.
9. Woodward PJ, Heidenreich A, Looijenga LH *et al.* Germ cell tumors. In Eble JN, Sauter G, Epstein JI, Sesterhenn IA eds. *World Health Organization classification of tumours: pathology and genetics of tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2004; 221–249.
10. Berney DM, Looijenga LH, Idrees M *et al.* Germ cell neoplasia *in situ* (GCNIS): evolution of the current nomenclature for testicular pre-invasive germ cell malignancy. *Histopathology* 2016; **69**; 7–10.
11. Ulbright TM, Amin MB, Balzer B *et al.* Germ cell tumours. In Moch H, Humphrey PA, Ulbright TM, Reuter VE eds. *World Health Organization classification of tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2016; 189–226.
12. Berney DM, Lee A, Shamash J, Oliver RT. The association between intratubular seminoma and invasive germ cell tumors. *Hum. Pathol.* 2006; **37**; 458–461.
13. Lau SK, Weiss LM, Chu PG. Association of intratubular seminoma and intratubular embryonal carcinoma with invasive testicular germ cell tumors. *Am. J. Surg. Pathol.* 2007; **31**; 1045–1049.
14. Oosterhuis JW, Kersemaekers AM, Jacobsen GK *et al.* Morphology of testicular parenchyma adjacent to germ cell tumours. An interim report. *APMIS* 2003; **111**; 32–40; discussion 41–42.

15. Berney DM, Lee A, Randle SJ, Jordan S, Shamash J, Oliver RT. The frequency of intratubular embryonal carcinoma: implications for the pathogenesis of germ cell tumours. *Histopathology* 2004; **45**; 155–161.
16. Balzer BL, Ulbright TM. Spontaneous regression of testicular germ cell tumors: an analysis of 42 cases. *Am. J. Surg. Pathol.* 2006; **30**; 858–865.
17. Rakheja D, Hoang MP, Sharma S, Albores-Saavedra J. Intratubular embryonal carcinoma. *Arch. Pathol. Lab. Med.* 2002; **126**; 487–490.
18. Berney DM, Lee A, Shamash J, Oliver RT. The frequency and distribution of intratubular trophoblast in association with germ cell tumors of the testis. *Am. J. Surg. Pathol.* 2005; **29**; 1300–1303.
19. Eble JN. Spermatocytic seminoma. *Hum. Pathol.* 1994; **25**; 2.
20. Oosterhuis JW, Looijenga LH. Testicular germ-cell tumours in a broader perspective. *Nat. Rev. Cancer* 2005; **5**; 210–222.
21. von Hochstetter AR, Sigg C, Saremaslani P, Hedinger C. The significance of giant cells in human testicular seminomas. A clinico-pathological study. *Virchows Arch. A Pathol. Anat. Histopathol.* 1985; **407**; 309–322.
22. Henley JD, Young RH, Wade CL, Ulbright TM. Seminomas with exclusive intertubular growth: a report of 12 clinically and grossly inconspicuous tumors. *Am. J. Surg. Pathol.* 2004; **28**; 1163–1168.
23. Ulbright TM, Young RH. Seminoma with tubular, microcystic, and related patterns: a study of 28 cases of unusual morphologic variants that often cause confusion with yolk sac tumor. *Am. J. Surg. Pathol.* 2005; **29**; 500–505.
24. Zavala-Pompa A, Ro JY, el-Naggar AK *et al.* Tubular seminoma. An immunohistochemical and DNA flow-cytometric study of four cases. *Am. J. Clin. Pathol.* 1994; **102**; 397–401.
25. Ulbright TM, Young RH. Seminoma with conspicuous signet ring cells: a rare, previously uncharacterized morphologic variant. *Am. J. Surg. Pathol.* 2008; **32**; 1175–1181.
26. Ulbright TM, Tickoo SK, Berney DM, Srigley JR; Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group. Best practices recommendations in the application of immunohistochemistry in testicular tumors: report from the International Society of Urological Pathology consensus conference. *Am. J. Surg. Pathol.* 2014; **38**; e50–e59.
27. Tickoo SK, Hutchinson B, Bacik J *et al.* Testicular seminoma: a clinicopathologic and immunohistochemical study of 105 cases with special reference to seminomas with atypical features. *Int. J. Surg. Pathol.* 2002; **10**; 23–32.
28. Percarpio B, Clements JC, McLeod DG, Sorgen SD, Cardinale FS. Anaplastic seminoma: an analysis of 77 patients. *Cancer* 1979; **43**; 2510–2513.
29. Mostofi FK. Proceedings: testicular tumors. Epidemiologic, etiologic, and pathologic features. *Cancer* 1973; **32**; 1186–1201.
30. Gallegos I, Valdevenito JP, Miranda R, Fernandez C. Immunohistochemistry expression of P53, Ki67, CD30, and CD117 and presence of clinical metastasis at diagnosis of testicular seminoma. *Appl. Immunohistochem. Mol. Morphol.* 2011; **19**; 147–152.
31. Som A, Zhu R, Guo CC *et al.* Recurrent seminomas: clinical features and biologic implications. *Urol. Oncol.* 2012; **30**; 494–501.
32. Ulbright TM, Henley JD, Cummings OW, Foster RS, Cheng L. Cystic trophoblastic tumor: a nonaggressive lesion in postchemotherapy resections of patients with testicular germ cell tumors. *Am. J. Surg. Pathol.* 2004; **28**; 1212–1216.
33. Gondim D, Cheng L, Jones C, Ulbright T, Idrees M. Cystic trophoblastic tumor of the testis: a spontaneous testicular and postchemotherapy neoplasm. *Lab. Invest.* 2014; **94**; 231A.
34. Idrees MT, Kao CS, Epstein JI, Ulbright TM. Nonchoriocarcinomatous trophoblastic tumors of the testis: the widening spectrum of trophoblastic neoplasia. *Am. J. Surg. Pathol.* 2015; **39**; 1468–1478.
35. Ulbright TM, Young RH, Scully RE. Trophoblastic tumors of the testis other than classic choriocarcinoma: 'monophasic' choriocarcinoma and placental site trophoblastic tumor: a report of two cases. *Am. J. Surg. Pathol.* 1997; **21**; 282–288.
36. Suurmeijer AJ, Gietema JA, Hoekstra HJ. Placental site trophoblastic tumor in a late recurrence of a nonseminomatous germ cell tumor of the testis. *Am. J. Surg. Pathol.* 2004; **28**; 830–833.
37. Allan RW, Algood CBShih I M. Metastatic epithelioid trophoblastic tumor in a male patient with mixed germ-cell tumor of the testis. *Am. J. Surg. Pathol.* 2009; **33**; 1902–1905.
38. Petersson F, Grossmann P, Vanecek T *et al.* Testicular germ cell tumor composed of placental site trophoblastic tumor and teratoma. *Hum. Pathol.* 2010; **41**; 1046–1050.
39. Mirkovic J, Elias K, Drapkin R, Barletta JA, Quade B, Hirsch MS. GATA3 expression in gestational trophoblastic tissues and tumours. *Histopathology* 2015; **67**; 636–644.
40. Shih IM. Trophogram, an immunohistochemistry-based algorithmic approach, in the differential diagnosis of trophoblastic tumors and tumorlike lesions. *Ann. Diagn. Pathol.* 2007; **11**; 228–234.
41. Ulbright TM. Gonadal teratomas: a review and speculation. *Adv. Anat. Pathol.* 2004; **11**; 10–23.
42. Ulbright TM, Loehrer PJ, Roth LM, Einhorn LH, Williams SD, Clark SA. The development of non-germ cell malignancies within germ cell tumors. A clinicopathologic study of 11 cases. *Cancer* 1984; **54**; 1824–1833.
43. Ulbright TM, Hattab EM, Zhang S *et al.* Primitive neuroectodermal tumors in patients with testicular germ cell tumors usually resemble pediatric-type central nervous system embryonal neoplasms and lack chromosome 22 rearrangements. *Mod. Pathol.* 2010; **23**; 972–980.
44. Motzer RJ, Amsterdam A, Prieto V *et al.* Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. *J. Urol.* 1998; **159**; 133–138.
45. Ahmed T, Bosl GJ, Hajdu SI. Teratoma with malignant transformation in germ cell tumors in men. *Cancer* 1985; **56**; 860–863.
46. Michael H, Hull MT, Foster RS, Sweeney CJ, Ulbright TM. Nephroblastoma-like tumors in patients with testicular germ cell tumors. *Am. J. Surg. Pathol.* 1998; **22**; 1107–1114.
47. Michael H, Hull MT, Ulbright TM, Foster RS, Miller KD. Primitive neuroectodermal tumors arising in testicular germ cell neoplasms. *Am. J. Surg. Pathol.* 1997; **21**; 896–904.
48. Idrees MT, Kuhar M, Ulbright TM *et al.* Clonal evidence for the progression of a testicular germ cell tumor to angiosarcoma. *Hum. Pathol.* 2010; **41**; 139–144.
49. Allen EA, Burger PC, Epstein JI. Microcystic meningioma arising in a mixed germ cell tumor of the testis: a case report. *Am. J. Surg. Pathol.* 1999; **23**; 1131–1135.
50. Emerson RE, Ulbright TM, Zhang S, Foster RS, Eble JN, Cheng L. Nephroblastoma arising in a germ cell tumor of testicular origin. *Am. J. Surg. Pathol.* 2004; **28**; 687–692.
51. Kasai T, Moriyama K, Tsuji M, Uema K, Sakurai N, Fujii Y. Adenocarcinoma arising from a mature cystic teratoma of the testis. *Int. J. Urol.* 2003; **10**; 505–509.

52. Williamson SR, Kum JB, Shah SR *et al.* Signet ring cell carcinoma of the testis: clinicopathologic and molecular evidence for germ cell tumor origin—a case report. *Am. J. Surg. Pathol.* 2012; **36**; 311–315.
53. Guo CC, Punar M, Contreras AL *et al.* Testicular germ cell tumors with sarcomatous components: an analysis of 33 cases. *Am. J. Surg. Pathol.* 2009; **33**; 1173–1178.
54. Kum JB, Ulbright TM, Williamson SR *et al.* Molecular genetic evidence supporting the origin of somatic-type malignancy and teratoma from the same progenitor cell. *Am. J. Surg. Pathol.* 2012; **36**; 1849–1856.
55. Howitt BE, Magers MJ, Rice KR, Cole CD, Ulbright TM. Many postchemotherapy sarcomatous tumors in patients with testicular germ cell tumors are sarcomatoid yolk sac tumors: a study of 33 cases. *Am. J. Surg. Pathol.* 2015; **39**; 251–259.
56. Ulbright TM, Young RH. Testicular and paratesticular tumors and tumor-like lesions in the first 2 decades. *Semin. Diagn. Pathol.* 2014; **31**; 323–381.
57. Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. *Mod. Pathol.* 2005; **18** (Suppl. 2); S61–S79.
58. Ulbright TM, Srigley JR. Dermoid cyst of the testis: a study of five postpubertal cases, including a pilomatrixoma-like variant, with evidence supporting its separate classification from mature testicular teratoma. *Am. J. Surg. Pathol.* 2001; **25**; 788–793.
59. Zhang C, Berney DM, Hirsch MS, Cheng L, Ulbright TM. Evidence supporting the existence of benign teratomas of the postpubertal testis: a clinical, histopathologic, and molecular genetic analysis of 25 cases. *Am. J. Surg. Pathol.* 2013; **37**; 827–835.
60. Bussey KJ, Lawce HJ, Olson SB *et al.* Chromosome abnormalities of eighty-one pediatric germ cell tumors: sex-, age-, site-, and histopathology-related differences—a Children's Cancer Group study. *Genes Chromosom. Cancer* 1999; **25**; 134–146.
61. Cornejo KM, Cheng L, Church A, Wang M, Jiang Z. Chromosome 12p abnormalities and IMP3 expression in prepubertal pure testicular teratomas. *Hum. Pathol.* 2016; **49**; 54–60.
62. Grady RW, Ross JH, Kay R. Epidemiological features of testicular teratoma in a prepubertal population. *J. Urol.* 1997; **158**; 1191–1192.
63. Visfeldt J, Jorgensen N, Muller J, Moller H, Skakkebaek NE. Testicular germ cell tumours of childhood in Denmark, 1943–1989: incidence and evaluation of histology using immunohistochemical techniques. *J. Pathol.* 1994; **174**; 39–47.
64. Cheng L, Zhang S, MacLennan GT *et al.* Interphase fluorescence *in situ* hybridization analysis of chromosome 12p abnormalities is useful for distinguishing epidermoid cysts of the testis from pure mature teratoma. *Clin. Cancer Res.* 2006; **12**; 5668–5672.
65. Wang WP, Guo C, Berney DM *et al.* Primary carcinoid tumors of the testis: a clinicopathologic study of 29 cases. *Am. J. Surg. Pathol.* 2010; **34**; 519–524.
66. Abbosh PH, Zhang S, Maclennan GT *et al.* Germ cell origin of testicular carcinoid tumors. *Clin. Cancer Res.* 2008; **14**; 1393–1396.
67. Cornejo KM, Frazier L, Lee RS, Kozakewich HP, Young RH. Yolk sac tumor of the testis in infants and children: a clinicopathologic analysis of 33 cases. *Am. J. Surg. Pathol.* 2015; **39**; 1121–1131.
68. Lombardi M, Valli M, Brisigotti M, Rosai J. Spermatocytic seminoma: review of the literature and description of a new case of the anaplastic variant. *Int. J. Surg. Pathol.* 2011; **19**; 5–10.
69. Albores-Saavedra J, Huffman H, Alvarado-Cabrero I, Ayala AG. Anaplastic variant of spermatocytic seminoma. *Hum. Pathol.* 1996; **27**; 650–655.