Clinical Ophthalmic Oncology

Retinoblastoma

Jesse L. Berry
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Bertil E. Damato
Arun D. Singh
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ISBN 978-3-030-11122-9 ISBN 978-3-030-11123-6 (eBook)
https://doi.org/10.1007/978-3-030-11123-6

Library of Congress Control Number: 2019934958

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Ophthalmic tumors are rare and diverse, so their diagnosis can be quite complex. Treatment usually requires special expertise and equipment and, in many instances, is controversial. The field is advancing rapidly, because of accelerating progress in tumor biology, pharmacology, and instrumentation. Increasingly, the care of patients with an ocular or adnexal tumor is provided by a multidisciplinary team, consisting of ocular oncologists, general oncologists, radiotherapists, pathologists, psychologists, and other specialists.

For all these reasons, we felt that there was a need for the new edition of the textbook providing a balanced view of current clinical practice. Although each section of *Clinical Ophthalmic Oncology* now represents a standalone volume, each chapter has a similar layout with boxes that highlight the key features, tables that provide comparison, and flow diagrams that outline therapeutic approaches.

The enormous task of editing a multi-author, multivolume textbook could not have been possible without the support and guidance by the staff at Springer: Caitlin Prim, Melanie Zerah, ArulRonika Pathinathan, and Karthik Rajasekar. Michael D. Sova kept the pressure on to meet the production deadlines.

It is our sincere hope that our efforts will meet the high expectation of the readers.

Los Angeles, CA, USA — Jesse L. Berry
Los Angeles, CA, USA — Jonathan W. Kim
Oxford, UK — Bertil E. Damato
Cleveland, OH, USA — Arun D. Singh

Acknowledgments

I want to acknowledge my friend and mentor, Linn Murphree; my grandmother, Jeannette, for always believing in me; my husband, Paul, and our growing family. (JB)

I want to acknowledge and thank my teachers, A. Linn Murphree, Bertil Damato, and David Abramson, for their wonderful mentorship over the years. I would also like to thank my parents, Heja and Jinku, for inspiring a young boy to become a physician. To Diana and Devin, I dedicate all of my work here and forever to both of you. (JWK)

To my family, Frankanne, Erika, Stephen, and Anna. (BED)

To my parents who educated me beyond their means, my wife Annapurna, and my children, Nakul and Rahul, who make all my efforts worthwhile. (ADS)

A. Linn Murphree, MD, Professor of Ophthalmology and Pediatrics at the Keck School of Medicine, University of Southern California (USC), and former Director of the USC Ocular Oncology Service and the Children's Hospital Los Angeles (CHLA) Retinoblastoma Program

Following his training as a Fulbright Fellow in Human Genetics at the University of Copenhagen, Dr. Murphree began his medical training at Baylor College of Medicine with an interest in human genetics. He discovered a passion for both ophthalmology and pediatrics in medical school and subsequently combined those three interests by focusing his career on ophthalmic genetic diseases including retinoblastoma.

Dr. Murphree assumed the position of Division Head, Pediatric Ophthalmology, at CHLA upon completion of his fellowship in pediatric ophthalmology at Johns Hopkins Hospital. With his first NIH grant, he was one of the pioneers in discovering the location of the retinoblastoma gene on chromosome 13 by performing detailed deletion mapping. Subsequently, he developed a clinical referral practice focused on ocular oncology and developed the largest retinoblastoma referral center in the western USA.

In addition to the discovery of the retinoblastoma gene, Dr. Murphree's contributions to the field of pediatric ocular oncology are numerous and groundbreaking. In his clinical practice, Dr. Murphree recognized an unmet need for a wide-field retinal camera to document the intraocular findings associated with retinoblastoma. He recruited a team of engineers and collaborated with optical engineers in private industry to develop the RetCam, which is the most widely used retinal camera in the world to document pediatric retinal abnormalities. Dr. Murphree's work on systemic chemotherapy in the 1990s caused a paradigm shift in the treatment of intraocular retinoblastoma away from enucleation and external beam radiation. Dr. Murphree also created the International Classification system for retinoblastoma, which is still the most popular method for diagnosing retinoblastoma for clinicians worldwide. He is the author or coauthor of more than 70 major papers on retinoblastoma genetics and treatment. Dr. Murphree's work over four decades revolutionized the field of retinoblastoma and improved the lives of countless children afflicted with retinoblastoma.

Dr. Murphree was the former editor of the *Retinoblastoma* volume of *Clinical Ophthalmic Oncology*, and we are indebted to him for his mentorship during the writing of this current edition. He is universally respected in the field of ocular oncology for his ingenuity, expertise, kindness, and generous spirit. As the current editors of the *Retinoblastoma* sections, we honor his legacy and thank him for all of his previous and current contributions.

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Retinoblastoma: Evaluation and Diagnosis

1

Brian Marr and Arun D. Singh

Historical Background

In 1809 a Scottish surgeon named James Wardrop wrote a monograph where he described a subset of "fungus haematodes" cases distinguishing them from other cases of "soft cancer," "medullary sarcoma," or "spongiod inflammation." He was the first to recognize retinoblastoma (RB) as a discrete tumor arising primarily from the retina [1]. Virchow in 1864 used the name of glioma retinae because of retinoblastoma's similarity to the intracranial glial tumors. Verhoeff, in 1922, observed the retinal origin and the presence of immature, embryonic cells that formed the tumor and coined the term retinoblastoma. In 1926 the American Ophthalmological Society accepted the term retinoblastoma, and the older terms, such as glioma retinae and fungus haematodes, were abandoned [2]. In 1809 it was the astute clinical observations and descriptions of the disease that made the diagnosis of what we now know as retinoblastoma.

Clinical Presentation

The symptoms of retinoblastoma are most often first detected by a parent or family member directly or occasionally from an abnormal light reflex in a photograph. To a lesser extent, sporadic cases of retinoblastoma are first discovered by a routine pediatric exam or screening, less commonly by pediatric ophthalmologists and rarely incidentally on imaging for other conditions. In the United States and other developed nations, the most common presenting findings in intraocular retinoblastoma are leukocoria or cat's eye reflex (45%) (Chap. 2), strabismus (25%), inflammatory symptoms (pseudo-preseptal cellulitis) (10%), and poor vision (10%) (Table 1.1) [3].

For several reasons discussed elsewhere in developing nations, retinoblastoma tends to be more advanced at presentation with greater proportion of cases with extraocular disease (Chap. 5). One of the major limitations to prompt treatment of retinoblastoma worldwide

Table 1.1 Presenting features of retinoblastoma (United States)

Leukocoria or cat's eye reflex	45%
Strabismus	25%
Inflammatory symptoms (preseptal cellulitis)	10%
Poor vision	10%
Screening due to family history	5%
Incidental detection	5%

Based on data from Abramson et al. [14]

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J. L. Berry et al. (eds.), *Clinical Ophthalmic Oncology*,
https://doi.org/10.1007/978-3-030-11123-6_1

is access and availability to healthcare. As retinoblastoma care providers, it is important for us to increase accessibility for our patients into a system that is equipped to treat this condition adequately. Community education and awareness and training of ancillary staff that are able to triage and arrange prioritized evaluations are some of the important components of this approach (Chap. 5).

Misdiagnosis

Histopathological studies of eyes enucleated report misdiagnosis rates from 11% to 40%, and clinical studies of referral patterns report misdiagnosis rates from 16 to 53% [3]. This may be attributed to many factors including rare incidence of retinoblastoma, multiple conditions that simulate retinoblastoma, the unfamiliarity of the primary healthcare providers, the age of presentation, and the difficulty in examining children (Chap. 2). Consequently, a thorough and detailed assessment should be done on patients suspected of having retinoblastoma.

Stepwise Evaluation for Retinoblastoma

A practical stepwise approach specifically to evaluate a child suspected to have retinoblastoma includes detailed history taking, initial office examination, and focused ophthalmic ultrasonography, followed by examination under anesthesia and neuroimaging, if necessary (Fig. 1.1). This approach is merely a guide that can be modified as needed based upon clinical setting.

History

For a child suspected of having retinoblastoma, it is important to examine the patient and family promptly upon referral, and the initial consultation may be performed in an office setting (Table 1.2). The story of how and over what time course the condition was noted, the healthcare professionals that saw the patient, and what was done to the child before they arrived must be recorded. A birth history including the pre- and perinatal history is important. Typically the gestational age at birth, type of delivery, birth weight, and any delivery or pregnancy complications, including infections or medications taken during the pregnancy, are noted. It is also important to inquire if any abnormalities were noted on the eye screening exam after birth or if there were any unusual birthmarks or malformations. The current history should include the child's health, any medical conditions, and environment including pets, recent trauma, or illness. For retinoblastoma suspects, the family history should include number of siblings, their health and ocular history, and any family medical disorders. It should be noted if there was any poor vision, blindness, or loss of an eye in the family. Both parents should be questioned about their ocular health and examined if no recent dilated exam has been performed. A small subset of parents of children with RB will have evidence of retinoma/retinocytoma and even unknown treated retinoblastoma (Chap. 8) [4].

Initial Examination

The initial examination of the child can be started in the office while taking the history, by observing the comfort and behavior of the child, and noting any size, proportion, or facial abnormalities (Table 1.3). It may be possible to observe leukocoria, strabismus, or periorbital swelling and visual behavior before initiating the formal examination. Assessing the vision is dependent on the age of the patient and the amount of cooperation; however, the condition of each eye should be assessed and recorded along with the pupillary response and the presence or absence of heterochromia of the irises. A brief observation of the periorbital tissues, cornea, conjunctiva, and sclera should be performed before administrating dilation drops. Using a direct ophthalmoscope, the pupillary light reflex can be noted in both eyes.