Experts' Perspectives on Medical Advances

Ying Mao *Editor*

Progress in the Diagnosis and Treatment of Gliomas

科学技术文献出版社
SCIENTIFIC AND TECHNICAL DOCUMENTATION PRESS

Springer

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ISSN 2948-1023 ISSN 2948-1031 (electronic)
Experts' Perspectives on Medical Advances
ISBN 978-981-99-0122-7 ISBN 978-981-99-0123-4 (eBook)
https://doi.org/10.1007/978-981-99-0123-4

Jointly published with Scientific and Technical Documentation Press

The print edition is not for sale in China (Mainland). Customers from China (Mainland) please order the print book from: Scientific and Technical Documentation Press.

The original submitted manuscript has been translated into English. The translation was done using artificial intelligence. A subsequent revision was performed by the author(s) to further refine the work and to ensure that the translation is appropriate concerning content and scientific correctness. It may, however, read stylistically different from a conventional translation.

Translation from the Chinese language edition: "胶质瘤毛颖2021观点" by Ying Mao, © Scientific and Technical Documentation Press 2021. Published by Scientific and Technical Documentation Press. All Rights Reserved.

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The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword

In 2014, the National Central Cancer Registry of China released a report on the 10 most deadly cancers in China in 2010, with brain tumors ranking as the ninth most lethal. According to the Shanghai Municipal Center for Disease Control and Prevention, the incidence of brain tumors was found to be 7–8/100,000, higher than the national incidence rate of 5/100,000. In terms of mortality, brain tumors were the eighth most deadly cancer in women and the ninth in men. Among brain tumors, gliomas had the highest incidence, making them a significant challenge. Despite significant progress made in modern science over the past 100 years since the discovery of gliomas, particularly malignant ones, a radical cure is still elusive. Nevertheless, researchers have made significant strides in the diagnosis and treatment of gliomas in recent years, thanks to advancements in neuroimaging, anesthesiology, surgery, radiotherapy, chemotherapy, and molecular biology. Currently, the standard treatment for gliomas is a combination of surgery, radiation therapy, and chemotherapy. Thanks to progress in diagnostic and treatment technologies, the mortality rate of glioma surgery has decreased significantly, from nearly 50% in the 1950s to 1–2% in the early twenty-first century. In the Department of Neurosurgery at Huashan Hospital, Fudan University, the mortality rate is now close to zero.

Due to the infiltrative nature of glioma growth, it is challenging to remove the tumor safely without harming adjacent neural structures, even with the use of surgical microscopes. However, advances in neuroimaging, neuronavigation (including intraoperative MRI), and intraoperative electrophysiological monitoring now allow neurosurgeons to remove the tumor while safeguarding neural structures, thus improving patients' quality of life and extending their survival. Postoperative radiotherapy and chemotherapy techniques have also evolved. Intensity-modulated local radiotherapy (IMRT) has replaced conventional whole-brain radiotherapy (WBRT) to accurately irradiate tumors while preserving normal tissues based on size, location, shape, and their relationship with critical functional structures. Combining chemotherapy (such as temozolomide) with radiotherapy and administering several courses of chemotherapy after radiotherapy are also new approaches. Selective chemotherapy can be tailored to patients with different biological targets, improving treatment efficacy, avoiding inappropriate drug use, and reducing harm.

Over the past 20 years, molecular biology has significantly impacted the research, diagnosis, and treatment of glioma. The classification of gliomas has evolved from relying solely on histomorphology to a combination of histomorphology and molecular biology. Given the heterogeneity of cells within gliomas and the overlapping morphology of different types, traditional histomorphological diagnosis is not only incomplete, but also fails to reflect the tumor's biological characteristics. For instance, some patients with low-grade glioma (LGG) may survive for a long time, while others may deteriorate rapidly, similar to patients with glioblastoma multiforme (GBM), a subtype of high-grade glioma (HGG). The detection of biomarkers, such as mutations in isocitrate dehydrogenase 1 (IDH1) or IDH2, loss of heterozygosity of chromosome 1p/19q, TERT promoter mutation or IDH mutation, TP53 mutation, and ATRX mutation in LGG, and wild-type IDH in GBM, can help identify the abnormal biological behavior of tumors.

Recent biological and clinical studies have highlighted the involvement of multiple genes and steps in the development of glioma. IDH1/IDH2 mutations are considered as an early biological event in most low-grade gliomas, while other genetic alterations occur during the development of different types of gliomas. For instance, oligodendrogliomas or oligodendroastrocytomas exhibit 1p/19q loss of heterozygosity, while astrocytomas have TP53 mutations and 17p loss. Anaplastic oligodendrogliomas, anaplastic astrocytomas, and anaplastic oligodendroastrocytomas display 9p loss and RB1 pathway abnormalities. Anaplastic oligodendrogliomas and anaplastic astrocytomas have 10q and 19q loss, respectively. Incidental LGGs, which are mostly located in non-functional areas and frontal lobes, are small and exhibit IDH mutations and 1p/19q co-deletion. Our group found that patients who underwent tumor resection for incidental LGGs had a 10-year overall survival rate of 74.3%. Therefore, we believe that incidental LGGs are early-stage gliomas that can be detected early by MRI and other examinations. They should not be left untreated, as these tumors are prone to malignant transformation if they grow or become symptomatic.

After the human genome and glioblastoma genome were discovered in 2001 and 2008, respectively, some politicians and scientists optimistically predicted that a cure for glioma would be imminent. However, in reality, there is still a long way to go. In-depth research and discovery have led people to move away from unrealistic optimism towards a more rational view. The complexity and variability of transcription from gene to mRNA, and then from mRNA to protein, make it difficult to recognize proteins from a genomic standpoint. This complexity, combined with the fact that a protein must undergo at least six common modifications to express its function, has made it challenging to achieve clinical success with gene therapy for glioma. Similarly, research focused on signaling pathways has not been successful, such as Bevacizumab, a targeted therapy that was once highly anticipated. Although Bevacizumab can inhibit the vascular endothelial growth factor receptor (VEGFR) in glioma blood vessels, it can activate the c-met gene to express the MET protein in tumor cells, leading to tumor proliferation, migration, and mesenchymal tran-

sition. Key genes and signaling pathways in gliomas have yet to be identified. Fortunately, the research paradigm has shifted towards collecting large amounts of data, both laboratory and clinical, and then searching for biological patterns, rather than testing hypotheses in the laboratory.

Immunotherapy and other treatments have not been effective in significantly improving the 5-year overall survival (OS) of patients with GBM, which remains less than 10% despite high costs. The standard treatments for glioma are unsatisfactory, and gene and targeted therapies are difficult. Immunotherapy has become popular due to three main reasons: (1) gliomas are heterogeneous, with various cell clones and signaling pathways coexisting; (2) chemotherapies, such as tyrosine kinase inhibitors, antibody-based or RNA-based therapies, are unable to eliminate all tumor cell populations; and (3) tumor cells can develop drug resistance by altering signaling pathways, rendering therapies ineffective. However, immunotherapy, specifically vaccines, can activate multiple specific immune responses, altering or enhancing the immune function against tumors, and killing tumor cells, making it a promising prospect for GBM treatment. According to incomplete data, 13 clinical phase I and II trials of DC vaccines for the treatment of GBM have been completed, and 14 phase I to III trials are currently under investigation, showing mild or minimal side effects while prolonging the progression-free survival (PFS) and OS of patients to varying degrees. Another novel treatment for GBM is tumor treating fields (TTF), also known as AC electric fields (AEF), which disrupts tumor cell mitosis selectively using electric fields. The Food and Drug Administration (FDA) approved TTF for the treatment of recurrent GBM in 2011, and recent interim reports showed that combining TTF with standard therapy was more effective than standard therapy alone, resulting in PFS and OS of 7 months, 4 months, 21 months, and 16 months, respectively, ($P < 0.05$) in the treatment of primary GBM. This physical therapy results in immunogenic cell death-inducing cells, with calreticulin and high-mobility group box1 (HMGB1) depositing on the cell membrane's surface, inducing the adoptive immune response to kill the residual tumor and cancer stem cells. TTF is now included in the National Comprehensive Cancer Network (NCCN) Guidelines for CNS Cancers published in October 2015.

To conclude, while there is promise for the future of glioma treatment, there is still a considerable way to go. It is essential to continue putting forth great efforts and continually gather experience to move forward. Professor Mao Ying recognized this and quickly organized experts from the Department of Neurosurgery at Huashan Hospital, Fudan University, who have an interest in glioma research. They collected both domestic and foreign literature and combined their own experiences to create this book. The book's authors are all young surgeons and postgraduates who are actively involved in clinical work, have an academic mindset, and are knowledgeable about the latest scientific advancements. They are adept at pioneering and forging ahead. As such, this book not only reflects the current state of glioma research in China and abroad but also highlights the achievements of glioma research at

Huashan Hospital, Fudan University. It is my hope that the publication of this book will serve as a valuable reference for neurosurgeons and contribute to the treatment of glioma. I am delighted to write this at the editor-in-chief's invitation, as we welcome the New Year.

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Preface

In 1986, when I entered Shanghai Medical University (now as Shanghai Medical College, Fudan University to pursue my medical career, I could not have imagined that I would be working with the most intricate organ in the human body—the brain. Neuroscience had always awed me, as it is the most complex and uncharted field in medical studies and exploring it would require a lifetime of dedication and facing many obstacles. Despite this, I chose to embrace the challenge and delve into the unknown world of neurosurgery, where I could physically touch this enigmatic organ. Along the way, my goal has been to treat brain lesions and save the lives of my patients, making it the purpose of my life.

As a neurosurgeon, I never expected that I would choose brain tumors as the focus of my research, especially gliomas, which have a poor prognosis compared to other brain diseases. Initially, I started my work with my mentor, Academician Zhou Liangfu, treating cerebrovascular diseases. As I gained more experience and successfully performed surgeries to save stroke patients' lives by clipping cerebral aneurysms, I began to consider taking on new challenges. I contemplated whether to shift my focus towards brain tumors, specifically gliomas, and make it my new starting point, with the ultimate goal of improving the quality of life for cancer patients.

Glioma is a classic disease in neurosurgery that requires a multifaceted approach to diagnosis and treatment, including surgical skills, functional positioning, neuroimaging, and comprehensive care. With the development of new technologies, such as multimodal imaging, intraoperative MRI, intraoperative fluorescence, and intraoperative electrophysiological techniques, the diagnosis and treatment of glioma have reached new heights. Furthermore, the latest advances in molecular biology, genomics, and bioinformatics have challenged some of our outdated perspectives. As a result, new molecular typing and targeted therapies are rapidly advancing. Experts predict that there will be significant breakthroughs in the diagnosis and treatment strategies for glioma within the next decade.

Initially, my research focused on cerebrovascular diseases, and I had limited experience with glioma. At the start, I faced considerable pressure as I discovered that performing successful glioma surgery is a challenging task. However, with the support of the Shanghai spirit of "inclusiveness and pursuit of excellence" and Fudan University's school motto of "knowledge and determination, inquiring and thinking," and under the guidance and encouragement of Academician Zhou Liangfu, I began to study and explore glioma. Over the

years, the concepts of glioma diagnosis and treatment have undergone constant updates and changes. Some of the previous "golden rules," such as the extent of glioma resection, the so-called silent zones surrounding the tumor, and treatment strategies after tumor recurrence, have been challenged and refreshed. This created opportunities for innovation and growth. My experience and skills in the diagnosis and treatment of cerebrovascular diseases have given me an advantage in the comprehensive care of glioma patients. Today, my experience and skills in treating both brain tumors and cerebrovascular diseases provide me with confidence and a competitive edge in my work.

Glioma's unique growth pattern and highly heterogeneous genetic background have made it a popular intersection for basic and clinical research. This book draws on the latest developments in glioma research both domestically and abroad, beginning with epidemiological research, followed by molecular pathology, genomics, and the application of new neurosurgical technologies (intraoperative MRI, navigation, etc.), as well as a comprehensive analysis of brain function. The book also covers the latest achievements in basic research and clinical treatment of glioma from the perspective of protection, advocates for the construction of MDT for glioma, and emphasizes interdisciplinary integration. This book provides a comprehensive understanding of glioma from multiple perspectives, with typical cases, rich images, texts, and novel arguments. It not only presents the author's extensive clinical work and basic research accumulation but also reflects the latest research results in the field at home and abroad. It is expected that this book will offer an academic feast for glioma researchers, and be a source of inspiration for readers, standing on their desk as a timeless reference.

This book aims to provide clinicians and basic research workers with a reference to better understand and grasp the important directions in the field of glioma research. It is hoped that the book will be beneficial to readers. Many young doctors from our department participated in writing this book, and I express my gratitude to them for their hard work. With the inspiration of the concepts of translational medicine and precision medicine, I hope that young physicians will bravely push the boundaries of research, make persistent efforts, and inherit the spirit of steadfastness, diligence, and innovation of the older generation. It is my hope that they will contribute to the advancement of glioma research.

I would like to express my gratitude to my mentor, Academician Zhou Liangfu, for his unwavering support and tolerance towards me. I am also thankful for the remarkable glioma research team that I have. They are a group of young and enthusiastic individuals who are dedicated to acquiring knowledge and are willing to complete heavy clinical work, even if it means staying late at night. Their clinical insights and understanding often provide the most pragmatic approach to glioma research, which I hope readers can appreciate in this book. As the field of glioma research is continuously evolving, and the author's proficiency is limited by time constraints, it is inevitable that some information may be omitted or out of date. Therefore, I welcome readers to provide constructive criticism and corrections.

Shanghai, China Ying Mao

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