

The WHO 2016 Classification of Testicular Germ Cell Tumours: a Review and Update from the ISUP Testis Consultation Panel

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ABSTRACT

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 (ISUP) 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, as well as distinction of prepubertal (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 gynecologic tract. Currently, reporting of anaplasia (seminoma or spermatocytic tumour) or immaturity (teratoma) are 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 behavior and should be reported.

Key words:

Germ cell neoplasia in situ, spermatocytic tumour, germ cell tumour, postpubertal type teratoma.

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 in the classification of germ cell tumours, the WHO draft classification system for the genitourinary organs² was discussed at 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 assessing current practice patterns in testicular tumour classification, microscopy, and staging.

Classification system

With regard to 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 Panel³ (BTTP) in tandem with WHO (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 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 Similar to 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 germ cell neoplasia in situ (GCNIS) was accepted as an abbreviated but precise replacement for these terms in the 2016 WHO system, which combines elements from the two most widely used terms, IGCNU and carcinoma in situ.¹¹

Other intratubular neoplasms

Apart from GCNIS, the significance of other forms of intratubular neoplasia in the testis is less clearly understood. Intratubular seminoma (**Figure 1C-D**), for example, refers to complete filling of seminiferous tubules by cells with a similar appearance and immunohistochemical staining profile to 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 preexisting seminiferous tubules by embryonal carcinoma cells, often accompanied by intratubular necrosis and calcification (**Figure 1E-F**).¹³⁻¹⁵ This tendency for intratubular necrosis and calcification also has implications for 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 preexisting 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 both adjacent to seminoma and nonseminomatous germ cell tumours, similar to GCNIS.¹² In contrast, since intratubular embryonal carcinoma is rarely encountered as a sole lesion¹⁷ without associated invasive nonseminomatous germ cell 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 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 nonseminomatous 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 illustrated 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 tumours¹¹ is the division into two main groups (**Figure 2**): 1) tumours predominantly (but not exclusively) occurring in prepubertal patients, considered not to be derived from GCNIS, and 2) tumours derived from GCNIS. This method of division was suggested previously as ‘type I and type II’ germ cell tumours,²⁰ but this typing has not been specifically adopted by the WHO. In the same schema, spermatocytic tumour was considered separately as a type III tumour. This change reflects the different behavior, pathogenesis, and tumour biology of similar histologic patterns occurring in different contexts.

Seminoma

Although seminoma has been recognized to exhibit a variety of histologic 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 elevation in serum beta-hCG.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 on 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} 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 metastatic carcinoma 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 histologic features correlate with behavior and outcome in pure seminoma is currently largely mixed and inconclusive. It is possible that these atypical cytologic features represent an early stage in the transition from seminoma to another tumour type, particularly embryonal carcinoma. Even so, however, studies that have assessed for 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 behavior 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 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 tumour³² refers to a unique lesion that to date exhibits nonaggressive behavior, composed of cystic spaces lined by trophoblastic cells with smudged nuclei, often containing luminal fibrin (**Figure 3A-B**). Based on the eosinophilic cytoplasm of the cells and their low nuclear to cytoplasmic ratio, this may in some cases remain unrecognized and interpreted as squamous epithelium or another type of teratomatous epithelium. This phenomenon is most often encountered in post-chemotherapy lymph node dissection specimens, 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 elevation of serum beta-hCG, if at all.³² Since patients with this finding do not appear to have the high rate of disease progression observed in patients with residual post-chemotherapy nonteratomatous 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 Similar to trophoblastic neoplasia in general,³⁹ GATA3 has emerged as a useful immunohistochemical marker of these various trophoblastic cell lineages, which appears to also hold true in their occurrence from testicular origin.³⁴ This, in combination with other trophoblastic lineage markers such as human placental lactogen (HPL), beta-hCG, placental alkaline phosphatase, inhibin, and others, may be helpful in both 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 Based on work from the gynecologic counterparts, epithelioid trophoblastic tumours have been characterized as typically exhibiting diffuse immunoreactivity for p63 and negative 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 (4/8 examples in the series, **Figure 3C-D**).³⁴ The behavior of these tumours is not entirely understood;

however, currently distinguishing them from choriocarcinoma appears to be warranted, based on comparatively less aggressive behavior.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 theorized to derive from nonteratomatous 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 that even pure mature teratomas of the postpubertal testis are overwhelmingly derived from a malignant germ cell tumour precursor. As such, patients may have metastases composed of either teratomatous or nonteratomatous 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. Similar 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 intermingled with usual teratoma. However, overgrowth of primitive neuroectodermal elements to the exclusion of other teratoma is the principal criterion for the diagnosis of primitive neuroectodermal tumour (PNET) arising from germ cell tumour (discussed in the next section).⁴² Of note, recent investigation into PNET of germ cell tumour origin has found that such tumours typically resemble pediatric-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 described 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, hematologic neoplasms, and nephroblastoma-like (Wilms) tumour.^{42, 44-54} Since 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, 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, teratoma with “malignant transformation”, among others. The latter (“malignant transformation”) is not recommended, for the reasons discussed previously, since 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 diameter).⁴² In the case of carcinoma, destructive overgrowth with associated desmoplastic reaction may also be a helpful distinguishing feature. However, due to the relative rarity of this phenomenon, it remains incompletely understood whether a single low-magnification field inherently imparts more aggressive behavior when it is found within the testicular primary tumour^{44, 53} rather than at metastatic sites (retroperitoneal lymph nodes), where this is typically encountered.

Cytologic atypia, in contrast, is not inherently indicative of a somatic-type neoplasm. Postpubertal type teratomas often exhibit some degree of cytologic atypia, reflecting their origin from a malignant cell type (**Figure 4B**). For example, cartilage within a teratoma often exhibits increased cellularity and cytologic atypia that would be regarded as chondrosarcoma if found in a primary bone tumour. Similarly, epithelial elements of teratoma may have cytologic atypia that would be considered dysplasia or carcinoma in situ in another organ; however, there is no evidence that this imparts a 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 pre- 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, thought to occur through a pathway of differentiation of seminoma, or possibly GCNIS, to other tumour types (yolk sac tumour, embryonal carcinoma, 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 cytologic 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 pre- or postpubertal status of the patient is helpful, there has been 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 dermoid⁵⁸ and epidermoid⁶⁴ 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 confirmed the existence of benign teratomas occurring in the postpubertal testis, supported by *absence of* a number of features, including: cytologic atypia, GCNIS, tubular atrophy or scarring, impaired spermatogenesis (**Figure 4D**), microlithiasis, and chromosome 12p gain (isochromosome 12p or other overrepresentation).⁵⁹ Such teratomas may have an increased representation of certain histologic elements, including ciliated respiratory epithelium, sometimes encircled by smooth muscle, creating an organoid bronchus-like structure. Intestinal-type epithelium conversely may be underrepresented compared to 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 2 of 11 prepubertal teratomas despite the absence of GCNIS in these cases⁶¹ and in contrast to the entirely negative findings in prior cytogenetic studies.⁶⁰ This finding calls into question the accuracy of the fluorescence in situ hybridization (FISH) for the detection of isochromosome 12p, making its corroboration by other laboratories crucial. Nonetheless, the accumulating evidence supports that rare teratomas in postpubertal patients are 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, which in the 2016 WHO Classification is considered under prepubertal-type teratoma as a form of monodermal teratoma. Some have 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 histologic features and patterns to 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 postpubertal patients), and in the uncommon mixed examples, yolk sac tumour is only associated with teratoma and not other germ cell tumour types.⁵⁶ Association 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), compared to 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 labeled as “primary” retroperitoneal tumours, current thinking is that these uniformly represent metastases from an occult or regressed testicular primary tumour. Findings in the testis 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 nonneoplastic scarring are limited to: 1) GCNIS in the adjacent parenchyma and 2) coarse, large intratubular calcifications. The latter is 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: Firstly, labeling this entity as a tumour rather than unequivocal malignancy emphasizes that the behavior of usual spermatocytic tumour is nonaggressive, 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 behavior 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 nonspecific spindle cell and pleomorphic sarcoma patterns.^{11, 68} Secondly, removing the term seminoma from the name of this tumour stresses that it has no true relationship to usual seminoma, apart from potential for diagnostic confusion histologically. Spermatocytic tumour has shown no evidence of derivation from GCNIS, occurs in an older patient population (mean age in 6th decade), does not possess chromosome 12p abnormality, is negative for OCT3/4, and has no extragonadal counterpart.^{11, 19, 68} Thirdly, this terminology reduces the possibility of confusion and miscommunication, since both seminoma and spermatocytic tumour can occur in a wide range of ages.

Similar to seminoma, an area that has also received some attention for spermatocytic tumour is the presence of “anaplasia,” characterized by increased cytologic atypia and giant tumour cells.^{68, 69} Similarly to usual seminoma, and in contrast to spermatocytic tumour with sarcoma, this finding has not been clearly shown to have an adverse impact on behavior.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. Most notable changes including GCNIS (germ cell neoplasia in situ) as an abbreviated but precise replacement for intratubular germ cell neoplasia, unclassified type (IGCNU) and carcinoma in situ (CIS), 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 nonaggressive behavior 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 gynecologic 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 cytologic 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).

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Figure Legends:

Figure 1: Germ cell neoplasia in situ (GCNIS) typically exhibits 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 demonstrating both intratubular and invasive components (D). Intratubular embryonal carcinoma is characteristically associated with intratubular necrosis and calcification (E-F).

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. (Abbreviations: YST = yolk sac tumour, NOS = not otherwise specified)

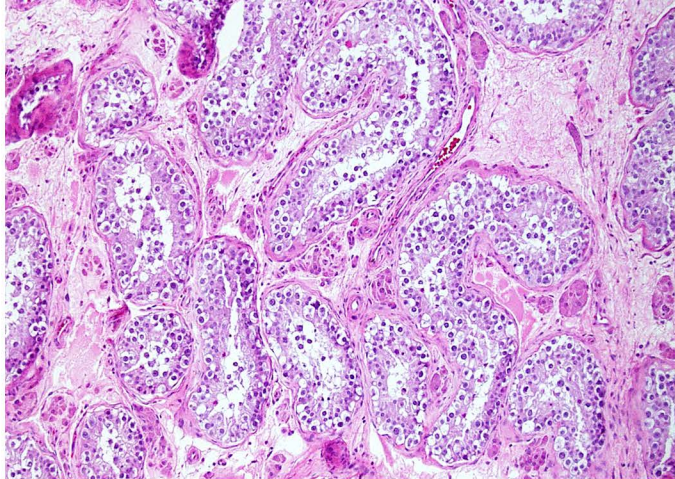
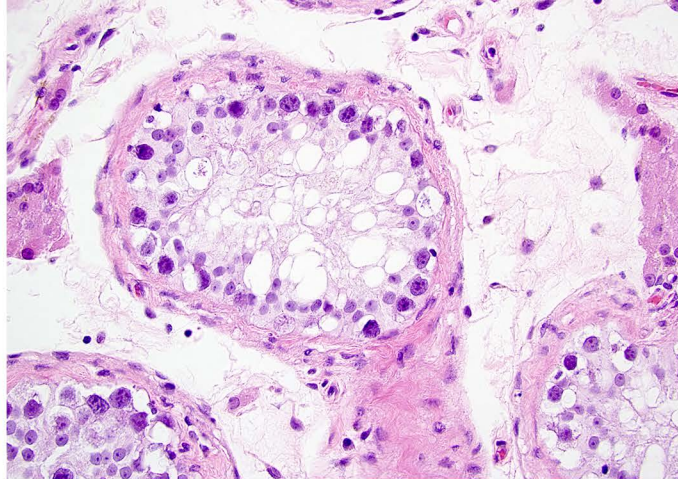
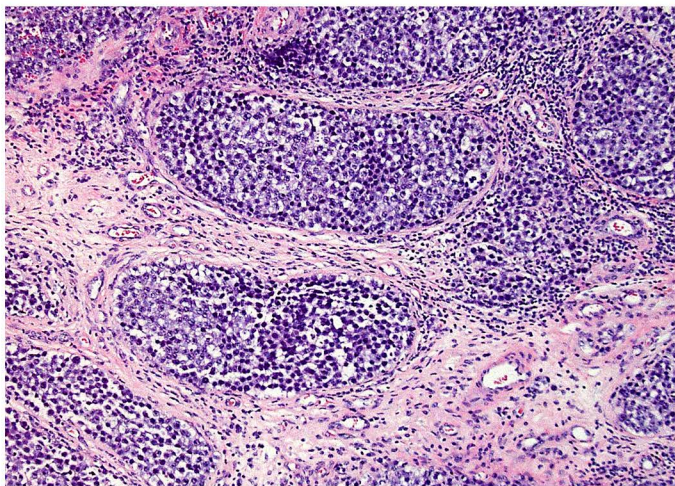
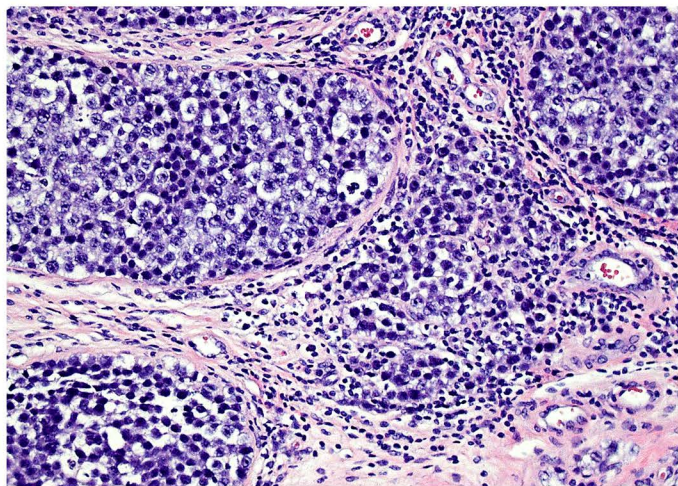
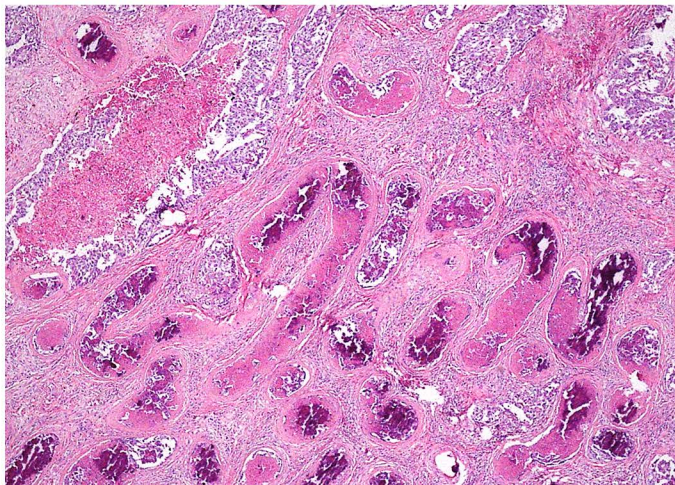
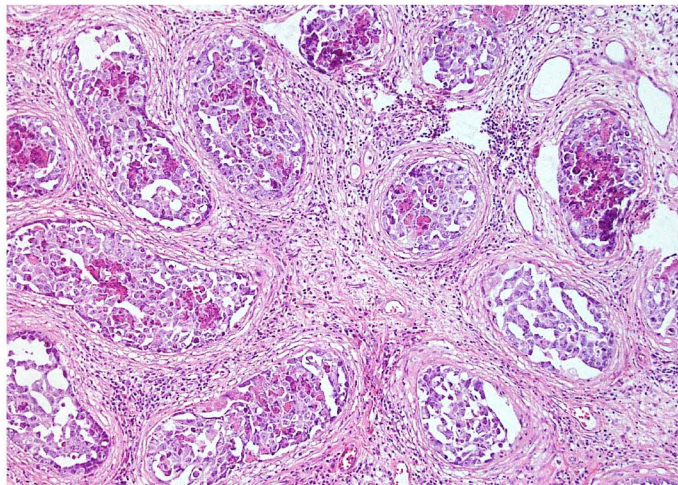
Figure 3: Discussion of trophoblastic tumours has been expanded in the 2016 World Health Organization Classification of testicular tumours. Cystic trophoblastic tumour (A-B) is often associated with teratoma, composed of cystic spaces lined by trophoblastic cells with enlarged, hyperchromatic or smudged nuclei (B) and fibrinoid luminal contents. Despite the trophoblastic differentiation of this lesion, it appears to have similar behavior 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).

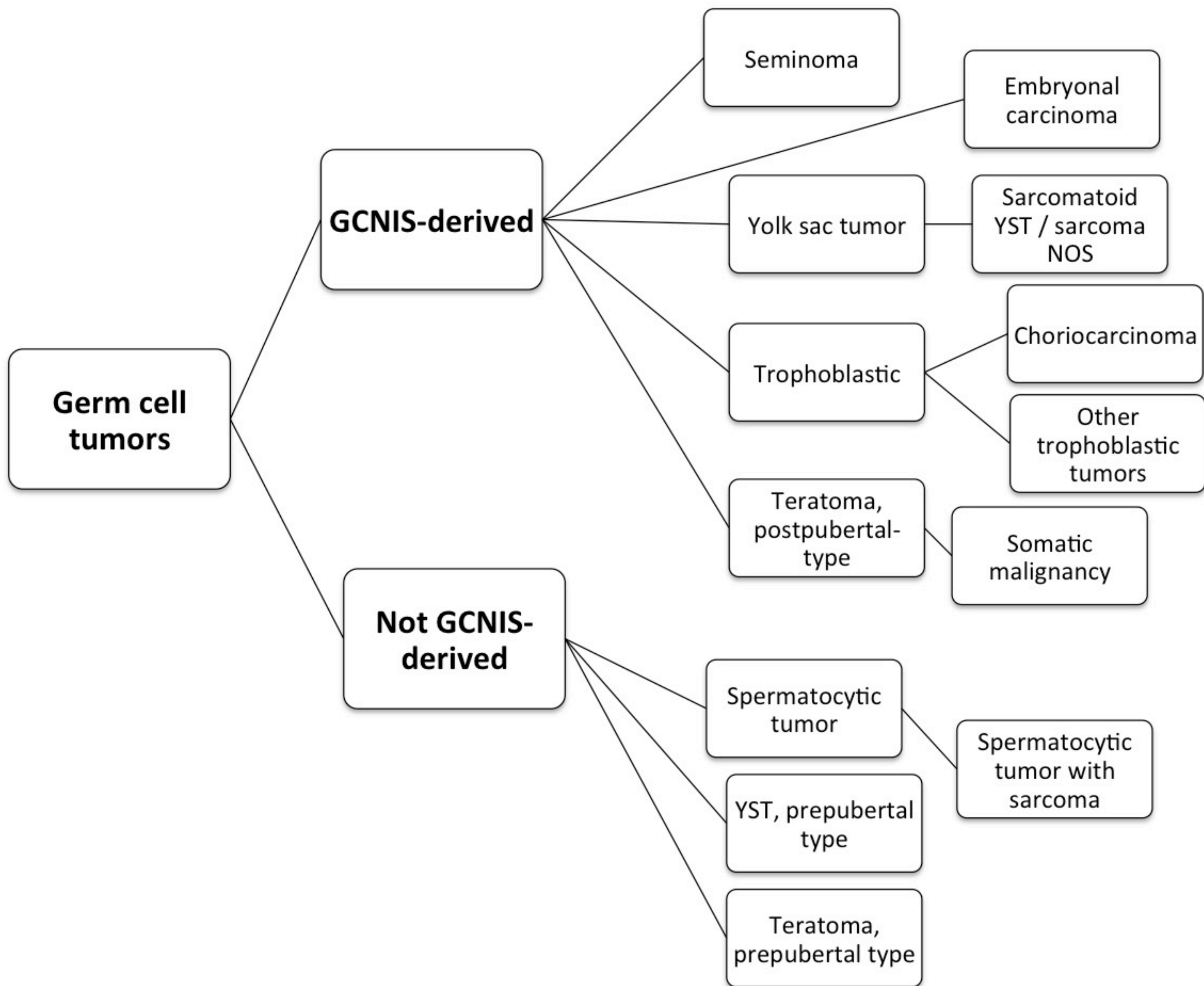
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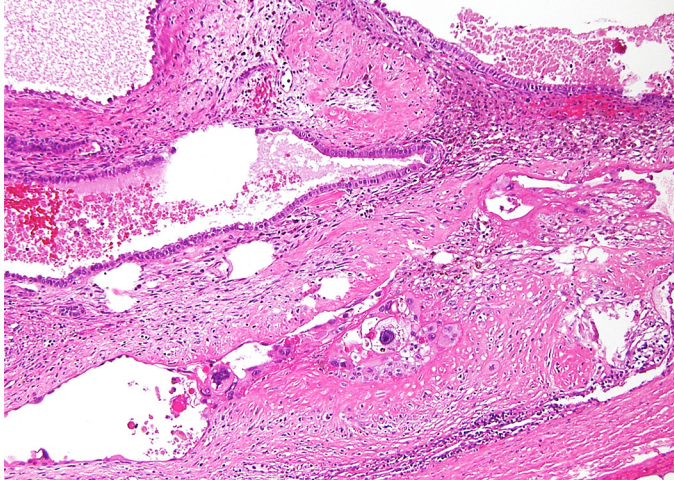
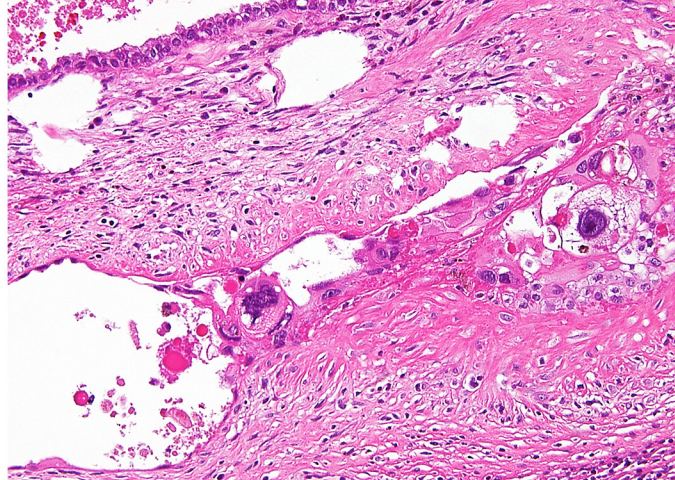
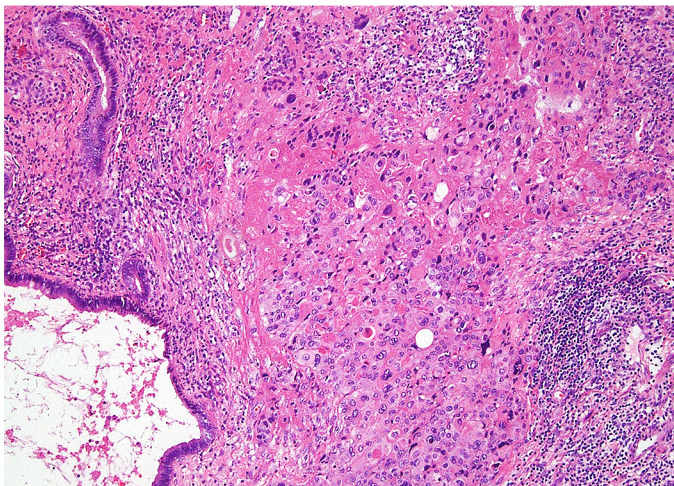
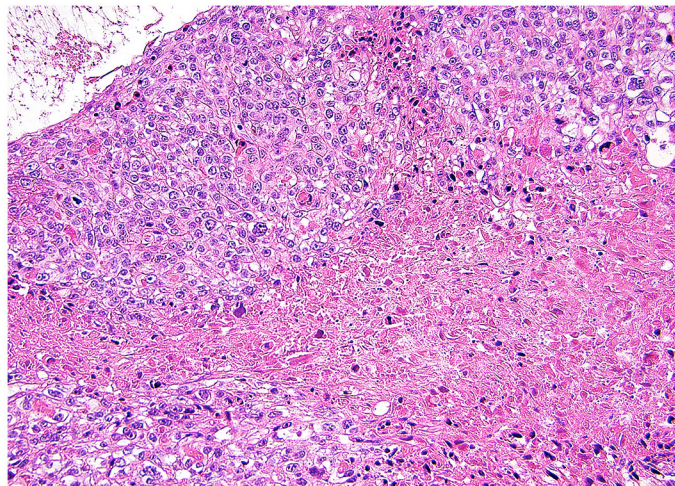
638 **Figure 4:** Postpubertal-type teratoma (A) is composed of a haphazard arrangement varying
 639 amounts of ectodermal, mesodermal, or endodermal elements, sometimes with substantial
 640 cytologic atypia (B). In the absence of overgrowth or destructive invasion by a single
 641 element, cytologic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

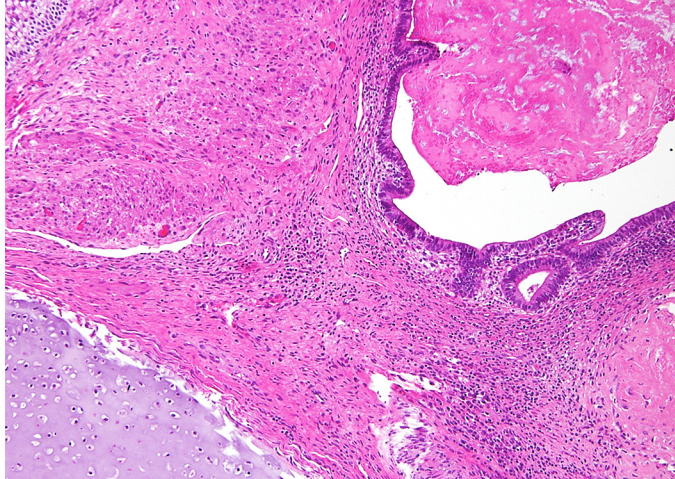
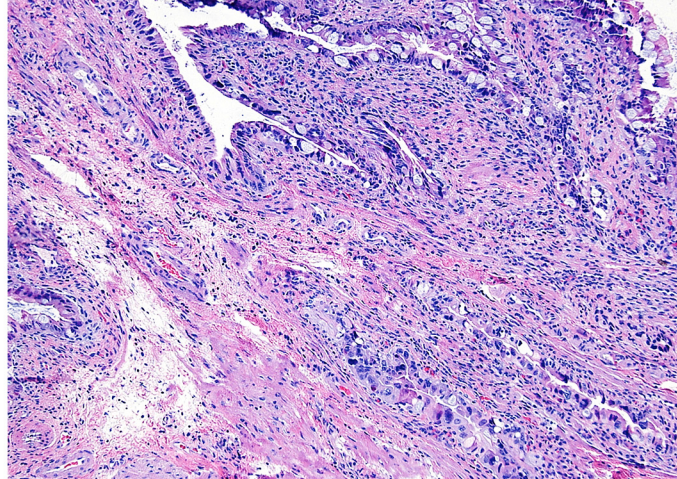
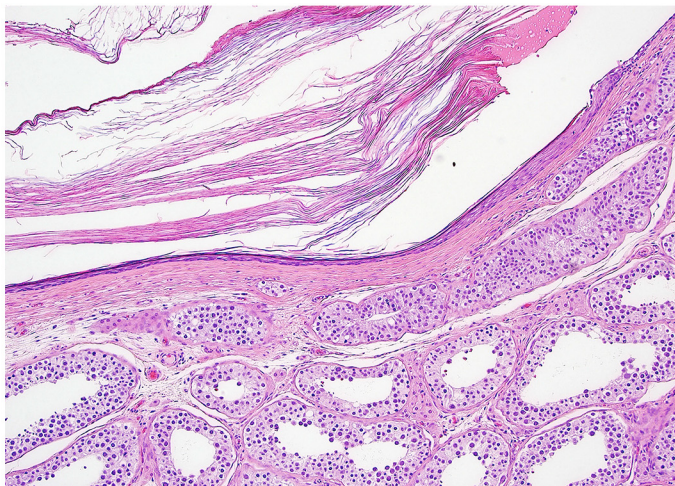
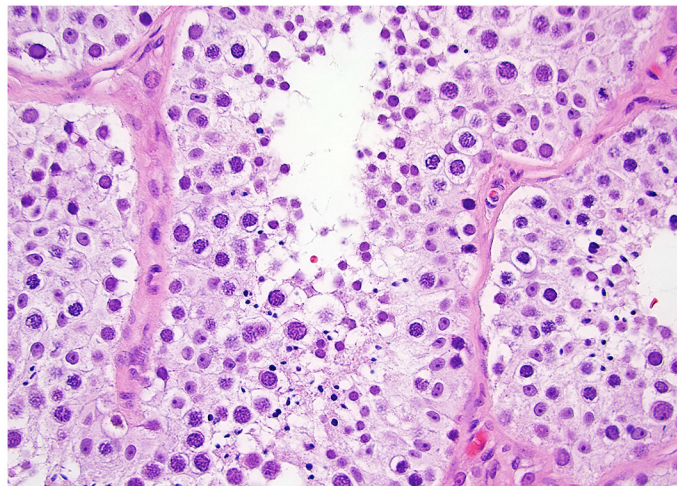
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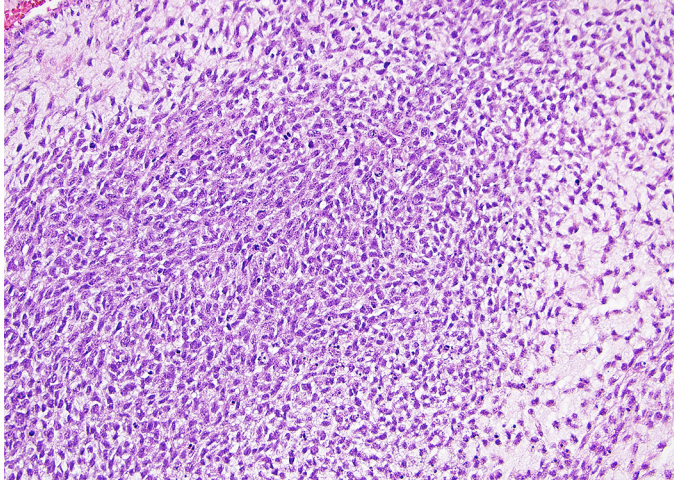
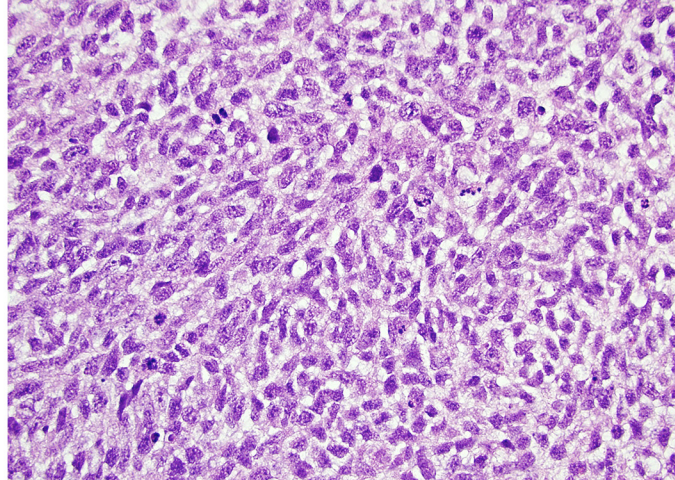
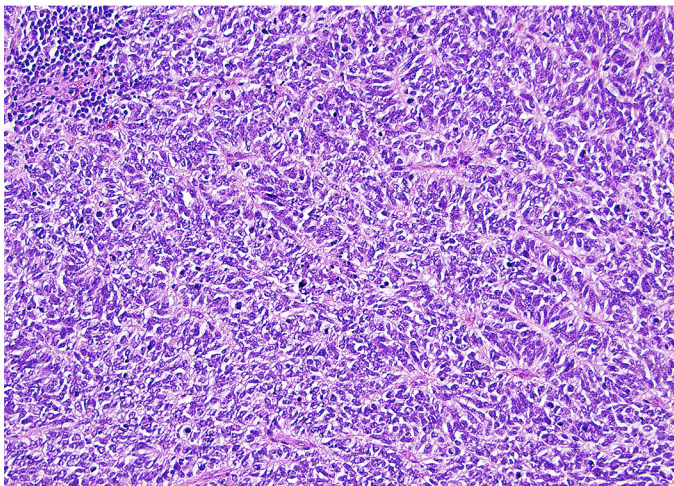
646 **Figure 5:** Secondary, somatic-type malignancy arising from germ cell tumour may assume
 647 various histologies. Sarcomas are common, including embryonal rhabdomyosarcoma (A-
 648 B), here forming a primitive small cell neoplasm with spindle-shaped cells and brisk
 649 mitotic activity. Immunohistochemical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

A**B****C****D****E****F**



A**B****C****D**

A**B****C****D**

A**B****C****D**