Principles of Ocular Oncology

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Springer

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ISBN 978-3-031-82952-9 ISBN 978-3-031-82953-6 (eBook)
https://doi.org/10.1007/978-3-031-82953-6

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

To the eye tumor patients and their families, I have learned from your endurance.

To my teachers and mentors, I will always remain indebted to each one of you.

To the future ocular oncologists, keep learning and innovating.

To my family, I am deeply grateful for your continuous support.

Foreword

Importance of the Field of Ocular Oncology

The field of Ophthalmology is broad and is primarily dedicated to the study of the structure, function, and diseases of the eye, with the ultimate goal of protecting visual acuity. An important subfield of Ophthalmology is Ocular Oncology, which includes the study of cancers of the eye region involving the eyelids, conjunctiva, orbit, and intraocular structures. The goals of management in Ocular Oncology are more profound and more overwhelming as the focus is on saving the patient's life, then protecting the patient's eye, and lastly, safeguarding visual acuity. Indeed, Ocular Oncology is a vital subspecialty of Ophthalmology and perhaps more challenging than other subspecialties as it involves a patient's life.

Years ago, the management of ocular cancers was somewhat haphazard with little interest in the field as ocular cancers were deemed rare. However, in the 1970s, the field of Ocular Oncology was born. Five centers in North America were developing in Boston, New York, San Francisco, Philadelphia, and Toronto. As interest in the field grew, it was realized that ocular cancers might be more prevalent than suspected and required a high level of expertise for appropriate diagnosis and proper management. Diagnostic imaging for tumor detection developed and was studied including methods of fluorescein angiography, ultrasonography, computed tomography, and magnetic resonance imaging. Later, optical coherence tomography and fine-needle aspiration biopsy for cytologic and cytogenetic testing were perfected. The field of Ocular Oncology was maturing and demonstrating great forward strides.

Soon thereafter, more centers flourished worldwide, including the powerful center in Toronto, under the direction of Dr. Hatem Krema. Centers were created in Turkey, Italy, Spain, Sweden, Ireland, Finland, Israel, Argentina, Chile, India, Japan, China, Nigeria, South Africa, and others. Despite this progress, there remain numerous areas worldwide that are devoid of Ocular Oncology, and patients struggle to receive appropriate care.

In this book, Dr. Krema shares his knowledge on the basics of oncology and available treatment methods, and then elaborates on the specific tumors of the eyelids, ocular surface, orbit, and intraocular structures, including the uvea, retina, and optic disc. In addition, he explores the eye in systemic cancers, including solid cancers and hematopoietic cancers, such as leukemia, lymphoma, plasma cell neoplasia, and histiocytosis. He further educates us on systemic cancers that can lead to ophthalmic paraneoplastic syndromes, and he describes some of the ocular toxicities that result from systemic chemotherapy, targeted therapy, and immunotherapy.

The precious vitality of this book begins with an understanding of "What is oncology?" In Chap. 1, Dr. Krema touches upon regulation of the cell cycle and cell signaling, gene mutations, hereditary cancer syndromes, carcinogens, and epigenetics that can all contribute to cancer. In Chap. 2, principles of surgery, radiotherapy, laser therapy, cryotherapy, chemotherapy, and targeted therapy are discussed. The targeted therapy section is robust with discussion on the Hedgehog pathway, mTOR pathway, and inhibitors of BRAF, MEK, HIF-2α, proteomase, and protein kinase C, all of which are crucial in our understanding and management of cancers. That section is a "must-read" segment to improve understanding of how medications work.

As the clinical portion of the book unfolds, Chap. 3 focuses on eyelid tumors with a discussion on clinical features and management of over 50 various eyelid tumors, with comprehensive organization into epidermal, sebaceous, melanocytic, neural, vascular, sweat gland, hair follicle, and metastatic origins. Similarly, well-organized Chap. 4 on ocular surface tumors, Chap. 5 on orbital tumors, Chap. 6 on uveal tumors, Chap. 7 on retinal tumors, and Chap. 8 on systemic cancers are evident.

Dr. Hatem Krema is to be congratulated on organizing an excellent textbook on the topic of Ocular Oncology for residents, fellows, general ophthalmologists, and for all of us to read and digest. This all-encompassing book from the single-cell mutation that leads to an eye cancer to the clinical features and management of the cancer is exceptional. This book should be read and easily accessible on the bookshelf, an arm-length away, for every ophthalmologist for years to come.

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Preface

Ocular oncology is a disease-centered ophthalmic subspecialty that focuses on the diagnosis and management of tumors of the eye and related structures. This subspecialty has emerged because of the common bases underlying the pathogenesis and treatment approaches of various ophthalmic tumors, in addition to the rapid advances in the oncology sciences over recent decades. The primary objective in ocular oncology is to achieve tumor control while preserving as much of the ophthalmic structure and function as possible.

The practice of ocular oncology requires understanding and collaboration between the ocular oncologist and several other tumor-managing specialists, including radiation oncologists, radiation physicists, medical and pediatric oncologists, histopathologists, cytopathologists, and geneticists. The ocular oncologist's role is central in formatting the multidisciplinary treatment plan, implementing the ophthalmic treatment, coordinating the comprehensive care required for effective treatment, and managing any treatment-related ocular complications.

Recent decades have witnessed significant advancements in oncology, which have favorably impacted the diagnosis and management of several ophthalmic tumors.

Innovations in multimodal imaging of ocular tumors and fine biopsy techniques of extraocular and intraocular tumors, along with advances in cytopathology and immunohistochemistry, have greatly enhanced our diagnostic capabilities. A profound understanding of tumor biology, including the roles of genetics and epigenetics in tumor development and prognostication, coupled with new molecular diagnostic technologies, have contributed to more precise and personalized care for ophthalmic tumor patients.

Furthermore, standardized radiotherapy protocols for various tumors of the eye, adnexa, and orbit, together with the use of systemic and regional chemotherapy drugs and novel targeted therapy and immunotherapy medications, have revolutionized the treatment of ophthalmic tumors. Such new treatments provide higher tumor control rates and, in most cases, obviate the need for extensive or disfiguring surgeries.

This book is an updated, inclusive, and concise reference intended primarily for ocular oncology clinicians and trainees, general ophthalmologists, and allied cancer care specialists who manage ophthalmic tumors. I hope the reader will find it a comprehensive, resourceful guide in the field of ocular oncology.

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Acknowledgments

I am grateful to the late Dr. Danny Ghazarian, Dr. Zaid Saeed Kamil, and Dr. Bruno Fernandes for providing most of the pathology micrograph images in this book.

I am also thankful to Mr. Allan Connor, an ex-ophthalmic imaging specialist in my department, for some of the high-quality fundoscopy, ultrasonography, and angiography images of our patients presented in this book.

About This Book

This book is an updated, single-volume, all-inclusive, concise reference in ocular oncology. It is addressed to ocular oncology specialists and trainees, general ophthalmologists, and allied cancer care specialists who manage ophthalmic tumors.

The book is divided into eight chapters. The first chapter is an introduction to oncology in general that covers basic concepts in cell biology, tumorigenesis, the hallmarks of cancer, and tumor pathology. The second chapter discusses the standard treatment methods employed in ocular oncology, including surgical approaches and techniques; treatment with physical energy such as radiotherapy, lasers, and cryotherapy; and the indications and toxicities of systemic and regional drug therapy. The following five chapters demonstrate the examination, classifications, clinical and imaging presentation, and current specific management options of tumors and relevant lesions that involve the eyelid, ocular surface, orbit, uveal tract, and retina. The final chapter highlights the direct and indirect impact of systemic cancers on the ophthalmic tissues and their management.

The book has been richly illustrated with over 350 original figures, schematic representations, and comparison tables.

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About the Author

Hatem Krema, MD, MSc, FRCS, FICO (Hon.) Professor Dr. Hatem Krema is the director of the ocular oncology program at the hospitals of the University of Toronto, Canada.

He has over 25 years of profound experience in ocular oncology practice. He was trained in ocular oncology at the Royal Liverpool University Hospital, England, United Kingdom; Wills Eye Institute of Thomas Jefferson University, Philadelphia, Pennsylvania, USA; and Princess Margaret Cancer Centre of the University of Toronto.

Dr. Krema is interested in translational clinical research in ophthalmic oncology. He focuses on developing combined multimodal treatment protocols for ocular, adnexal, and orbital cancers, introducing innovative surgical techniques, establishing management algorithms for treatment complications, and applying molecular genomics to the personalized care of ophthalmic tumor patients.

Dr. Krema is frequently invited as a guest speaker and moderator at several national and international conferences. He is an ad hoc peer reviewer for several high-ranked ophthalmology journals and has served as the ocular oncology section editor for the *Canadian Journal of Ophthalmology* for 15 years.

He has mentored several international ocular oncology fellows, has been invited to provide courses and teaching sessions in ocular oncology to residents and fellows in several countries, and was granted several national and international teaching awards.