Paediatric extracranial germ-cell tumours

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Management of paediatric extracranial germ-cell tumours carries a unique set of challenges. Germ-cell tumours are a heterogeneous group of neoplasms that present across a wide age range and vary in site, histology, and clinical behaviour. Patients with germ-cell tumours are managed by a diverse array of specialists. Thus, staging, risk stratification, and treatment approaches for germ-cell tumours have evolved disparately along several trajectories. Paediatric germ-cell tumours differ from the adolescent and adult disease in many ways, leading to complexities in applying age-appropriate, evidence-based care. Suboptimal outcomes remain for several groups of patients, including adolescents, and patients with extragonadal tumours, high tumour markers at diagnosis, or platinum-resistant disease. Survivors have significant long-term toxicities. The challenge moving forward will be to translate new insights from molecular studies and collaborative clinical data into improved patient outcomes. Future trials will be characterised by improved risk-stratification systems, biomarkers for response and toxic effects, rational reduction of therapy for low-risk patients and novel approaches for poor-risk patients, and improved international collaboration across paediatric and adult cooperative research groups.

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Introduction

Although malignant germ-cell tumours are often referred to as rare paediatric cancers, germ-cell tumours represent 3·5% of all childhood cancers that occur before 15 years of age. Thus, their incidence is similar to childhood rhabdomyosarcomas, osteosarcomas, or retinoblastomas.[1] However, in adolescents aged 15–19 years, malignant germ-cell tumours represent 13·9% of neoplasms. They are the most common solid tumour, and the second most common malignancy after Hodgkin's lymphoma in this age group for both sexes. Based on data from the Surveillance, Epidemiology and End Results database, the age-adjusted incidence of extracranial germ-cell tumours in the USA is 11·7 per million in boys and 6·7 per million in girls. About 900 new cases of malignant germ-cell tumours are diagnosed in the USA every year in patients younger than 20 years of age. Two distinct peaks in incidence are reported, one in young children (0–4 years) and another from the onset of puberty through to young adulthood (11–35 years).[2]

In this Review, the biology, clinical presentation, diagnostic work-up, staging and risk classification, treatment, late effects, and future directions in germ cell tumours are discussed.

Biology

An improved understanding of the molecular basis of germ-cell tumours is likely to enhance risk stratification and identification of targets for the development of novel therapies, to increase overall survival for poor-risk groups, and rationalise therapy reductions in low-risk groups.

Germ-cell tumours are postulated to occur as a result of events in utero, although the cause remains largely unknown. Strong estimates of heritability suggest a genetic susceptibility.[3] Potential risk factors include parental demographic characteristics, in utero chemical or hormone exposures, parental lifestyle factors, and congenital abnormalities.[4] Of these congenital abnormalities, cryptorchidism and Klinefelter's syndrome are associated with an increased risk of testicular and mediastinal tumours in boys, and Turner's syndrome with an increased risk of ovarian tumours in girls. Disorders of sexual differentiation, such as Frasier's syndrome, Swyer's syndrome, and other androgen insensitivity syndromes, are associated with an increased risk of germ-cell tumours in the streak gonads, principally gonadoblastoma.[4]

Germ-cell tumours arise from molecular defects in early germline progenitors known as primordial germ cells. The broad range of possible germ-cell tumour histologies is attributed to the totipotent nature of primordial germ cell (figure 1). The hypothetical model of tumorigenesis proposed by Teilum[5] (figure 2) postulates that germinomas (seminomas in testicular sites and dysgerminomas in ovarian sites) arise directly from undifferentiated primordial germ cells and therefore retain their pluripotency. Embryonal carcinomas display early embryonic differentiation and can further differentiate into tumours containing all three germ layers (endoderm, ectoderm, and mesoderm), thereby producing teratomas. By contrast, primordial germ cells that follow an extra-embryonic differentiation pathway result in either yolk-sac tumours (formerly known as endodermal sinus tumours) or choriocarcinomas (tumours resembling the trophoblast).[6] Tumours that contain various malignant histologies are termed mixed malignant germ-cell tumours.

Primordial germ cells migrate from the yolk sac to the gonadal ridge through the midline of the developing embryo during early gestation. Several factors are needed for the survival and migration of primordial germ cells, including the chemokine receptor *CXCR4* and the *KIT* ligand *KITLG*,[3,7] which is expressed in an increasing gradient from the yolk sac to the gonadal ridge. Disruption of this migration process is likely to explain the occurrence of extragonadal germ-cell tumours and

their midline propensity. Single nucleotide polymorphisms (SNPs) in the *KITLG* gene have been associated with the development of germ-cell tumours in adults[7,8] and adolescents[3] in genome-wide association studies. More than 25 SNPs in genes at 19 independent loci have been identified.[9] Genes involved in five main mechanisms, including *KIT*/*KITLG* signalling, male germ-cell development, telomerase, microtubule, and DNA damage repair pathways, were implicated. The odds ratios reported in the genome-wide association studies are among the highest for any cancer type. In the future, it might be possible to derive a polygenic risk score to inform potential screening strategies. Exactly how many of these SNPs are relevant to paediatric tumours remains to be established.

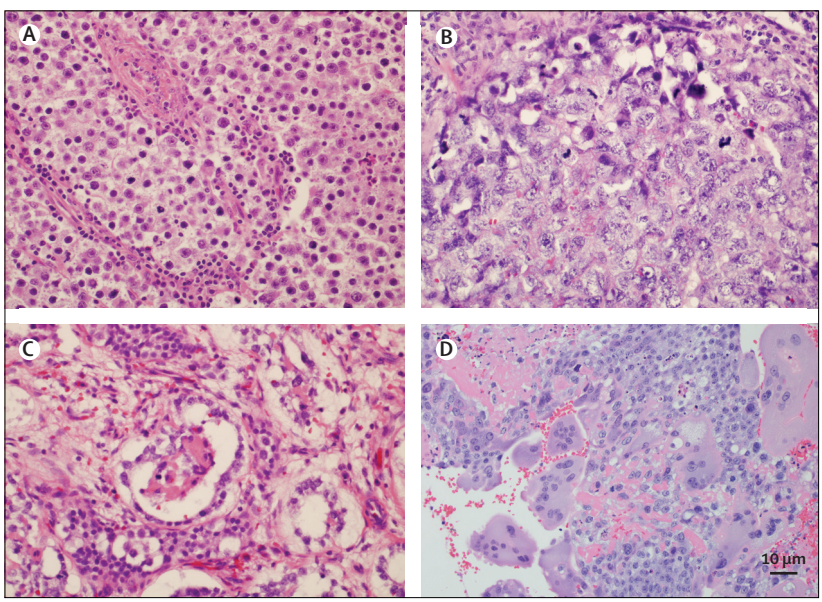

Figure 1: **Histology of paediatric germ-cell tumours**
Germinoma (A); embryonal carcinoma (B); yolk-sac tumour (C); and choriocarcinoma (D).

Epigenetic mechanisms could contribute to germ-cell tumour development.[10] Migrating primordial germ cells undergo methylation erasure at imprinted genes, followed by sex-specific reimprinting during gametogenesis.[11] The imprinting patterns of loci such as *IGF2/H19* differ in paediatric germ-cell tumours from those arising in adulthood, suggesting that tumours in children arise from more immature primordial germ cells. In paediatric malignant germ-cell tumours, yolk-sac tumours have increased methylation at many gene regulatory loci compared with germinomas and display a methylator phenotype, including silencing of genes associated with apoptosis and suppression of *WNT* signalling.[12]

Gain of chromosome 12p, which is usually caused by isochromosome 12p formation, is a universal feature of adult testicular malignant germ-cell tumours and occurs irrespective of histological subtype.[13] Seminomas and embryonal carcinomas express key stem cell genes in this 12p region, including *NANOG* and *STELLA/DPPA3*,

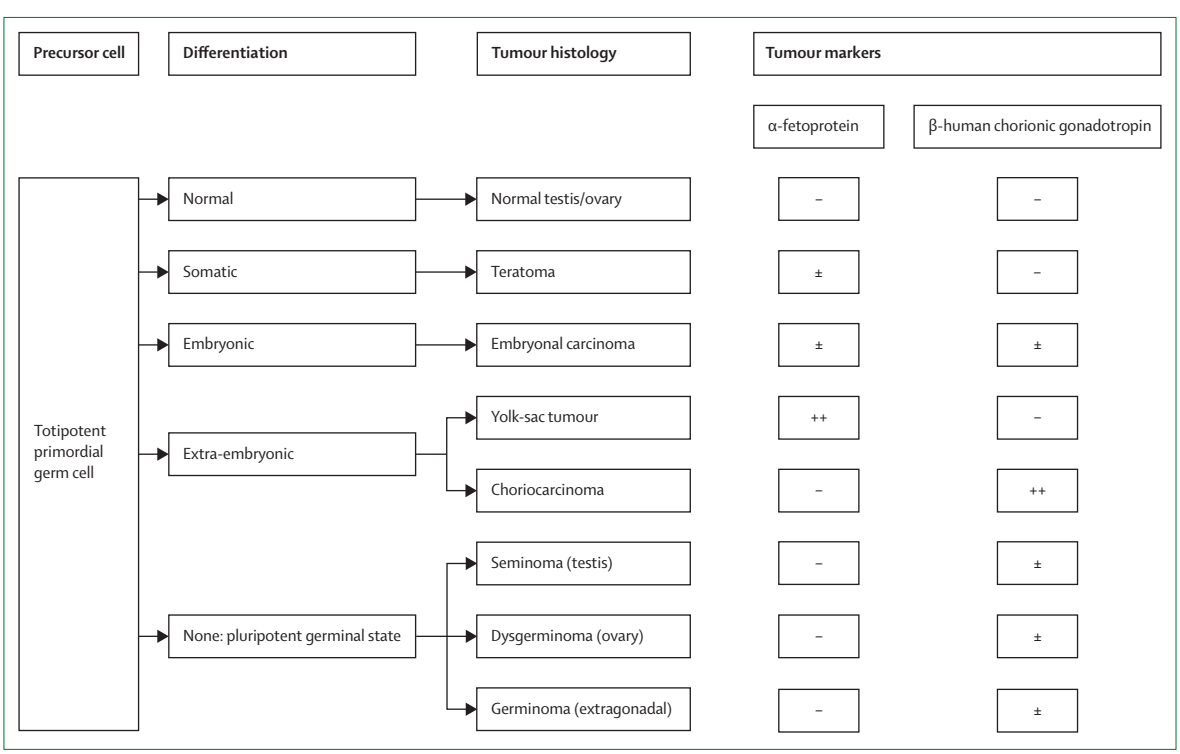

Figure 2: **Teilum's model of germ-cell tumour histogenesis**
Data from Murray and Nicholson.[6] ++=strongly positive. ±=occasionally positive. –=negative.