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Perspectives on testicular germ cell neoplasms☆

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Summary Our knowledge of testicular germ cell neoplasms has progressed in the last few decades due to the description of germ cell neoplasia in situ (GCNIS) and a variety of specific forms of intratubular germ cell neoplasia, the discovery of isochromosome 12p and its importance in the development of invasiveness in germ cell tumors (GCTs), the identification of specific transcription factors for GCTs, and the recognition that a teratomatous component in mixed GCT represents terminal differentiation. Isochromosome 12p and 12p overrepresentation, collectively referred to as 12p amplification, are fundamental abnormalities that account for many types of malignant GCTs of the testis. Embryonal carcinoma is common in the testis but rare in the ovary, whereas the converse is true for mature cystic teratoma. Spermatocytic tumor occurs only in the testis; it has not been described in the ovary or extragonadal sites. The origin of ovarian mature cystic teratoma is similar to that of prepubertal-type testicular teratoma and dermoid cyst at any age in that it arises from a nontransformed germ cell, whereas postpubertal-type testicular teratoma arises from a malignant germ cell, most commonly through the intermediary of GCNIS. Somatic neoplasms, often referred to as monodermal teratomas, arise not infrequently from mature cystic teratoma of the ovary, whereas such neoplasms are rare in testicular teratoma with the exception of carcinoid. Integration of classical morphologic observations and emerging novel molecular studies will result in better understanding of the pathogenesis of GCTs and will optimize patient therapy.
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1. Introduction

Germ cell tumors (GCTs) are the most common category of testicular neoplasms. It is important to correctly diagnose the various types of GCT and to distinguish them from epithelial and sex cord–stromal tumors so that optimal therapy and an accurate prognosis can be determined [1,2]. In this article, we discuss the latest classification of testicular GCTs in the recently published *WHO Classification of Tumours of the Urinary System and Male Genital Organs* [3]. The topics of tumors composed of germ cells and sex cord derivatives and disorders of sex development are beyond the scope of this article.

2. Histogenesis and putative precursors of GCTs

Both genetic and epigenetic factors are likely responsible for the myriad of differences between testicular and ovarian

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GCTs [4,5]. Most fundamental is the development of the testis and its neoplasms under the influence of the sex-determining region Y (*SRY*) gene on the short arm of the Y chromosome, whereas the ovary and its tumors develop without its influence [6]. Because of genomic imprinting, the paternal and maternal sets of chromosomes have different functionality due to parent-specific epigenetic modification of the genome [4]. The genetic hallmark of the postpubertal types of malignant GCT is chromosome 12p abnormalities, including isochromosome 12p and chromosome 12p overrepresentation (Fig. 1) [7,8].

3. Classification of germ cell neoplasms

Our current classification of testicular GCTs modified from the most recent *WHO Classification of Tumours the Urinary System and Male Genital Organs* is shown in Table 1 [3]. One of the major features of the current classification of testicular GCTs is the adoption of the division of teratoma and yolk sac tumor into prepubertal and postpubertal types; however, after this distinction was made, it was recognized that the prepubertal types could be detected in patients at a postpubertal age. On reflection, this observation should not be considered surprising because it is not currently possible to determine the time of inception of a neoplasm. The age of the patient at the time of detection presumably would be dependent on the age at inception of the neoplasm; its growth rate; its location in a cryptorchid or descended testis; and the frequency of examination by the individual, family, or clinician. None of these factors can be controlled. Furthermore, postpubertal types can occur in prepubertal individuals who have a disorder of sex development. Although it is well documented that prepubertal-type neoplasms can present at an age beyond childhood, they, nevertheless, maintain discrete characteristics that distinguish them from adult-type testicular GCTs [9].

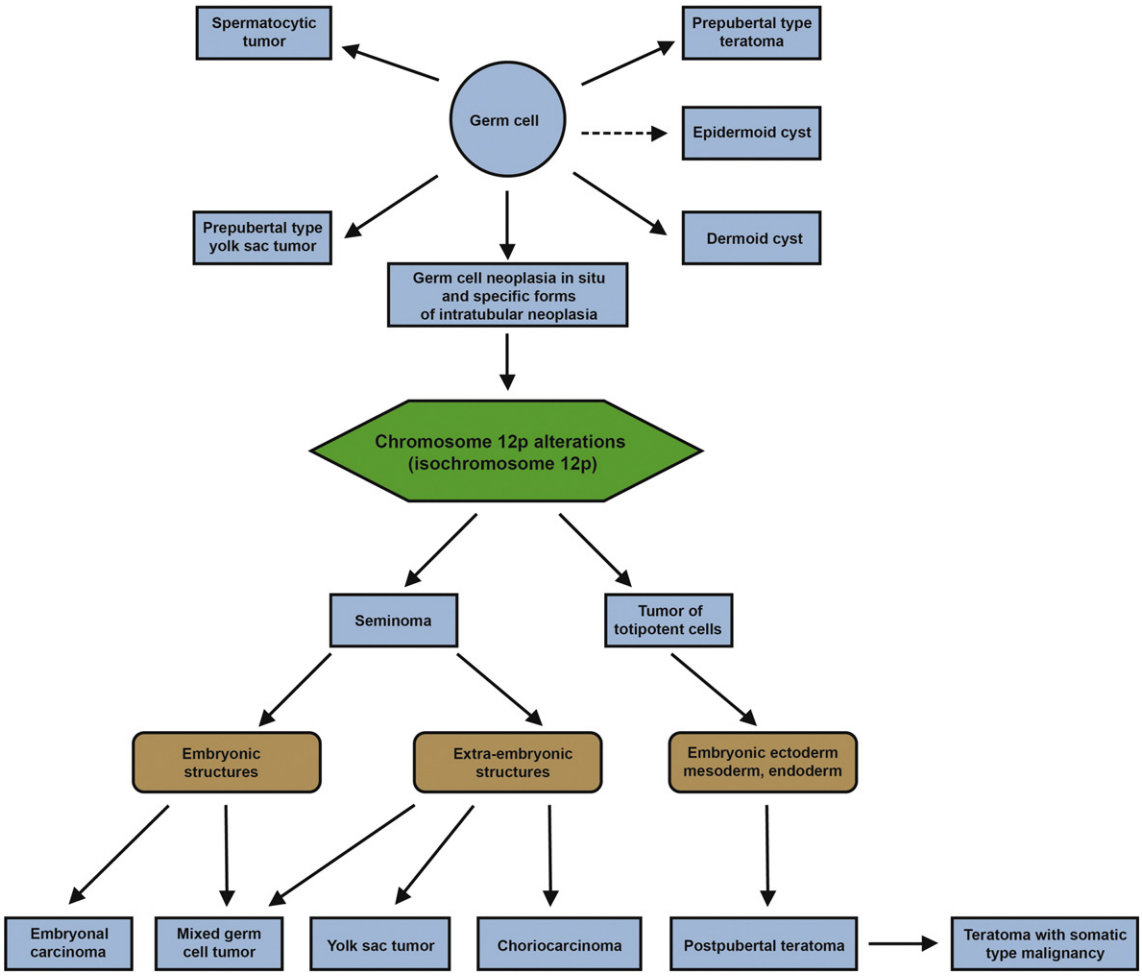

Fig. 1 Major pathways for the development of testicular GCTs. Rectangle with perpendicular corners indicates type of neoplasm. Rectangle with rounded corners indicates cell or tissue type, process, or structure. Solid arrow indicates a recognized pathway; dashed arrow indicates that the pathway has not been established.

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