HIGH-GRADE GLIOMAS
CURRENT CLINICAL ONCOLOGY

Maurie Markman, MD, SERIES EDITOR

Colorectal Cancer: Evidence-Based Chemotherapy Strategies, edited by Leonard B. Saltz, 2007
High-Grade Gliomas: Diagnosis and Treatment, edited by Gene H. Barnett, 2006
Cancer in the Spine: Comprehensive Care, edited by Robert F. McLain, Kai-Uwe Lewandrowski, Maurie Markman, Ronald M. Bukowski, Roger Macklis, and Edward C. Benz, 2006
Squamous Cell Head and Neck Cancer, edited by David J. ADELSTEIN, 2005
Hepatocellular Cancer: Diagnosis and Treatment, edited by Brian I. Carr, 2005
Biology and Management of Multiple Myeloma, edited by James R. Berenson, 2004
Colorectal Cancer: Multimodality Management, edited by Leonard Saltz, 2002
Melanoma: Biologically Targeted Therapeutics, edited by Ernest C. Borden, 2002
Cancer of the Lung: From Molecular Biology to Treatment Guidelines, edited by Alan B. Weitberg, 2001
Renal Cell Carcinoma: Molecular Biology, Immunology, and Clinical Management, edited by Ronald M. Bukowski and Andrew Novick, 2000
Current Controversies in Bone Marrow Transplantation, edited by Brian J. Bolwell, 2000
Regional Chemotherapy: Clinical Research and Practice, edited by Maurie Markman, 2000
Intraoperative Irradiation: Techniques and Results, edited by L. L. Gunderson, C. G. Willett, L. B. Harrison, and F. A. Calvo, 1999
HIGH-GRADE GLIOMAS

Diagnosis and Treatment

Edited by

GENE H. BARNETT, MD

Brain Tumor Institute, Department of Neurological Surgery
Cleveland Clinic Foundation, Cleveland, OH
Preface

This is truly an exciting time in the field of neuro-oncology, particularly in the area of high-grade gliomas. The management of patients with high-grade gliomas has historically been one of the most challenging and disheartening fields in medicine, where failure is the rule and longevity is the exception. The jaded often state that despite purported advances in surgical and radiotherapeutic techniques and a myriad of clinical trials of medical therapies, the survival statistics for glioblastoma have not changed in the last three decades. The nihilism associated with these tumors is such that some practitioners still advise against treatment or even biopsy, recommending palliative care with the diagnosis based only on history and an MRI scan. If the current state-of-the-art in the diagnosis and management of high-grade gliomas was truly so bleak, there would be no reason to compile and publish a monograph on the subject. The fact is that we have recently entered an era where real progress is being made in our understanding and treatment of high-grade gliomas that is directly benefiting some patients.

We are slowly but surely chipping away at this problem. One approach has exploited correlations between particular molecular markers and therapeutic response. The first such “breakthrough” in high-grade glioma was the observation that loss of chromosomes 1p and 19q uniformly predict chemosensitivity in anaplastic oligodendrogliomas (1). Subsequent work has refined this relationship using additional markers to forecast longevity in patients with these tumors (2). More recently we have seen similar observations in glioblastoma where methylation of the methyl-guanine-methyl transferase (MGMT) gene promoter is associated with better response to temozolomide (TMZ) (3). Similarly, co-expression of the vIII mutation of epidermal growth factor receptor (EGFR) and the PTEN tumor suppressor gene predicts response to EGFR inhibitors (4).

Another approach has been large multi-center clinical trials using conventional and unconventional agents. Stupp et al have shown that radiotherapy with concurrent low dose temozolomide and subsequent high dose TMZ leads to longer survival than radiotherapy alone for newly diagnosed glioblastoma (5). Presently a large multicenter trial is comparing the use of an immuotoxin (IL13-PE39QQR) delivered by convection enhanced delivery against carmustine-impregnated biodegradable wafers in patients with operable glioblastoma at first recurrence. Yet another avenue of investigation is to use preclinical animal testing to improve response by refining traditional therapeutic delivery schedules, combining agents and investigating various modes of delivery and concentrations of agents achieved in tumor, brain and CSF.

So in this volume we present the spectrum of issues pertaining to high-grade gliomas from the basics of clinical characteristics and management to the state-of-the-art in diagnosis and therapeutics, as well as current areas of investigation that may lead to the treatments of tomorrow. We explore whether molecular diagnosis complements histology or is likely to supercede it, the most current information in imaging techniques to assist us in diagnosing and monitoring treatment, and the latest in “conventional” treatments such as surgery, radiation, and cytotoxic chemotherapy.
After decades of uniformly poor outcomes, we have entered an era where meaningful advances are being made in our understanding of the biology of high-grade gliomas that is leading to better, more rational, patient-specific treatments. I hope you find this book informative and useful.

*Gene Barnett, MD, FACS*

**REFERENCES**

Preface .....................................................................................................................................v
Contributors ........................................................................................................................... ix
Companion CD ROM ......................................................................................................... xiii

PART I: CLASSIFICATION OF HIGH-GRADE GLIOMA
1. Histologic Classification of High-Grade Gliomas ........................................................3
   Richard A. Prayson
2. Molecular Classifications ............................................................................................ 37
   Gregory N. Fuller

PART II: CLINICAL CHARACTERISTICS
3. Pediatric High-Grade Glioma ..................................................................................... 45
   Bruce H. Cohen
4. Adult High-Grade Glioma .......................................................................................... 59
   Nicholas Butowski and Susan Chang

PART III: DIAGNOSTIC TOOLS FOR HIGH-GRADE GLIOMA
5. Computerized Tomography ........................................................................................ 73
   Manzoor Ahmed and Thomas J. Masaryk
6. Magnetic Resonance Imaging ................................................................................... 105
   Paul M. Ruggieri
7. Magnetic Resonance Spectroscopy .......................................................................... 133
   G. Evren Keles, Soonmee Cha, and Mitchell S. Berger
8. Imaging Tumor Biology: Physiological and Molecular Insights ............................ 141
   Timothy P. L. Roberts and Andrea Kassner
9. Nuclear Imaging of Gliomas ..................................................................................... 161
   Alexander M. Spence, David A. Mankoff, Mark Muzi, and Kristin Swanson
10. Magnetoencephalography ...................................................................................... 187
    Michael P. Steinmetz, Jürgen Lüders, and Edward C. Benzel

PART IV: MANAGEMENT
11. General Considerations ............................................................................................ 199
    Glen H. J. Stevens
12. Surgery for High-Grade Gliomas ............................................................................. 213
    Gene H. Barnett
13. Radiation Therapy ..................................................................................................... 231
    Hiral K. Shah and Minesh P. Mehta
14. Brachytherapy ........................................................................................................... 245
    Marcus L. Ware, P. K. Sneed, and Michael W. McDermott
15. Radiosurgery ............................................................................................................. 257
   *John H. Suh and Gene H. Barnett*

16. Chemotherapy ........................................................................................................... 267
   *Manmeet Singh Ahluwalia and David M. Peereboom*

17. Nursing Considerations ............................................................................................. 283
   *Kathleen Lupica and Gail Ditz*

**PART V: CONTEMPORARY INVESTIGATIONAL TREATMENTS**

18. Convection-Enhanced Delivery ................................................................................ 303
   *Andrew A. Kanner*

19. Immunotoxins for Glioma Therapy .......................................................................... 315
   *Syed Rafat Husain and Raj K. Puri*

20. Small Molecule Agents ............................................................................................. 337
    *Michael Vogelbaum and Tina Thomas*

21. Cytokine Immuno-Gene Therapy for Malignant Brain Tumors .............................. 357
    *Roberta P. Glick, Terry Lichtor, Henry Lin, and Edward P. Cohen*

22. Monoclonal Antibodies ............................................................................................. 373
    *Abraham Boskovitz, David A. Reardon, Carol J. Wikstrand,
    Michael R. Zalutsky, and Darell D. Bigner*

23. Clinical Trials of Oncolytic Viruses for Gliomas .................................................... 391
    *E. Antonio Chiocca and M. L. Lamfers*

24. Biological Modifiers ................................................................................................. 405
    *Alexander Mason, Steven Toms, and Aleck Hercbergs*

25. Gene Therapy for High-Grade Glioma ..................................................................... 419
    *Maciej S. Lesniak and Alessandro Olivi*

26. Boron Neutron Capture Therapy of Brain Tumors:
    *Current Status and Future Prospects* ................................................................. 431
    *Rolof F. Barth, Jeffrey A. Coderre, M. Graça H. Vicente,
    Thomas E. Blue, and Shin-Ichi Miyatake*

27. Photodynamic Therapy ............................................................................................. 461
    *Bhadra Kavar and Andrew H. Kaye*

Index ................................................................................................................................... 485
Contributors

MANMEET SINGH AHLUWALIA, MD • Fairview Hospital, Cleveland, OH
MANZOOR AHMED, MD • Department of Diagnostic Radiology, The Cleveland Clinic Foundation, Cleveland, OH
GENE H. BARNETT, MD • The Brain Tumor Institute, Department of Neurological Surgery, The Cleveland Clinic Foundation, Cleveland, OH
ROLF F. BARTH, MD • Department of Pathology, The Ohio State University, Columbus, OH
EDWARD C. BENZEL, MD • Cleveland Clinic Spine Institute, Department of Neurological Surgery, The Cleveland Clinic Foundation, Cleveland, OH
MITCHELL S. BERGER, MD • Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA
DARELL D. BIGNER, MD, PhD • Department of Pathology, Neuro-Oncology Program, Duke University Medical Center, Durham, NC
THOMAS E. BLUE, PhD • Department of Nuclear Engineering Program, The Ohio State University, Columbus, Ohio
ABRAHAM BOSKOVITZ, MD • Neuro-Oncology Program, Department of Pathology, Duke University Medical Center, Durham, NC
NICHOLAS BUTOWSKI, MD • Neuro-Oncology Service, Department of Neurological Surgery, UCSF School of Medicine, San Francisco, CA
SOONMEE CHA, MD • Department of Radiology, University of California, San Francisco, San Francisco, CA
SUSAN CHANG, MD • Neuro-Oncology Service, Department of Neurological Surgery, UCSF School of Medicine, San Francisco, CA
E. ANTONIO CHIOCCA, MD, PhD • Dardinger Center for Neuro-Oncology, Department of Neurosurgery, The Ohio State University Medical Center, James Cancer Hospital and Solove Research Center, Columbus, OH
JEFFREY A. CODERRE, PhD • Department of Nuclear Engineering, Massachusetts Institute of Technology, Cambridge, MA
BRUCE H. COHEN, MD • Department of Neurology, The Cleveland Clinic Foundation, Cleveland, OH
EDWARD P. COHEN, MD • Department of Neurological Surgery, Rush Medical College, Cook County Hospital and Hektoen Institute for Medical Research; and Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL
GAILE DITZ, RN • The Brain Tumor Institute, The Cleveland Clinic Foundation, Cleveland, OH
GREGORY N. FULLER, MD, PhD • Department of Pathology, MD Anderson Cancer Center, Houston, TX
ROBERTA P. GLICK, MD • Department of Neurological Surgery, Rush Medical College, Cook County Hospital and Hektoen Institute for Medical Research; and Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL
ALECK HERCBERGS, MD • Department of Radiation Oncology, The Cleveland Clinic Foundation, Cleveland, OH
SYED RAFAT HUSAIN, PhD • Tumor Vaccines and Biotechnology Branch, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, FDA, Bethesda, MD

ANDREW A. KANNER, MD • Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ANDREA KASSNER, PhD • Department of Medical Imaging, University of Toronto, University Health Network, Toronto, Ontario

BHADRAKANT KAVAR, MD, ChB, FCS, FRACS • Departments of Neurosurgery and Surgery, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia

ANDREW H. KAYE, MB, BS, MD, FRACS • Departments of Neurosurgery and Surgery, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia

G. EVREN KELES, MD • Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA

M. L. LAMFERS, PhD • Division of Gene Therapy, Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands

MACIEJ S. LESNIAK, MD • Division of Neurological Surgery, The University of Chicago Pritzker School of Medicine, Chicago, IL

TERRY LICHTOR, MD, PhD • Department of Neurological Surgery, Rush Medical College, Cook County Hospital and Hektoen Institute for Medical Research; and Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL

HENRY LIN, MD • Department of Neurological Surgery, Rush Medical College, Cook County Hospital and Hektoen Institute for Medical Research; and Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL

JÜRGEN LÜDERS, MD • Neurosurgeon, Grand Rapids, MI

KATHLEEN LUPICA, MSN, CNP • The Brain Tumor Institute, The Cleveland Clinic Foundation, Cleveland, OH

DAVID A. MANKOFF, MD, PhD • Department of Radiology, University of Washington School of Medicine, Seattle, WA

THOMAS J. MASARYK, MD • Department of Diagnostic Radiology, The Cleveland Clinic Foundation, Cleveland, OH

ALEXANDER MASON, MD • Department of Neurosurgery, The Cleveland Clinic Foundation, Cleveland, OH

MICHAEL W. MCDERMOTT, MD • Departments of Neurosurgery and Radiation Oncology, University of California, San Francisco, CA

MINESH P. MEHTA, MD • Department of Human Oncology, University of Wisconsin, Madison, WI

SHIN-ICHI MIYATAKE, MD, PhD • Department of Neurosurgery, Osaka Medical College, Takatsuki, Osaka Prefecture, Japan

MARK MUZI, MS • Department of Radiology, University of Washington School of Medicine, Seattle, WA

ALESSANDRO OLIVI, MD • Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD

DAVID M. PEEREBOOM, MD • The Brain Tumor Institute, Department of Medical Oncology, The Cleveland Clinic Foundation, Cleveland, OH

RICHARD A. PRAYSON, MD • Department of Anatomic Pathology, The Cleveland Clinic Foundation, Cleveland, OH

RAJ K. PURI, MD, PhD • Tumor Vaccines and Biotechnology Branch, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, FDA, Bethesda, MD
DAVID A. REARDON, MD • Neuro-Oncology Program, Department of Surgery, Duke University Medical Center, Durham, NC
TIMOTHY P. L. ROBERTS, PhD • Department of Medical Imaging, University of Toronto, University Health Network; and Toronto Western Research Institute, Toronto, Ontario
PAUL M. RUGGIERI, MD • Department of Diagnostic Radiology, The Cleveland Clinic Foundation, Cleveland, OH
HIRAL K. SHAH, MD • Department of Human Oncology, University of Wisconsin, Madison, WI
P. K. SNEED, MD • Department of Radiation Oncology, University of California, San Francisco, CA
ALEXANDER M. SPENCE, MD • Department of Neurology, University of Washington School of Medicine, Seattle, WA
MICHAEL P. STEINMETZ, MD • Department of Neurological Surgery, The Cleveland Clinic Foundation, Cleveland, OH
GLEN H. J. STEVENS, DO, PhD • The Brain Tumor Institute, Department of Neurology, The Cleveland Clinic Foundation, Cleveland, OH
JOHN H. SUH, MD • The Brain Tumor Institute, Department of Radiation Oncology, The Cleveland Clinic Foundation, Cleveland, OH
KRISTIN SWANSON, PhD • Department of Neuropathology, University of Washington School of Medicine, Seattle, WA
TINA THOMAS, MD • The Brain Tumor Institute, The Cleveland Clinic Foundation, Cleveland, OH
STEVEN TOMS, MD, MPH • The Brain Tumor Institute, Department of Neurological Surgery, The Cleveland Clinic Foundation, Cleveland, OH
M. GRAÇA H. VICENTE, PhD • Department of Chemistry, Louisiana State University, Baton Rouge, LA
MICHAEL VOGELBAUM, MD, PhD • The Brain Tumor Institute, Department of Neurological Surgery, The Cleveland Clinic Foundation, Cleveland, OH
MARCUS L. WARE, MD, PhD • Departments of Neurosurgery and Radiation Oncology, University of California, San Francisco, CA
CAROL J. WIKSTRAND, PhD • Neuro-Oncology Program, Department of Pathology, Duke University Medical Center, Durham, NC
MICHAEL R. ZALUTSKY, PhD • Department of Radiology, Neuro-Oncology Program, Duke University Medical Center, Durham, NC
All illustrations, both black and white and color, are contained on the accompanying CD ROM.
Clinical Oncology is a peer-reviewed medical journal covering oncology. It was established in 1989 and is published ten times a year by Elsevier. It is the official journal of the Royal College of Radiologists. The editor-in-chief is Charlotte Coles (University of Cambridge). According to the Journal Citation Reports, the journal has a 2015 impact factor of 3.212. The Current Clinical Oncology series provides cutting-edge knowledge of cancer diagnosis, management, and treatment. World renowned experts share their insights in all the major fields of clinical oncology. From the fundamentals of pathophysiology to the latest developments in experimental and novel therapies, Current Clinical Oncology is an indispensable resource for today’s practicing oncologist. Your Shopping Cart. 0 eBook. Use the Advanced Search Close. Current Clinical Oncology. View all articles. Journal Information.Â by Springer Science and Business Media LLC. in Current Clinical Oncology. Current Clinical Oncology; doi:10.1007/978-3-319-47269-0. Show/hide abstract. The publisher has not yet granted permission to display this abstract.