Pathology and Biology of Human Germ Cell Tumors

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To Gordon Barry Pierce (1925–2015) who found the key to unlocking the magic of germ cell tumors.

Preface

August 2016

Since their first documented descriptions, germ cell tumors have always been a leading exhibit in an imaginary cabinet of scientific curiosities. The reason is their extraordinariness, resulting from the finding of distorted bodily structures in unexpected organs and at different ages. This distortion of the body image has prompted the evolution of thought, ideas, and theories about their origin and meaning ranging from the purely magical to the current ideas of their pathogenesis and differentiation potentials.

However, the key to the understanding of their multiple and complex differentiations lies in the concepts of pluripotentiality and tumor stem cells, an original idea developed by G. Barry Pierce (1925–2015), mentor and kind friend to some of the older contributors (FFN and ID) of this monograph. His farsighted work with L. Kleinsmith on murine teratocarcinoma [1] demonstrated, for the first time, the existence of pluripotent tumor stem cells. Thus, the study of these curious tumors turned out to be a biological Rosetta stone, linking embryonic and neoplastic development [2] in what Rupert A. Willis called a borderland of embryology and pathology, [3] eventually becoming the key to understanding tumor biology and especially pluripotentiality as the paradigm in the origin and histology of germ cell tumors.

Since Willis' [4] book in the early 1950s, no other reference book has provided a complete and integrated picture of germ cell tumors in the various organs and ages of life including their pathogenesis and surgical pathology, having been usually partially analyzed from pediatric, gynecologic, uropathologic, and other similarly specialized viewpoints. In this monograph, we have brought together the current knowledge on gonadal and extragonadal germ cell tumors and analyzed them from a broader perspective that includes basic clinical features and management, epidemiology, molecular biology, and an extensive clinicopathologic analysis, with emphasis on their most frequent locations: testicular, ovarian, and mediastinal. Since germ cell tumors exhibit a stereotyped histology in the various organs, a certain degree of overlap and repetition is unavoidable.

The characteristic histology of germ cell tumors in various organs has led to the general belief that tumors with a similar morphology share the same origin. This assumption obscures the understanding of their biology, since germ cell tumors behave differently depending on the age of the patient and the organ they arise from. The explanation for their diverse behavior lies not in a *generic* germ cell origin but in the developmental state of the precursor

stem cells, which are biologically different in the various anatomical sites and ages of life.

In this monograph, we attempt to analyze germ cell tumors, not only histopathologically but under the developmental perspective outlined by Oosterhuis and Looijenga in Chap. 3, thus lending support to G. B. Pierce's notion of germ cell tumors as caricatures of progressive stages of embryonal development. Their approach, focusing on the developmental potential of embryonic stem and germ cells, provides a unifying model for all germ cell tumors. This concept crystallizes in a pathogenetic classification of germ cell tumors into seven types, each of them reflecting a defined stem cell potency state. This classification also includes, for the first time, germ cell tumor patterns derived from somatic tumors that are the result of induced pluripotency of tumor stem cells. Their proposal provides a good explanation for the clinicopathologic diversity of germ cell tumors, answering many extant questions about their epidemiology, morphology, and behavior. Consequently, Oosterhuis and Looijenga's proposed classification will be followed in most chapters, especially in gonadal germ cell tumors.

Histopathologic terminology is updated to the recently proposed changes in the World Health Organization blue books in the testis, ovary, and mediastinum.

A brief summary of the contents follows:

Dr. Ivan Damjanov is a leading figure in the experimental pathology of germ cell tumors. In his introductory chapter, he reviews the flow of clinicopathologic and experimental knowledge, to which he has been an important contributor, leading to the present concepts and terminology.

A European-wide study on the epidemiology of germ cell tumors is presented by Drs. Trama and Berrino in Chap. 2. This study complements recent studies from the UK and USA.

As previously mentioned, Chap. 3 integrates a wealth of clinicopathologic with cytogenetic and basic stem cell research data to provide a rationale for a comprehensive biological classification of germ cell tumors.

Chapter 4 complements Chap. 3 with a practical approach, the analysis of antibody expression, reviewing current data on diagnostic immunohistochemistry and analyzing both stage-specific, pluripotency markers and organ-specific ones. The genes and developmental role of each antibody are discussed and a hands-on approach to the use of commercially available antibodies is provided.

In Chap. 5, the Mayo Clinic Medical Oncology team summarizes the management of germ cell tumors using testicular germ cell tumors as the prototype example.

Chapters 6, 7, 8, and 9 provide an extensive coverage of both histopathologic and clinicopathologic findings of germ cell tumors in their more frequent locations: gonads and mediastinum.

Chapter 6 is an update of the current histopathology of ovarian germ cell tumors, emphasizing the expression of characteristic pluripotency markers as a mandatory diagnostic tool for differential diagnosis. Yolk sac tumors

are reconsidered as primitive endodermal tumors applying a diagnostic immunohistochemical panel able to distinguish between extraembryonal and somatic variants. Prognostically relevant histologic grading of immature teratomas is reanalyzed, taking into account the presence of immature endodermal structures and the expression of pluripotency markers. Finally, an emerging category of highly malignant germ cell tumors originating not from germ cells but from somatic müllerian tumors in older patients (endometrioid carcinomas and clear cell tumors) is analyzed in depth.

Chapter 7 focuses on postpubertal testicular tumors. It incorporates recent terminology and classification of testicular neoplasms recently introduced by the World Health Organization. These include the new terminology of germ cell neoplasia in situ and spermatocytic tumor. The concepts of prepuberal- and postpubertal-type teratomas are defined and contrasted, concepts that are highly analogous to the premises of Oosterhuis and Looijenga's classification. The pathology of these tumors is analyzed in the context of their clinical implications. Sadly, the senior author of this chapter, Dr. Thomas J. Sebo, passed away during the preparation of this manuscript. The chapter pays tribute to his outstanding skills as diagnostic urologic pathologist.

Chapter 8 focuses on features of mediastinal GCT that might differ from their gonadal counterparts including imaging, immunophenotype, cytogenetic and molecular characteristics, and prognosis. Important differential diagnoses that should be considered before establishing a diagnosis of primary mediastinal GCT are also discussed.

Chapter 9 summarizes current knowledge about the clinicopathologic, phenotypic, and molecular characteristics of intracranial germ cell tumors, highlighting specific properties of intracranial sites.

Chapter 10 emphasizes differential findings relevant in the extensive and fascinating morphologic spectrum of pediatric germ cell tumors, particularly those associated with disorders of sex development.

Germ cell tumors found in miscellaneous sites are reviewed in Chap. 11 with special emphasis on their organ-related particularities and their differential diagnoses.

Finally, Chap. 12 covers, for the first time, another emerging category of tumors: somatic-type malignancies that develop in pre-existing germ cell tumors. The topic is presented in the context of the different types of germ cell tumors according to Oosterhuis and Looijenga's classification.

With its wide multiorganic and biopathologic approach, we hope that the present monograph will prove useful to the understanding of the pathology and biology of germ cell tumors.

The editors would like to thank the authors for their generosity with their time and knowledge and patience to bear innumerable and persistent requests from the editors. Ms. M. Himberger, project coordinator from Springer, stoically bore with us the delays due to the late appearance of the new WHO classifications of tumors. Dr. Heather Fulwood was a daily inspiration and great help throughout the edition of this book.

We are sad indeed that Dr. G. Barry Pierce did not live quite long enough to see the publication of this monograph which is our homage to his brilliant commitment and contribution to the understanding of germ cell tumors.

Finally, we would like to thank the partners and family of the authors and editors for their understanding of the time we have often robbed from family life.

Zahara de los Atunes, Spain — Francisco F. Nogales
Rochester, MN, USA — Rafael E. Jimenez

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Germ Cell Tumors: Classifications, Definitions, and Terminology

1

Ivan Damjanov

1.1 Introduction

The history of human ovarian, testicular, and extragonadal teratomas and, by extension, human germ cell tumors in general has been extensively reviewed on several occasions [1–10]. From these reviews it seems that the first fully documented case of teratoma of the ovary was reported in 1658 by Johann Scholz [also known under his Latin surname *Scultetus*] [4], while the first teratoid tumor of the testis was reported in 1696 by Saint Donat [10]. The first description of sacrococcygeal and retroperitoneal teratomas and other germ cell tumors cannot be determined exactly, although it seems that the Chaldean Babylonian cuneiform papyri 4000 years ago contained a description of child with a sacrococcygeal teratoma [2]. According to the literature review by Lamphier [8], the first case of a mediastinal dermoid cyst was reported by J. A. Gordon in an address to the Medico-Chirurgical Society of London in November 1823 and published later in the society proceedings in 1827. According to Wheeler [4], Maier reported a cerebral dermoid in a two-week-old boy, and Weigert in 1875 provided histologic evidence for a teratoma of the pineal gland. These two cases would qualify as the first intracranial germ cell tumors on record. According to the review of Lynch and Blewett [9], it was Askenazy in 1906 who first described an intracranial choriocarcinoma.

These early reports of human germ cell tumors were based on a vague understanding of their biology and histogenesis and usually included a lot of speculation and verbosity. Actually, in many cases the germ cell nature of tumors described was not even mentioned. The confusing terminology used by these pioneers of pathology was reviewed by James Ewing [10], who himself did not lack strong opinions and a tendency for speculation. Ewing also contributed to the confusing view that seminoma and embryonal carcinoma (EC) are more or less the same.

In summary, although I have tried to decipher some of the early thinking that went into these efforts to make the terminology of germ cell tumors consistent with the clinical requirements, I must admit that in retrospect that it was almost impossible for me to reconstruct the thinking of our predecessors. To this end I tend to agree with Rupert Willis [5] who in his very influential book wrote the following: “It would be of little use to recount the confused views which were held of the nature of testicular tumors during the later part of last century, when “sarcomas” and “endothelio-

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mas" abounded and when teratomas were called "chondromas", "chondro-carcinomas", "rhabdomyomas","myo-chondromas", etcetera, according to the tissues which had been detected in them." Accordingly, I will continue my discussion with the contributions of Friedman and Moore, who in essence initiated the modern era of germ cell research with their classical 1946 paper [11].

1.2 Classification of Testicular Germ Cell Tumors

All the modern classifications of testicular tumors can be traced to the groundbreaking work of Friedman and Moore who examined more than 900 testicular tumors removed from male members of the US military during the World War II [WWII] period [11]. These authors recognized four fundamental structural patterns corresponding to seminoma, embryonal carcinoma, chorioepithelioma, and teratomas and proposed that the germ cell tumors be classified in four groups: (1) seminoma [germinoma]; (2) embryonal carcinoma, including a subset of chorioepithelioma; (3) teratoma; and (4) teratocarcinoma (Fig. 1.1). As pointed out by Young [6], the most important contribution of these authors was their recognition of embryonal carcinoma [EC] as a neoplasm distinct from seminoma. I would also add that they recognized the capacity of embryonal carcinoma cells to differentiate into the chorioepitheliomatous elements and the somatic tissues forming the teratomatous part of mixed germ cell tumor (Fig. 1.2). Their insight was followed up by G. Barry Pierce [12] who proposed and experimentally proved that EC cells represent the developmentally pluripotent malignant stem cells of teratocarcinomas or mixed germ cell tumors as we usually call them today. Like other stem cells, EC cells can self-renew on one hand side and differentiate on the other. If unchecked, they propagate until they kill the host. They can metastasize but also differentiate into benign nonproliferating somatic tissues or extraembryonic structures such as yolk sac or trophoblast. The reversibility of malignancy of EC cells, a concept pioneered by Pierce in 1950 and later [13], has been by now generally accepted and confirmed in the murine models of teratocarcinoma and EC, pioneered by Ralph Brinster, Gail Martin, and Martin Evans, as reviewed by Davor Solter [14], and also at a recent international conference attended by most scientists who have experimentally contributed to this field [15]. In clinical practice these principles are confirmed repeatedly by the finding of mature teratomas in lymph nodes of testicular cancer patients treated by modern cis-platinum-based chemotherapy.

The original classification of Friedman and Moore [11] was first modified by Dixon and Moore and printed in the first edition of atlases of the Armed Forces Institute of Pathology [AFIP] in 1952 [16]. In that treatise, Dixon and Moore have in de facto divided testicular germ cell tumors in two groups: seminomas and all others, stating that embryonal carcinoma, choriocarcinoma, and teratomas are closely related tumors, as indicated in their drawing (Fig. 1.3). They also stated that there are numerous mixed forms, calculating at least 15 possible varieties and combinations which could be encountered in various tumors. To simplify the matters and to make the classification as clinically relevant as possible, Dixon and Moore [16] divided the germ cell tumors in five groups: (I) seminoma, pure; (II) embryonal carcinoma, pure or with seminoma; (III) teratoma, pure or with seminoma; (IV) teratoma with either embryonal carcinoma or choriocarcinoma or both and with or without seminoma; and (V) choriocarcinoma, pure or with either seminoma or embryonal carcinoma or both.

The classification proposed by Dixon and Moore [16] was modified several times over the last 60 some years [17–19], resulting in a clinically useful approach combined with an easily reproducible microscopic subdivision of testicular tumors. The 2004 classification sponsored by the World Health Organization [WHO] and recommended by the panel of WHO experts for general use has been further disseminated in the widely circulated in the AFIP series of atlases of pathology [19]. Even though this classification is primarily based on microscopic morphology of tumors [Table 1.1], it correlates well with the clinical requirements for subdividing testicular germ cell tumors into two major

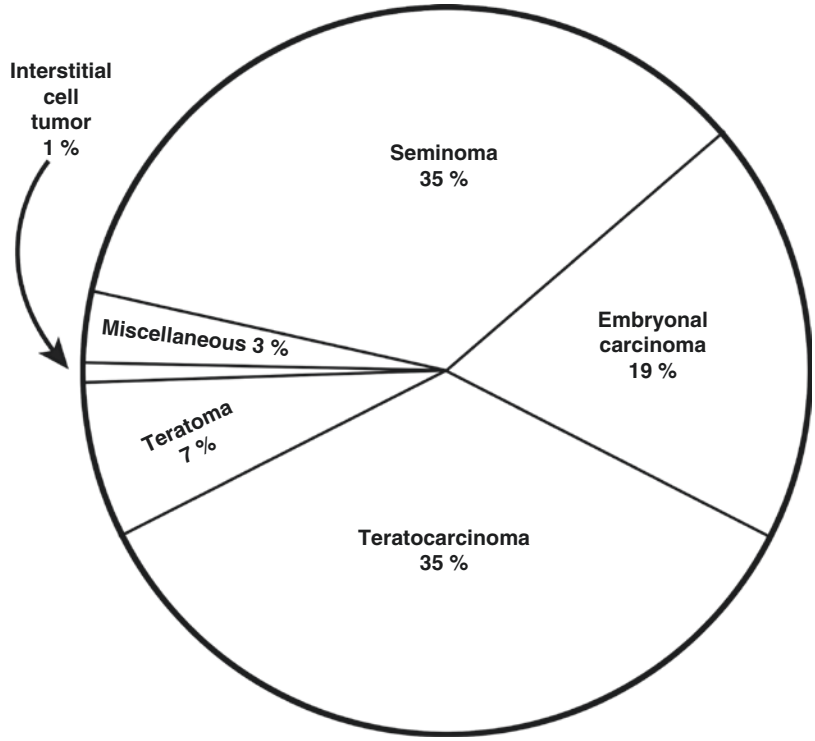

Fig. 1.1 The relative incidence of testicular tumors in the study of Friedman and Moore [11] (Reproduced with permission of the publisher)

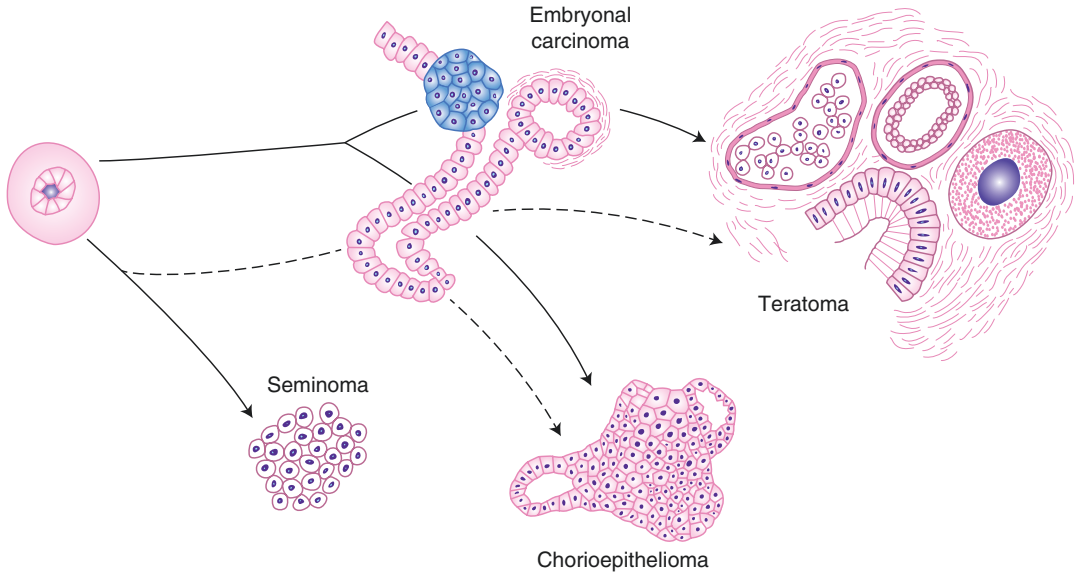

Fig. 1.2 Schematic drawing illustrating the developmental potential of embryonal carcinoma according to Friedman and Moore [11] (Reproduced with the permission of the publisher)

groups: seminomas and nonseminomas, also known as nonseminomatous germ cell tumors [NSGCT]. It also incorporates some of the basic histogenetic tenets and discoveries that were made over the years since the WWII. For epidemiologic research, for international studies, and for billing purposes, the International Classification of Diseases has produced its

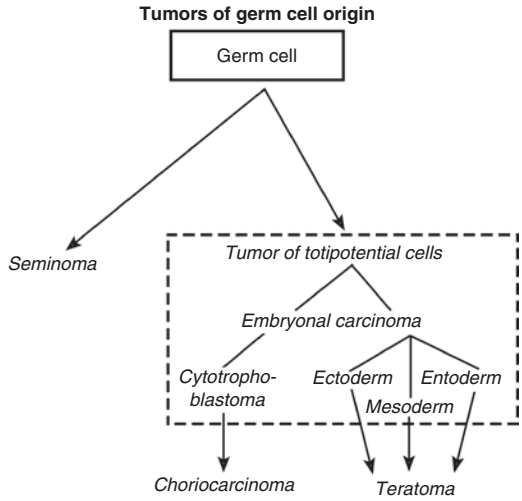

Fig. 1.3 Histogenesis of testicular tumors according to Dixon and Moore [16] (Reproduce with the permission of the publisher)

ICD-10 listing of testicular tumors, which is for completeness' sake included as Table 1.2.[1]

The limitations of space do not allow me to enumerate all the major figures who have played a critical role in advancing our knowledge about germ cell tumors during the last few decades. Thus, by necessity I will mention only five physician-scientists, realizing that this is a rather subjective choice, with a strong personal bias. Nevertheless, I feel that I would be remiss for not mentioning the comparative studies of Gunnar Teilum, which led to the better understanding of the similarities between ovarian and testicular germ cell tumors and the recognition of yolk sac carcinoma as a distinct entity [20]. Robert E. Scully was a true giant of urogenital and gynecologic pathology, whose contributions were recently lovingly reviewed by Oliva and Young [21–23]. His contributions are too many to list, but in essence his work over half a century helped us all to conceptualize and delineate some of the basic aspects of testicular and ovarian pathology. F. K. Mostofi was instrumental in defining the basic approaches to classifying testicular and other urogenital tumors promoting worldwide discussions under the aegis of the WHO [17, 24, 25]. The astute observations and persistence of Niels E. Skakkebæk led to the recognition of intratubular germ cell neoplasia [26]. G. Barry Pierce, my mentor and longtime friend, performed some of the fundamental experiments on mouse germ cell tumors and provided a new

[1]The latest 2016 WHO classification is commented in Chap. 3 [Eds].

Table 1.1 WHO 2004-based classification of testicular germ cell tumors

Testicular germ cell tumors
Precursor lesions
Intratubular germ cell neoplasia, unclassified
Intratubular germ cell neoplasia, specific types
Germ cell tumors of one histologic type
Seminoma
Spermatocytic seminoma
Embryonal carcinoma
Yolk sac tumor
Trophoblastic tumors
Teratoma
Germ cell tumors of more than one histologic type
Mixed germ cell tumors
Polyembryoma
Diffuse embryoma
Regressed ("burnt-out") germ cell tumors
Germ cell sex cord-stromal tumors
Gonadoblastoma
Unclassified

Abbreviated and slightly modified from Ulbright and Young [19]

Table 1.2 Classification of testicular germ cell tumors

2014 ICD-10-CM diagnosis code C62.90
Malignant neoplasm of testis NOS
Cancer of the testis
Cancer of the testis, choriocarcinoma
Cancer of the testis, nonseminomatous germ cell
Cancer of the testis, seminoma
Choriocarcinoma of testis
Mixed germ cell tumor of testis
Nonseminomatous germ cell neoplasm of testis
Primary malignant neoplasm of testis
Seminoma of testis
Testicular cancer
Testis, mixed germ cell tumor

According to the International Coding of Diseases (ICD) http://www.icd10data.com/

insight into the basic biology of human germ cell tumor based on sound scientific principles [13].

1.3 Classification of Ovarian Germ Cell Tumors

Ovarian germ cell tumors are basically equivalent to those originating from male germ cells. Yet there are some important biological and clinical differences between these two groups of tumors [27–29]. For example, in contrast to the malignant nature of the vast majority of testicular tumors, most ovarian tumors are benign, presenting clinically as mature teratomas.

Experimental data obtained in mice indicate that ovarian teratomas are formed from parthenogenetically activated ovarian germ cells [30]. Human parthenotes isolated from the ovaries can rise to embryonic stem cells [31], and thus by extrapolation, one can assume that these cells could give rise to teratomas and other germ cell tumors as well.

The histogenesis of teratoma can be readily explained by parthenogenetic activation of ovarian germ cells. The histogenesis of malignant ovarian germ cell tumors is a bit more complicated, and several histogenetic schemes have been proposed, as reviewed by J. Prat in the monograph which he has edited with G. Mutter [31]. Despite many attempts to modify our understanding of malignant ovarian germ cell, histogenesis is still incomplete. The panel of experts of WHO has thus decided to base the latest WHO classification of malignant germ cell tumors on the most popular model of histogenesis of these tumors dating back to the work of Teilum [20]. According to this scheme, the malignant germ cell can form either dysgerminoma or embryonal carcinomas, which in turn could give rise to choriocarcinoma, yolk sac carcinoma, or teratoid tumors. In the expanded histogenetic algorithm presented here (Fig. 1.4), we propose that the tumor formation depends in all cases on parthenogenetic activation of the ovarian germ cells [ova], which may give rise as such to benign tumors, i.e., teratomas. Alternatively, if the germ cells undergo malignant transformation, they may give rise to dysgerminoma or form embryonal carcinoma cells. EC cells may form either a monotypic tumor-embryonal carcinoma or by differentiating into somatic and extrasomatic cells and tissues form the malignant stem cells of a malignant mixed germ cell tumor. Even monotypic EC tumors contain syncytiotrophoblastic cells, which may be present in most of such tumors. EC cells can sometimes differentiate into yolk sac or choriocarcinoma cells, which as such may form tumors of the same name, overgrowing the EC component, which may be hard to find. Alternatively, EC cells may remain part of the mixed germ cell tumors which in such cases will contain several other distinct components: EC cells, teratomatous tissues, yolk sac tumor, and choriocarcinoma, or various combinations of these elements. There is also some evidence that dysgerminomas may give rise to embryonal carcinoma, but there is no doubt that they can be part of mixed germ cell tumors. An abbreviated most recent classification of all these ovarian germ cell tumors is presented in Table 1.3.

1.4 Definitions and Terminology of Testicular and Ovarian Germ Cell Tumors

For the sake of consistency and uniformity, most if not all definitions listed here were taken with slight modifications from the publications of the World Health Organization [18, 28], the fascicles of the Armed Forces Institute of Pathology [19, 27], and the recent textbook of pathology of the female reproductive tract [29]. These terms are listed following the order of their appearance in Tables 1.1, 1.2, and 1.3. Equivalent tumors arising in the testis as well as in the ovary are usually discussed under the same heading unless indicated otherwise.

Intratubular germ cell neoplasia, unclassified, is a preinvasive form of most testicular germ cell tumors, composed of malignant germ cells, which appear enlarged, which have a centrally located "boxy" nucleus surrounded by clear cytoplasm. Originally, it was named carci-

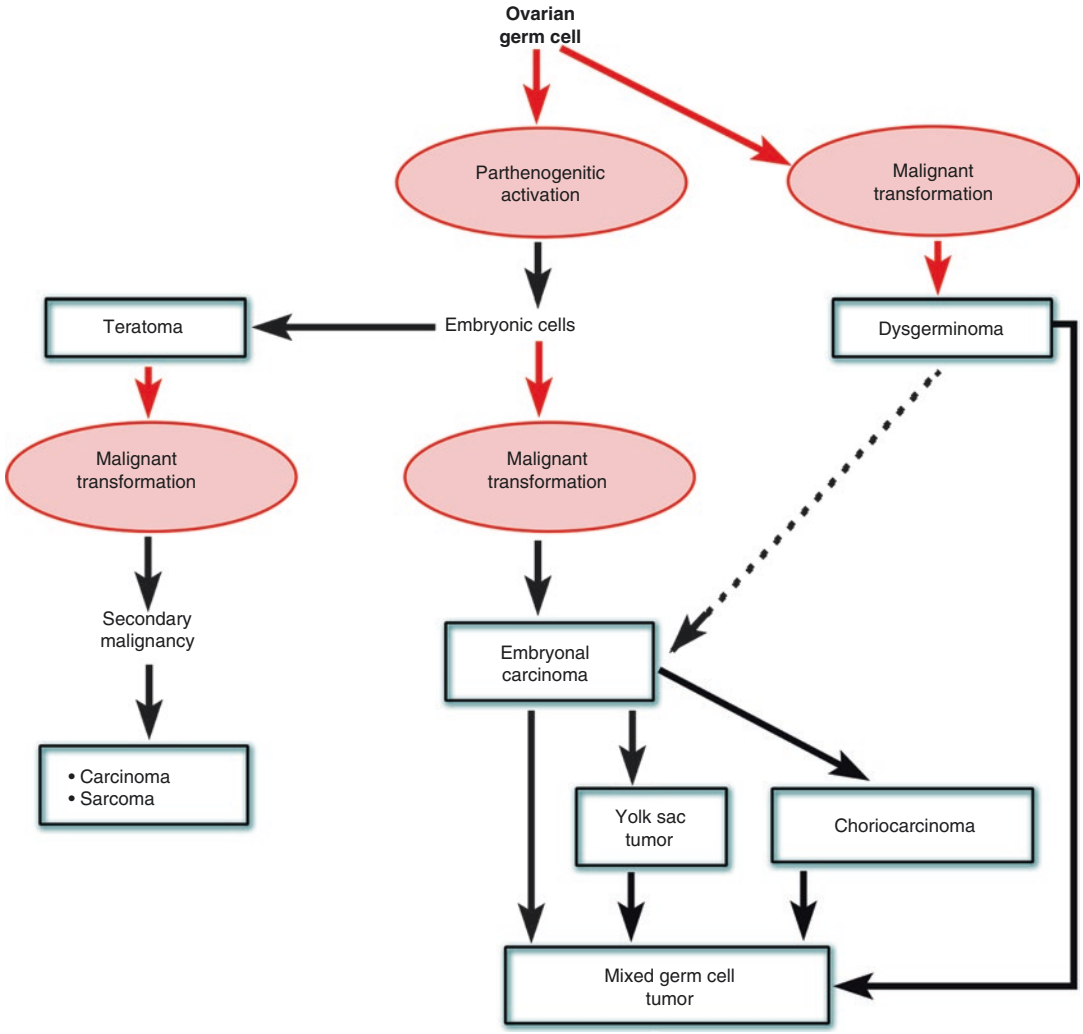

Fig. 1.4 Hypothetical histogenesis of ovarian germ cell tumors, based on the original concepts of Gunnar Teilum [20]. The key processes in the formation of various germ cell tumors, such as parthenogenetic activation of the oocytes, and the malignant transformation of their descendants (marked in *red*) remain still incompletely understood

noma in situ [CIS] by Skakkebaek who observed the atypical cells in the testicular biopsies of two infertile Danish men [32, 33]. Skakkebaek was the first to suggest that these cells are precursors of invasive germ cell tumors. Subsequently, CIS was replaced in 1980 by a more acceptable name *intratubular germ cell neoplasia*, *unclassified* [ICGNU], as it currently appears in the 2004 WHO classification [18, 19]. In the latest 2016 WHO classification it has been renamed and it has been listed as *germ cell neoplasia in situ*. An equivalent preinvasive malignancy has not been identified in the ovary.

Seminoma is a malignant germ cell tumor composed of uniform, round to polygonal cells measuring on average 15–25 μm in diameter, containing an enlarged vesicular nucleus with one or two nucleoli. Each cell has a well-developed, mostly clear, glycogen-filled cytoplasm with well-defined borders. Tumor cells are arranged into sheets, usually subdivided into smaller nests by fibrous septa, infil-

Table 1.3 WHO 2014 histologic classification of ovarian germ cell tumors

Dysgerminoma
Yolk sac tumor (primitive endodermal tumor)
Embryonal carcinoma
Polyembryoma
Non-gestational choriocarcinoma
Teratomas
Immature
Mature
Solid
Cystic
With secondary tumor
Monodermal
Struma ovarii
Carcinoid tumor
Neuroectodermal tumors
Sebaceous tumors
Mixed germ cell tumors
Gonadoblastoma
With mixed germ cell tumor
Mixed germ cell sex cord-stromal tumor

Abbreviated and slightly modified from Mutter and Prat [29]

trated by lymphocytes. The tumor was named *séminome* by the French surgeon-urologist Maurice-Auguste Chevassu in his book *Tumeurs du testicule*, Paris: G. Steinheil, 1906 [34]. Bell [35] introduced later on the term spermatocytoma, but it did not gain much popularity. Other synonyms used historically for this tumor are embryoma, embryonal carcinoma with lymphoid stroma, large cell carcinoma testis, and germinoma. Several histologic variants of seminoma have been described but such morphologic subtyping is of limited clinical significance. Seminoma can be admixed to other components of mixed germ cell tumors. Seminomas can occur in extragonadal sites. Morphologically, testicular seminomas are equivalent to ovarian dysgerminomas or germinomas of the mediastinum, pineal region, and other midline locations.

Spermatocytic seminoma is a germ cell tumor composed of three cell types [small, intermediate, and large to giant] ranging in size from 6 to 100 μm. Tumor cells grow in a diffuse or edematously nodular manner forming sheets that lack fibrous septa and lymphocytic infiltrates of classical seminoma. The tumor was first recognized by Pierre Masson [36], who separated "*le séminome spermatocytaire*" from the classical seminoma. In the latest edition of the WHO classification is was renamed and it is listed as *spermatocytic tumor*. Most spermatocytic seminomas have an indolent clinical course [18], but some can undergo sarcomatous transformation [37]. Spermatocytic seminomas do not occur outside of the testis.

Embryonal carcinoma is a malignant germ cell tumor composed of undifferentiated anaplastic epithelial cells with scant to well-developed cytoplasm and indistinct cell borders. Tumor cells grow in several patterns such as solid, papillary/tubular, or gland-like. EC cells may form the entire tumor, which is then classified as embryonal carcinoma composed of a one single cell type. In the British classification of testicular germ cell tumors, the term *malignant teratoma*, *undifferentiated* [MTU], is used as a synonym for embryonal carcinoma [38]. EC cells can also differentiate into somatic embryonic and also extraembryonic tissues (yolk sac and trophoblastic elements) and thus form mixed germ cell tumors. In these mixed germ cell tumors, embryonal carcinoma cells act as the rapidly proliferating malignant stem cells. EC cells account for the malignant nature of the tumor and its metastatic potential. Pure embryonal carcinoma is a rare tumor of the ovary, but it may be admixed to other germ cell tumoral elements and form the mixed germ cell tumors of the ovary. EC cells are the malignant equivalent of human embryonic stem cells (ESC) isolated from early human embryos [39]. Equivalent malignant stem cells have been isolated from murine teratocarcinomas [14].

Yolk sac tumor is a malignant germ cell neoplasm composed of cells and structures reminiscent of embryonic/fetal yolk sac, allantois, and extraembryonic mesenchyme. It is also known as primitive endodermal tumor and yolk sac carcinoma [41]. Older names such as endodermal sinus tumor or *mesoblastoma vitellinum* introduced by Gunnar Teilum [20, 40] or previous terms such as orchioblastoma and adenocarcinoma of the infant testis, polyvesicular vitelline tumor, extraembryonic mesoblastoma, malignant endothelioma of perithelioma type, and several

others have been more or less abandoned [41]. *Yolk sac tumors of the prepubertal type* occur in the testis of infants. In adults yolk sac elements are rarely forming a pure yolk sac tumor and are more often part of mixed germ cells tumors of the testis. Pure malignant yolk sac tumors occur as such in the ovary or admixed to the mixed germ cell tumors of the ovary [28, 29, 41].

Choriocarcinoma is a highly malignant tumor composed of syncytiotrophoblastic and mononuclear cytotrophoblastic cells. Other synonyms are chorionepithelioma, chorioma, chorioteratoblastoma, carcinoma syncytial, and trophoblastic carcinoma. In the British classification, choriocarcinoma is called *malignant teratoma trophoblastic* [MTT] [38]. Pure choriocarcinomas are extremely rare tumors. Choriocarcinoma elements may be found in testicular mixed germ cell tumors and their metastases. Equivalent tumors occur in the ovary and the extragonadal sites as well. Ovarian tumors are labeled as non-gestational choriocarcinomas to be distinguished from malignant tumors originating from the placenta.

Teratoma is a germ cell tumor composed of somatic tissues derived from all three embryonic germ layers, i.e., ectoderm, endoderm, and mesoderm. *Monodermal teratomas* are composed of derivatives of only one germ layer. In the testis teratomas may occur in a pure form, typically in infancy and childhood, or as part of mixed germ cell tumors, which are typically found in postpubertal persons. In general, the prepubertal testicular teratomas are benign, in contrast to those in postpubertal tumors which are malignant. Pure teratomas of the ovary are the most common germ cell tumor in that organ. They are also called dermoid cysts, which is not entirely correct because most of them contain not only skin and skin appendages but other tissues as well. Teratomas of the ovary may be further divided into cystic and solid tumors and mature and immature teratomas. Benign mature teratomas may undergo malignant transformation and give rise to various somatic type malignant tumors, such as carcinoma or sarcomas. Monodermal teratomas of the ovary may present as struma ovarii, carcinoid tumor, neuroectodermal tumor, or sebaceous tumor.

Mixed germ cell tumors are malignant germ cell tumors which contain more than one germ cell tumor component. Most of these tumors contain embryonal carcinoma cells which serve as their malignant stem cells. The four most common combinations within testicular germ cell tumors are as follows: (1) embryonal carcinoma and teratoma; (2) embryonal carcinoma and seminoma; (3) embryonal carcinoma, teratoma, and yolk sac tumor; and (4) embryonal carcinoma, teratoma, and choriocarcinoma. In the original classification of Friedman and Moore [11], such mixed germ cell tumors were mostly classified as teratocarcinomas, but that term has not been used recently in human clinical pathology.

Mouse teratocarcinomas are composed of embryonal carcinoma cells which serve as their stem cells and various somatic tissues. These tumors may also contain yolk sac components but only exceptionally trophoblastic elements. Experimental murine teratocarcinomas have been used extensively as laboratory equivalents of human mixed germ cell tumors of the testis [14].

Polyembryoma is a rare variant of mixed germ cell tumors composed of embryonal carcinoma and yolk sac tumor cells and usually teratoma. Embryonal carcinoma cells and yolk sac components form embryoid bodies resembling presomitic human embryos.

Diffuse embryoma is a rare malignant tumor composed of embryonal carcinoma and yolk sac tumor components arranged in form of numerous embryoid bodies.

Gonadoblastoma is a mixed germ cell tumor composed of germ cells resembling seminoma or dysgerminoma and sex cord-stromal cells resembling immature granulosa or Sertoli cells [27]. These tumors typically develop in dysgenetic gonads in individuals who have a Y chromosome. Invasive germ cell tumors developing from gonadoblastomas are most often diagnosed as germinoma [seminoma or dysgerminoma], but in a few instances, the tumors which developed from gonadoblastoma were histologically classified as embryonal carcinoma or yolk sac tumor or teratoma [28].

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2 The Epidemiology of Malignant Germ Cell Tumors: The EUROCARE Study

Annalisa Trama and Franco Berrino

2.1 Introduction

Germ cell tumors (GCTs) comprise a heterogeneous group of tumors in terms of histology, age at diagnosis, anatomical site and prognosis. Here we describe the epidemiology of GCT on the basis of data from European population-based cancer registries (CRs) analysed in the framework of the EUROCARE (European Cancer Registry-based study on survival and care of cancer patients) project, which has monitored cancer patients' survival since 1978 (www.eurocare.it).

2.2 Materials

We have chosen to use the EUROCARE data because, even if CRs collect data on the basis of the International Classification of Diseases for Oncology (ICD-O3) [1] which includes morphology and topography, cancer statistics are usually provided for broad cancer categories, based on the anatomic site of the malignancies. Thus, the current statistics do not provide specific information of germ cell tumors. We have used the morphology and topography data collected by different CRs and analysed by EUROCARE to describe the epidemiology of GCT in Europe. EUROCARE includes only overt malignant tumors, while in situ tumors are requested only for screening-target cancers (breast, cervix, colon-rectum and skin melanoma) and benign tumors are collected only for central nervous system and urinary bladder**.** The International Agency for Research on Cancer (IARC) provides, for selected cancers, the age-standardised incidence rates of microscopically verified cases by histological type and by gender in Cancer Incidence in 5 Continents (CI5X) [2]. Since information on GCT was only available for testis and ovary, in this chapter, we have used CI5X [2] data to analyse testicular and ovarian GCT outside Europe.

EUROCARE is the widest collaborative research project on cancer survival attempted in Europe. The project started in 1989, and the fifth edition, EUROCARE-5, includes data on more than 21 million cancer diagnoses provided by 116 CRs in 30 European countries (www.eurocare.it). The data analysed in this chapter are from EUROCARE-5 and consequently included only malignant tumors. CRs cover the whole national population in European countries such as Austria, Bulgaria, Croatia, Czech Republic, Estonia, Ireland, Latvia, Lithuania, Malta, Finland, Iceland, Norway, Sweden, Slovakia, Slovenia, the Netherlands and the UK, while in

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others CRs cover only one or several regions [3]. In 2000–2007 (the study period of EUROCARE-5), 54,000 GCTs were registered in the countries included in the incident analyses (Table 2.1). Table 2.1 shows the number of GCT cases contributed by the different countries. Please note that the differences by country might be due to the different CR coverage (national vs regional) and to the different incidence years that CR have contributed. Not all included the full period 2000–2007.

Table 2.1 Cancer registration coverage in EUROCARE-5 and the number of germ cell tumor cases registered in the countries included to the incident analyses

	Proportion of population covered by cancer registries included in EUROCARE-5 (%)[a]	Number of germ cell tumor cases registered in 2000–2007
Austria	100	2.610
Belgium (Flanders)	58	1.215
Bulgaria	100	1.457
Croatia	100	900
Czech Republic	100	3.491
Estonia	100	190
Finland	100	944
France	23	1.213
Germany	23	6.950
Iceland	100	79
Ireland	100	1.210
Italy	35	3.450
Latvia	100	267
Lithuania	100	268
Malta	100	76
Norway	100	2.185
Poland	13	904
Portugal	76	698
Slovakia	100	1.683
Slovenia	100	812
Spain	17	778
Switzerland	30	923
The Netherlands	100	5.078
UK	100	16.626
Total		54.007

[a]Cancer registration is continuously improving since EUROCARE-5

GCTs include different histological subtypes, internationally grouped as seminomas and non-seminomas. Throughout this chapter, the generic term seminoma and non-seminoma will be used. Seminoma, dysgerminoma and germinoma are histopathologic equivalent terms for a neoplasm of identical morphology in testis, ovary and extragonadal locations. Seminoma includes all seminoma histological types (ICD-O3 codes 9060–9064); non-seminomas in their turn include embryonal carcinoma (ICD-O3 codes 9070, 9072), yolk sac tumor (ICD-O3 code 9071), choriocarcinoma (ICD-O3 codes 9100, 9102), teratoma (ICD-O3 codes 9080,9082,9083), mixed germ cell tumors (ICD-O3 codes 9081,9085,9101), malignant struma ovarii (ICD-O3 code 9090), cystic teratoma with somatic malignant transformation (ICD-O3 code 9084) and other non-seminomatous germ cell tumors (ICD-O3 codes 9065). Spermatocytic tumor, an exclusively testicular neoplasm, is clinically and pathologically distinct from classic seminoma; thus data are provided separately for this specific type.

2.3 Incidence

The crude and age-adjusted (European standard population) incidence rates of GCT in Europe were both equal to 34/1.000.000 with marked differences between male (64/1.000.000) and female (4/1.000.000). In the USA, the incidence rate was 56/1.000.000 in white males contrasting with 3.2/1.000.000 in white females, over a period of more than 30 years from 1973 to 2007 [4]. In the same country, the incidence in black males was much lower (10/1.000.000), due to a lower incidence of seminomas, while no difference was reported between white and black females [4]. More than 90 % of testicular tumors were indeed GCT. Figure 2.1 shows incidence of testicular cancer across different continents in 2012. White males living in Western industrialised countries, particularly in Northern and Western Europe, showed the highest incidence rates of testicular tumors (12/100.000 in Denmark,

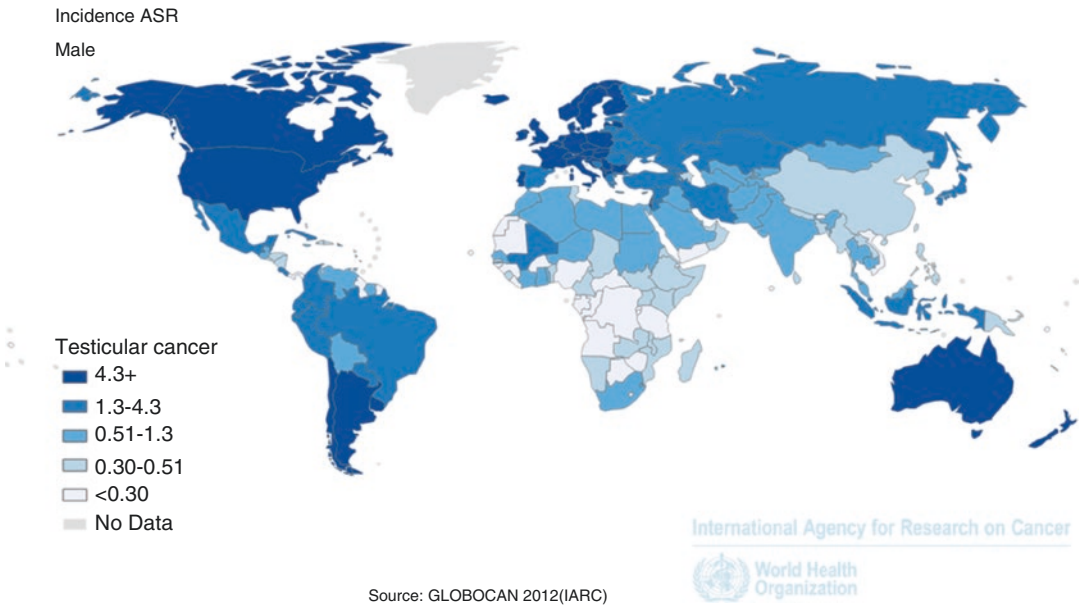

Fig. 2.1 Testicular cancer age-standardised (world) incidence rate per 100.000 (Source http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)

Norway and Switzerland), whereas black males in Africa showed the lowest (<0.5/100.000 in the majority of African countries). In Australia and New Zealand, the incidence was 7/100.000. In North America (USA and Canada), it was 5/100,000; in South and Central America, it was 2/100.000 with differences among countries (Chile 7/100.000, Uruguay 6/100.000, Argentina and Costa Rica 5/100.000, Mexico and Colombia 3/100.000, Brazil 2/100.000 and remaining countries <1/100.000). In Japan, the incidence was 2/100.000; in South, Eastern and Central Asia, it was <1/100.000, being higher in Western Asia, 1.7/100.000, with regional countries (5/100.000 in Israel, 3/100.000 in Georgia and <1 in Oman, Qatar, Iraq and Azerbaijan). In China, the incidence was 0.5/100.000 [5].

Incidence of malignant ovarian GCT was low in all continents: ≤0.9/100.000 in Japan, ≤0.7/100.000 in Central and South America and in China, ≤0.5/100.000 in Australia and Asia, 0.4/100.000 in Canada and <0.4/100.000 in Africa except Malawi where the incidence was 1.3/100.000 [2].

Gonadal GCT (GGCT) Most GCTs arise in the gonads. The incidence in Europe is 33/1.000.000 being substantially higher in males than in females (62/1.000.000 vs 2.5/1.000.000, respectively). Histologic differences are observed between both genders: in males, seminomas are more common than non-seminomas, contrary to women who have more non-seminomas than seminomas (Table 2.2). In males, non-seminomas are mixed germ cell tumors, embryonal carcinoma and teratoma, while in females they are (immature) teratomas and yolk sac tumors (Table 2.2). In males, spermatocytic tumor is very unusual (Table 2.2).

Testicular GCTs have an early incidence peak in the age group 0–4 years followed by a second peak in adolescents and young adults (15–19 and 25–29 and 30–34 years) (Fig. 2.2). The first peak is due to non-seminomas (incidence 1.5/1.000.000 vs 0.07/1.000.000 of seminomas) and mainly due to yolk sac tumour and teratoma, which have an incidence of 1/1.000.000 and 0.3/1.000.000, respectively.

Non-seminomas are more common than seminomas until the age of 30 years; however, the histologic types of those between 15 and 30 years