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Anti-Angiogenic Agents for the Treatment of Brain Tumors 477
Michael J. Fisher and Peter C. Adamson

The importance of angiogenesis, the formation of new blood vessels from pre-existing ones, has been recognized for more than 30 years. Many primary brain tumors appear to be angiogenesis dependent. Preclinical and clinical studies suggest that angiogenesis inhibition may be a promising new treatment strategy for brain tumors. This article reviews the biology of angiogenesis and its role in brain tumors, discusses antiangiogenic agents in clinical trials, and presents neuroimaging approaches to the study of the angiogenic process and its inhibition.

Dynamic Susceptibility Contrast MRI of Gliomas 501
Hannu J. Aronen and Jussi Perkiö

Angiogenesis is gaining in interest as several antiangiogenic drugs for cancer treatment are in clinical trials. At the same time, the importance of imaging the angiogenesis has grown, since it may help to identify the patient material optimal for therapy, monitor the effect of treatment and detect failures as early as possible. Dynamic susceptibility contrast MRI is able to describe several aspects of normal and diseased microvascular system. In recent years, dynamic susceptibility MRI has been the target of intense research, and the information content it can provide has increased and is increasing dramatically. This article describes the dynamic susceptibility contrast MRI technique and its applications in the characterization of gliomas.

Importance of Hypoxia in the Biology and Treatment of Brain Tumors 525
Jonathan P.S. Knisely and Sara Rockwell

Brain tumors contain extensive regions in which the tumor cells are subjected acutely or chronically to unphysiological levels of hypoxia. The resistance of cells that are hypoxic at the time of therapy to radiation and to anticancer drugs influences the efficacy of the treatment with radiation, chemotherapy, and combined modality regimens. Moreover, exposure of cells to adverse microenvironments produces transient changes in gene expression, induces mutations, and selects for cells with altered genotypes, thus driving the evolution of the cell population toward increasing malignancy and increasingly

aggressive phenotypes. Hypoxia therefore may be involved in the evolution of cells in low-grade malignancies to the resistant, aggressive phenotype characteristic of glioblastomas. During the past 50 years, many attempts have been made to circumvent the therapeutic resistance induced by hypoxia. These include improving tumor oxygenation by using oxygen-mimetic radiosensitizers, by adjuvant therapy with drugs that are preferentially toxic to hypoxic cells, by using hyperthermia, or by devising radiation sources and regimens that are less affected by hypoxia. Past clinical trials have provided tantalizing suggestions that the outcome of therapy can be improved by many of these approaches, but none has produced the significant, reproducible improvement in the therapeutic ratio needed for any of these approaches to become the standard therapy for these diseases. Ongoing clinical trials are addressing other, hopefully better regimens; it will be interesting to see the results of these studies.

Hypoxia Imaging in Brain Tumors 537
F. Zerrin Yetkin and Dianne Mendelsohn

This article summarizes the diagnostic and prognostic importance of imaging tumor hypoxia. Noninvasive imaging techniques capable of detecting and measuring oxygenation status are needed to assess hypoxic fraction of tumors. With the improvement and validation of new imaging techniques, better diagnostic and treatment monitoring capabilities can be provided for patients with brain tumors. This article reviews relevant information, provided with existing imaging modalities, and presents new imaging techniques.

Viruses in the Treatment of Brain Tumors 553
Peter E. Fecci, Matthias Gromeier, and John H. Sampson

In the 1920s, Walter Dandy performed five right cerebral hemispherectomies in an effort to save the lives of glioma patients who expressed the desire to live at even the cost of permanent hemiplegia. Of the three who survived the procedure, all eventually perished from tumor recurrence, even when complete resection seemingly had been the case. This account testifies to the extraordinary aggressiveness of malignant gliomas. This is reflected similarly in survival statistics. Despite advancements in surgery, radiotherapy, and chemotherapy, recurrence is essentially 100%, and median survival for primary glioblastoma multiforme receiving optimized therapy is only 4.6 to 17.9 months, depending on several defined prognostic factors. Resistance to current modalities has ushered forth the desire for fresh approaches to treatment. Viruses have received increasing levels of attention as antineoplastic agents for possible use as vehicles for delivery in gene therapy and as infectious agents capable of selectively lysing tumor cells (oncolysis). This article discusses the clinical experiences with both applications.

Viral Imaging in Gene Therapy: Noninvasive Demonstration of Gene Delivery and Expression 571
Dawid Schellingerhout and Alexei A. Bogdanov, Jr.

Gene therapy is a rapidly developing modality of treatment, with applications in acquired and inherited disorders. Gene delivery vehicles ("vectors") are the main impediment in the evolution of gene therapy into a clinically acceptable mainstream therapy. Vectors based on viral particles are the most commonly used vehicles to carry genes to the organs and tissues of interest. Despite initial promise and substantial progress in the development of experimental gene therapy protocols, human gene therapy still is based on technologies that so far do not allow for routine clinical use. Recent progress in viral vector production and better understanding of molecular aspects of vector delivery and targeting issues has created the need for imaging techniques that would be useful in

addressing the problems and opportunities inherent in viral gene therapy development. Two integral components of gene therapy monitoring, the imaging of gene delivery and the imaging of resultant exogenous gene expression, are recognized. These molecular imaging components provide a realistic means for assessment of safety and efficacy of preclinical and clinical development of gene therapy.

Innovations in Design and Delivery of Chemotherapy for Brain Tumors 583
Sridharan Gururangan and Henry S. Friedman

Although surgery and radiotherapy long have been established as treatment modalities of patients with brain tumors, the role of chemotherapy in such patients is far from certain. Nevertheless, it has continued to play a significant part in the therapeutic armamentarium against these tumors in the last several decades and might have contributed to disease stabilization and cure of some patients with brain tumors. Concurrently, it has become obvious that a significant proportion of patients with brain tumors also suffer progressive disease during or following chemotherapy. The causes for such therapeutic failure have been explored and reported extensively. Invariably, the lack of response to chemotherapy has been caused by the presence of the blood–brain barrier and drug resistance. This article initially discusses factors that contribute to chemotherapy failure followed by a discussion of recent advances in design and delivery of chemotherapy that have attempted to overcome some of these obstacles and improve antitumor responses and survival in patients with brain tumors.

Characterization of Untreated Gliomas by Magnetic Resonance Spectroscopic Imaging 599
Sarah J. Nelson, Tracy R. McKnight, and Roland G. Henry

The prognosis, choice of therapy, and management of adult gliomas are dependent upon the accurate diagnosis of tumor grade. The evaluation of tumor grade is performed by histological analysis of image-guided biopsy or of tissue samples obtained during surgical resection. This is a major problem because gliomas are known to be extremely heterogeneous, both in terms of the morphological characteristics of tumors with similar grade and in terms of the variability within individual lesions. Predicting which portion of the lesion is likely to be the most malignant and directing the surgeon to this location is critical for accurate diagnosis. Magnetic resonance imaging and spectroscopy are noninvasive imaging techniques that have been proposed for the evaluation of tumor grade in patients with untreated gliomas.

Positron Emission Tomography Imaging of Brain Tumors 615
Terence Z. Wong, Gert J. van der Westhuizen, and R. Edward Coleman

This article's primary focus is on positron emission tomography (PET) imaging using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG), because it is the most widely used PET radiopharmaceutical. FDG has several advantages for routine evaluation of brain tumors. FDG-PET can provide information about tumor grade and prognosis. Flourine-18 has a longer physical half-life (110 minutes) than most of the other positron-emitting radionuclides used in brain imaging, such as ^{11}C ($t_{1/2}$ = 20 min) and ^{15}O ($t_{1/2}$ = 2 min), making off-site production of fluorine-based radiopharmaceuticals practical. FDG can be delivered to PET imaging facilities through commercial vendors, allowing them to operate without the need for an on-site cyclotron.

Molecular Abnormalities and Correlations with Tumor Response and Outcome in Glioma Patients 627
Ian F. Pollack, Ronald L. Hamilton, Sydney D. Finkelstein, and Frank Lieberman

Gliomas are the most common intrinsic brain tumors. Historically, a major emphasis has been placed on stratifying therapy for these tumors based on histological features. In recent years, it has become apparent that these tumors exhibit characteristic patterns of molecular abnormalities that correlate with the progression from well differentiated (ie, grades I and II) to poorly differentiated (grades III and IV) histology. These abnormalities incorporate dysregulation of p53 function, inactivation of cell cycle control functions, and autocrine stimulation of growth factor receptor-mediated signaling pathways. With the increasing application of molecular approaches to refine the evaluation of these tumors, it also has become apparent that histologically comparable lesions may exhibit diverse patterns of gene expression and genomic alterations. In some instances, these differences may reflect alternate mechanisms for altering a single common target, but in others, these distinctions may highlight differences in molecular tumorigenesis that correlate with important prognostic distinctions. This article summarizes these observations and discusses examples of how the tools of molecular analysis are being applied in a preliminary fashion as a foundation for risk-adapted stratification of glioma therapy.

Clinical Immunotherapy for Brain Tumors 641
Peter E. Fecci and John H. Sampson

Malignant primary brain tumors now cause more deaths each year than melanoma. Despite advances in surgery, radiotherapy, and chemotherapy, recurrence remains essentially 100%. The desire for more effective and more tumor-specific treatment modalities has spawned interest in immunotherapeutic approaches to anticancer therapy. These may be grouped into passive, adoptive, and active strategies. Clinical trials have had varying levels of success, employing each of these strategies and combating such challenges as central nervous system immune privilege and tumor-mediated immunosuppression. This article discusses the rationales and results of these trials, and highlights recent successes with dendritic cell-based immunization platforms. The current understanding of antigen presentation and antitumor responses by the immune system implies that dendritic cell-based immunization platforms may be particularly promising as a mode of active immunotherapy.

Intraoperative Magnetic Resonance Imaging and Magnetic Resonance Imaging–Guided Therapy for Brain Tumors 665
Ferenc A. Jolesz, Ion-Florin Talos, Richard B. Schwartz, Hatsuho Mamata, Daniel F. Kacher, Kullervo Hynynen, Nathan McDannold, Pairash Saivironporn, and Lei Zao

The aim of brain tumor surgery is to target, access, and remove intracranial lesions without damaging normal functioning brain tissue, thus preserving essential neurologic function. To achieve this goal, the surgeon must exhibit complete mastery of structural and functional anatomy—a prerequisite to achieving maximal lesion removal while avoiding postoperative neurologic deficits. Even under the most ideal circumstances, this information is difficult to obtain intraoperatively. Indeed, distinguishing infiltrating tumors from the surrounding normal brain tissue (based solely on the visual appearance of the lesion) is an especially challenging task. Complete resection of infiltrating gliomas is almost impossible to accomplish because of the difficulty in recognizing tumor margins.

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