Pathology, Epidemiology and Classification

GCT-04 Advances in the classification of germ cell tumours: Getting therapy right

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Background: There have been numerous advances in the understanding, classification, immunohistochemistry and genetics of testicular germ cell tumours. Due to their rarity and problems in nomenclature there remains a significant error rate in non-specialist centres, and potential for inappropriate therapy based on misdiagnosis or misunderstanding.
Methods: This was considered in the 2015 International Society of Urological Pathology Consultation on Testicular Cancer and informed the WHO 2016 classification.
Results: 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-type tumours (non-GCNIS-derived) from postpubertal-type tumours (GCNIS-derived. Spermatocytic tumour is the new name for spermatocytic seminoma, to avoid potential mistreatment. Trophoblastic tumours now include epithelioid and placental site trophoblastic tumours similar to those in the gynaecological tract. We have emphasised that some features are not prognostically important (anaplasia in seminoma or spermatocytic tumour or immaturity in teratoma) while others (dedifferentiation to somatic-type malignancy) should be reported. Application of these changes has not yet been apparent in non-testicular germ cell tumours, and there is a need to ensure that these tumours are also treated appropriately. Some authors have proposed a more universal classification for all germ cell tumours, and the advantages and disadvantages of this will be discussed, particularly with reference to ovarian germ cell neoplasms.

GCT-05 Building a scalable and sustainable data commons for germ cell tumour research

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Background: Rare tumour study suffers from paucity of data for research. In addition, investigators lack access to high-performance resources for data analysis. Data commons are collections of data from disparate sources, harmonized to a common data standard, with cohort discovery and analytic capabilities. Germ cell tumours (GCTs) are rare malignancies that require data commons for effective study. Here we demonstrate how a GCT data commons can be built to facilitate research.
Methods: The Malignant Germ Cell International Consortium (MaGIC) is a collection of 6 independent clinical trial organizations. Each group has their respective national paediatric/adult GCT clinical trials data, but information collected is non-uniform. Working with MaGIC and clinical and statistical experts, a GCT data dictionary was built. Clinical trials data from each consortium will be harmonized to this new data standard and added to the data commons. The Pediatric Cancer Data Commons team at University of Chicago will house this commons alongside existing neuroblastoma and rhabdomyosarcoma commons. Governance will be established to regulate use of MaGIC commons.
Results: Over 100 clinical and genetic data elements have been balloted and mapped to standard elements in NCI's Enterprise-Vocabulary-Service (NCIt or ICD-O). Cohort discovery and basic analytic tools will be available to researchers to search/request data from MaGIC commons. Transparent governance policies/procedures will regulate contribution of/access to data. A process will be established to allow researchers to request line-level data from MaGIC. Sustainability and long-term functionality of the platform will be discussed, including integration into the larger NCI data ecosystem.

GCT-06 Overlapping genetic aetiology in adult and paediatric germ cell tumours

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Background: Germline genetic susceptibility has not been evaluated in an agnostic fashion in paediatric germ cell tumours (GCT), mainly due to a lack of an adequate number of samples. We may be able to gain some insight from studies of adult testicular GCT where at least 40 low penetrance susceptibility loci have been identified. We evaluated associations between these SNPs and paediatric GCT to identify variants that served as shared susceptibility loci.
Methods: Illumina Human CoreExome BeadChips were used to genotype germline DNA samples from 1,600 GCT cases, 771 population controls and 1,497 biological parents. Due to the inclusion of both family-based and case-control data, effect estimates were computed separately and then meta-analyzed. All analyses controlled for age, sex and ancestry. A Bonferroni correction was used to account for multiple comparisons ($p < 0.0016$ for 31 tests).
Results: Fourteen SNPs were statistically significantly associated with GCT risk ($p < 0.0016$), with two reaching genome-wide significance [rs4624820 near *SPRY4*: OR = 1.42, $p = 1.45 \times 10^{-10}$; rs210138 near *BAK1*: OR = 1.76, $p = 2.94 \times 10^{-17}$] and remaining significant even after removing children with testicular cancer. There was no global inflation in the genome-wide type 1 error (lambda = 1.0X), and yet seven additional SNPs were marginally associated with risk for a total of 21 of the 31 SNPs tested ($p < 0.05$), which is far more than would be expected by chance alone (expected count<2), suggesting that many of these same variants are playing a role in paediatric GCTs and that they will exceed statistical significance should they be analyzed together with more samples.