Glioma Imaging

Physiologic, Metabolic, and Molecular Approaches

Whitney B. Pope
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Editor
Whitney B. Pope
David Geffen School of Medicine at UCLA
Los Angeles, CA
USA

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Preface

This book is intended to provide the most up-to-date synthesis of imaging with glioma biology and to highlight areas of unmet clinical need. Its focus is gliomas in adult patients. Gliomas are the most frequently occurring primary brain tumor. They range in grade from I to IV, with grade IV (glioblastoma) being not just the most malignant but also the most common. MRI is central to the clinical management of gliomas. Clinicians use MRI to generate differential diagnoses, improve neurosurgical planning, assess resection extent, and follow changes in tumor burden over the course of treatment. Though critically important, tracking tumor burden has historically presented significant challenges for MRI, particularly in distinguishing treatment effect from recurrent or residual disease. Addressing some of these difficulties, brain tumor treatment response has been formalized using Response Assessment in Neuro-Oncology (RANO) criteria based on measurements of enhancing tumor. Complementary to MRI, PET scans can refine characterization of tumor burden, adding value to standard imaging, especially when coupled with newer amino acid tracers that serve as markers for protein synthesis. This book explores the ever-expanding role of MR and PET in managing glioma patients, as reflected both in contemporary medical practice and in new applications being developed and validated for clinical use.

In many ways, the future is here. The molecular characterization of brain tumors has substantially advanced over the past decade and is now fundamental to the identification of many gliomas, as reflected in the updated 2016 World Health Organization (WHO) guidelines for brain tumor classification. Imaging techniques have advanced apace. Once used almost exclusively to characterize anatomic features of a tumor, newer approaches can now interrogate a wide range of tumor physiologic and metabolic characteristics. Additionally, entirely new fields such as “radiomics” and “imaging genomics” are emerging, and with them are enormous data sets that ultimately may be most effectively mined by artificial intelligence/machine learning-based paradigms. Yet a fundamental challenge remains: how can researchers and clinicians leverage these vast quantities of data into imaging-generated biomarkers that improve patient outcomes? Although traditionally it is the primary marker of disease burden, measurement of contrast enhancement retains its manifold limitations. Even with T2-weighted and FLAIR sequences, standard imaging can lack sufficient specificity and sensitivity for tumor in common clinical scenarios like pseudo-progression and pseudoresponse. Looking forward, this book examines path-breaking efforts to move beyond contrast

enhancement in addressing imaging needs of glioma patients—whether for predictive markers tailored to emerging treatments like immunotherapy or early response markers to hasten assessment of therapy effectiveness—that remain unmet.

The contributors for this volume are renowned leaders from around the world in fields encompassing clinical neuroradiology, neuro-oncology, and basic science imaging research. This work should be highly useful for general as well as subspecialized radiologists who interpret brain tumor imaging, as well as for neuro-oncologists, clinicians developing brain tumor trials who rely on imaging endpoints, neurosurgeons who resect gliomas, and also those researchers looking for perspective in understanding imaging-based global assessment of tumor status.

The book begins by outlining the current standard of care for high-grade gliomas and the role of MR imaging in providing that standard of care. It then details the biological underpinnings of blood-brain barrier breakdown, as bidimensional measurements of contrast enhancement remain the accepted quantitative measure of tumor burden. In subsequent chapters, the theoretical basis for important and widely available physiologic imaging techniques, including perfusion- and diffusion-weighted protocols and analysis, is examined in detail. A separate chapter is dedicated to major changes in the recent WHO reclassification of brain tumors—changes that are crucial to the daily practice of clinical neuroradiologists. Additional chapters explore the transformation of lower-grade tumors into more malignant ones, together with a raft of new technologies that advance our ability to image tumor physiology and metabolism, including CEST, amino acid PET, and spectroscopy. Informatics-based approaches that encompass "big data" and machine learning in the context of imaging genomics and radiomics are also addressed. Turning to treatment, the book reviews important recent advances in immunotherapy and its impact on brain tumor imaging interpretation. The book concludes with a review of multi-institutional efforts to standardize imaging protocol and interpretation—a matter of paramount importance for ongoing and future clinical trials.

In marrying "state of the practice" and "state of the science" assessments, this work is intended to help integrate emerging imaging technologies with clinical practice while also providing a more precise understanding of underlying tumor biology. This understanding, in turn, should facilitate individualized patient treatment, improve the application of imaging in clinical trials, and illustrate areas where new approaches can yield needed improvements in glioma characterization, all with the ultimate goal of lengthening and bettering the lives of brain tumor patients.

Los Angeles, CA, USA Whitney B. Pope

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Contributors

Ovidiu C. Andronesi, PhD, MD Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Ramon F. Barajas Jr., MD Departments of Radiology and Advanced Imaging Research Center, Knight Cancer Institute, Translational Research Program, Oregon Health and Science University, Portland, OR, USA

Tracy T. Batchelor, MD, MPH Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Ankush Bhatia, MD Department of Neurology and the Brain Tumor Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Jerrold L. Boxerman, MD, PhD, FACR Department of Diagnostic Imaging, Rhode Island Hospital, Providence, RI, USA

Daniel P. Cahill, MD, PhD Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Michael Cardenas, MD Department of Radiation Oncology, University of California Davis, Sacramento, CA, USA

Peter D. Chang, MD Department of Radiology, University of California, Irvine, Irvine, CA, USA

Thomas L. Chenevert, PhD Department of Radiology, University of Michigan Medical School, Ann Arbor, MI, USA

Daniel S. Chow, MD Department of Radiology, University of California, Irvine, Irvine, CA, USA

Francesco Cicone, MD Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital, Lausanne, Switzerland

Unit of Nuclear Medicine, Sant' Andrea Hospital, Sapienza University of Rome, Rome, Italy

Benjamin M. Ellingson, PhD UCLA Brain Tumor Imaging Laboratory, Center for Computer Vision and Imaging Biomarkers, Department of Radiological Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

UCLA Neuro-Oncology Program, Department of Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

UCLA Jonsson Comprehensive Cancer Center (JCCC), David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Julie Ferris, BS/BA University of California, Irvine, Irvine, CA, USA

Craig J. Galban, PhD Department of Radiology, University of Michigan Medical School, Ann Arbor, MI, USA

Norbert Galldiks, MD Department of Neurology, University Hospital Cologne, Cologne, Germany

Institute of Neuroscience and Medicine (INM-3, -4), Research Center Juelich, Juelich, Germany

Center of Integrated Oncology (CIO), Universities of Aachen, Bonn, Cologne, and Duesseldorf, Cologne, Germany

Caterina Giannini, MD, PhD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Elke Hattingen, PhD Neuroradiology, University Hospital Frankfurt, Frankfurt am Main, Germany

Raymond Y. Huang, MD, PhD Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA

Derek R. Johnson, MD Department of Radiology, Mayo Clinic, Rochester, MN, USA

Timothy J. Kaufmann, MD Department of Radiology, Mayo Clinic, Rochester, MN, USA

Cymon N. Kersch, PhD Departments of Neurology, Blood-Brain Barrier Program, Oregon Health and Science University, Portland, OR, USA

Philipp Kickingereder, MD, MBA Department of Neuroradiology, Heidelberg University Hospital, Heidelberg, Germany

Karl-Josef Langen, MD Institute of Neuroscience and Medicine (INM-3, -4), Research Center Juelich, Juelich, Germany

Department of Nuclear Medicine, University of Aachen, Aachen, Germany

Juelich-Aachen Research Alliance (JARA) - Section JARA-Brain, Juelich, Germany

Peter S. LaViolette, PhD Medical College of Wisconsin, Milwaukee, WI, USA

Yan Li, PhD Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA

Philipp Lohmann, PhD Institute of Neuroscience and Medicine (INM-3, -4), Research Center Juelich, Juelich, Germany

Janine M. Lupo, PhD University of California San Francisco, Department of Radiology and Biomedical Imaging, San Francisco, CA, USA

Michelle Miller-Thomas, MD Department of Neuroradiology, Washington University School of Medicine, St. Louis, MO, USA

Melanie A. Morrison, PhD Department of Radiology and Biomedical Imaging at UCSF, San Francisco, CA, USA

Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Scotland, UK

Department of Medicine, Imperial College London, London, UK

Daniel Paech, MD, MSc German Cancer Research Center (DKFZ), Division of Radiology, Heidelberg, Germany

Ji Eun Park, MD, PhD Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Alexander Radbruch, MD, JD German Cancer Research Center (DKFZ), Division of Radiology, Heidelberg, Germany

University Hospital Essen, Department of Diagnostic and Interventional Radiology and Neuroradiology, Essen, Germany

Sabrina M. Ronen, PhD Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA

Brian D. Ross, PhD Department of Radiology, University of Michigan Medical School, Ann Arbor, MI, USA

University of Michigan School of Medicine, Departments of Radiology and Biological Chemistry, Center for Molecular Imaging, Ann Arbor, MI, USA

Marion Smits, MD, PhD Department of Radiology and Nuclear Medicine, Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

Christina Tsien, MD Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO, USA

Javier E. Villanueva-Meyer, MD University of California San Francisco, Department of Radiology and Biomedical Imaging, San Francisco, CA, USA

Pavithra Viswanath, PhD Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA

Adam D. Waldman, FRCR, FRCP, PhD Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Scotland, UK

Department of Medicine, Imperial College London, London, UK

Elise Wang Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Patrick Y. Wen, MD Dana-Farber Cancer Institute, Boston, MA, USA

Robert J. Young, MD Department of Radiology and the Brain Tumor Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

1 Indications and Limitations of Conventional Imaging – Current Clinical Practice in the Context of Standard Therapy

Raymond Y. Huang and Patrick Y. Wen

Introduction

Gliomas, the most common malignant primary tumors of the central nervous system, have an annual incidence of about 6 in 100,000 [1]. They are subdivided into four World Health Organization (WHO) grades (I–IV). Glioblastoma, a World Health Organization (WHO) grade IV tumor, is the most aggressive subtype and accounts for about 47% of malignant central nervous system tumors [1]. The prognosis of glioblastoma is among the worst of all cancers, with a 5-year survival rate of merely 5.5% [1]. While distant metastasis is rare, glioblastomas are locally aggressive with a high rate of tumor recurrence following initial standard treatment [2]. The prognosis for lower-grade gliomas (WHO grades II and III) is less dismal; the five-year survival rates are 30% for anaplastic astrocytoma and 57% for anaplastic oligodendroglioma [1], and more than half of patients with WHO grade II gliomas survive over 5 years. Recent discovery of isocitrate dehydrogenase (IDH) 1/2 mutations and 1p19q co-deletion as key molecular markers of glioma with distinct clinical behavior and prognosis has led to integration of these markers into the newly revised WHO grading of gliomas [3]. This new grading system results in classification of gliomas better matching their prognostic features and therapeutic modalities. IDH-mutant gliomas with 1p/19q codeletion had the most favorable outcome clinically with median survival more than 10–15 years, whereas IDH-mutant gliomas without 1p/19q codeletion have median survival of 5–10 years; patients with IDH wild-type grade II and III tumors resemble glioblastomas in their molecular profile and therefore have had the least favorable outcome [4]. Even for patients who live longer, the infiltrative nature of these tumors often leads to recurrence and require repeated surgical resections, radiation, as well as chemotherapy.

Imaging is instrumental in aiding diagnose and guiding management for both high- and low-grade gliomas. With modern clinical magnetic resonance imaging (MRI) scanners, gliomas are frequently detected and diagnosed with high accuracy prior to surgical resection, and high-resolution preoperative imaging can facilitate surgical planning for maximal resection to increase chance of longer-term survival. For high-grade gliomas, chemoradiation is currently the standard-of-care treatment, and imaging can outline regions of residual tumor for radiation planning and allow noninvasive evaluation of posttreatment response. Serial imaging is also routinely performed to monitor tumor activities for both high- and low-grade gliomas.

R. Y. Huang (✉)
Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA
e-mail: ryhuang@bwh.harvard.edu

P. Y. Wen
Dana-Farber Cancer Institute, Boston, MA, USA

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Despite these important roles of imaging, the genetic complexity of gliomas and the rapidly evolving therapeutic strategies that are increasingly more targeted to specific tumor subtypes require constant improvement of diagnostic capability of imaging methodology. Furthermore, treatment-induced changes to tumor or brain tissues can frequently mimic tumor, thereby bring challenges to the use of imaging for assessing treatment response. In this chapter, conventional MRI approaches to evaluation of both high- and low-grade gliomas will be presented in the context of standard therapy, and limitations to the standard techniques will be discussed.

Preoperative Diagnosis of Gliomas

When a brain mass is suspected following evaluation of neurological symptoms, imaging is the key diagnostic step both to confirm presence of a mass or mass and to characterize the mass(s) if there is one. Although computed tomography (CT) can often detect mass lesions in symptomatic patients and provides rapid triage of patients due to its wide availability, its role in lesion characterization and preoperative planning is limited for a majority of CNS neoplasm. In particular, low-grade gliomas are frequently similar in density compared to normal brain and lack perilesional edema and significant mass effect, making them difficult to detect by CT. MRI is currently the imaging modality of choice for evaluation of brain mass due to its imaging resolution and exquisite tissue contrast that are both essential for diagnosis and treatment planning.

Gliomas exhibit a wild spectrum of findings on conventional imaging that are influenced by tumor grade, location, and molecular subtypes. Glioblastomas are most frequently characterized by their irregular margins, complex patterns of enhancement, and presence of necrosis, edema, and varying degrees of intratumoral hemorrhage (Fig. 1.1). These features are readily captured by a combination of T2-weighted and gadolinium contrast-enhanced T1-weighted MRI sequences. Other features such as subependymal or leptomeningeal spread of tumor as well as diffuse infiltration that involve multiple brain locations can also be detected on conventional imaging and alter disease prognosis and influence management approach [5, 6]. In contrast, low-grade gliomas such as astrocytomas and oligodendrogliomas are often non-enhancing and well circumscribed (Fig. 1.2), while anaplastic astrocytomas and oligodendrogliomas can have overlapping imaging findings of low-grade gliomas and glioblastoma (Fig. 1.3). It is important to recognize the limitation of conventional MR imaging in defining tumor margins of infiltrative glioma since there is ample evidence that tumor cells are often present beyond the border of abnormality delineated by conventional sequences such as T2/FLAIR [7, 8].

The main diagnostic challenges for high-grade glioma in adult patients include other CNS tumors including primary CNS lymphoma and metastasis from systemic cancers, as well as non-neoplastic diseases such as infarct, demyelination, and abscess. Compared to glioblastomas, lymphomas exhibit more homogeneous enhancement and, when untreated, rarely found to have intratumoral hemorrhage. This distinction can be helpful to recognize preoperatively since standard management of CNS lymphoma is biopsy rather than resection, whereas maximal surgical resection improves prognosis for high-grade glioma [9]. Brain metastases, when solitary, can show overlapping features with glioblastoma including necrosis, hemorrhage, and edema, but they do not show infiltration and expansion of cerebral cortices with blurring of gray-white matter margins that are more characteristics of gliomas. Brain abscesses typically manifest as peripherally enhancing lesion(s) with surrounding edema that can resemble a necrotic neoplasm including high-grade glioma. The walls of tumors, however, are typically thicker and more irregular. Despite these imaging characteristics, differentiation among these tumor types and tumor mimickers can be challenging based on qualitative interpretation of conventional imaging features alone. Imaging findings are often combined with clinical data such as age, gender, and presenting symptoms and signs to increase the accuracy of diagnosis. Greater diagnostic accuracy