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
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http://www.springer.com/978-3-662-53773-2

Pathology and Biology of Human Germ Cell Tumors
Nogales, F.F.; Jimenez, R.E. (Eds.)
2017, XIV, 449 p. 193 illus., 183 illus. in color.,
Hardcover
ISBN: 978-3-662-53773-2