

Brain Tumor Therapy: What Lies Clearly at Hand

"But words are things, and a small drop of ink, falling like dew, upon a thought, produces that which makes thousands, perhaps millions think."

— Lord Byron (1788-1824)

"The brain is the crown jewel of creation and evolution. . . . The brain holds the greatest unexplored biological frontiers. It is the most frequent site of crippling, incurable disease. . . . Its status determines whether the humanity within us lives or dies. It yields all that we know of the world. It controls both the patient and the surgeon."

— Albert L. Rhoton, Jr, MD
in the forward to *Neurosurgery*.
2002;51:4(suppl).

"Our main business is not to see what lies dimly at a distance, but to do what lies clearly at hand."

— Thomas Carlyle (1795-1881)

The words, ideas, and information in this issue of *Cancer Control* should inspire the tens of thousands of patients who each year have the misfortune to be diagnosed with a brain tumor. The contributions represent the "best of the best" in neuro-oncology, and their words represent and reflect the rapid progress being made in our field. New frontiers are continually opening up. Brain tumors that were considered inoperable 25 years ago are now routinely removed. The outcomes in surgery are immeasurably superior with minimally invasive, stereotactic, volumetric surgery, using neuronavigation for precise surgical planning and less trauma to the brain and spinal cord. We share Dr. Rhoton's reverence for the brain, so articulately expressed in his elegant writ-

ings and masterful work. The current technology lets us focus on performing "tumor surgery" rather than "brain surgery." Radiation therapy today is also making progress with the introduction of advanced computer-driven systems that can provide local control at the margins of the tumor without injuring the brain. The advent of molecular, targeted therapy offers the promise of safer and more effective medical therapies. The FDA-approved use of temozolomide for anaplastic astrocytomas is being extended, with promising early results, to other forms of brain tumors, including low-grade gliomas, metastatic cancer, and glioblastomas. Finally, biological therapies including antiangiogenesis therapy, immunotherapy, stem cell therapy, and signal transduction inhibitors are being evaluated in phase I and phase II clinical trials. The future is ever bright. Many in the field echo the confidence of the President of the United States that a cancer cure is not a matter of "if" but "when." Given the march of progress, as illustrated in this issue, control of cancer in the brain appears inevitable. For those patients suffering from brain tumors, that time cannot be too soon. Never before has so much been handed to neuro-oncologists. As noted by Thomas Carlyle (1795-1882), we must "do what lies clearly at hand."

Dr. Stephen J. Hentschel and Dr. Raymond Sawaya present important data coming from the M. D. Ander-

son Cancer Center that clearly demonstrates the survival advantage to "maximal safe resections" of 98% or more of the tumor volume. Using modern technology in the hands of an experienced team, at a center that conducts a high volume of brain tumor surgery, the authors provide compelling evidence that maximal resections are important to maximize outcomes. These findings support the data coming from multicenter studies such as the Glioma Outcomes Project, led by Dr. E. Laws. Patients who have "gross-total resections" do better than those with subtotal resections, even when other prognostic factors are taken into account, thus dispelling the misconception that "less is more" with gliomas. Likewise, it has been the observation in the NABTT NCI-sponsored brain tumor consortium that patients treated with a variety of agents, but who have microscopic disease at the onset, show longer survival than those who have a subtotal removal. The paper by Drs. Hentschel and Sawaya on optimizing outcomes with maximal surgical resection of gliomas raises the bar for all neurosurgeons in the United States in treating patients with a brain tumor.

Dr. Michael Scholder and Dr. Peter Carmel describe the introduction, indications, techniques, outcomes, and their institutional experience with the 0.12-Tesla intraoperative MRI (the PoleStar N-10 system), which enables intraoperative MR imaging (iMRI) within

the normal operating room environment. Because the imaging is “real-time,” it eliminates the theoretical problems of other forms of intraoperative imaging that use preoperative MR studies for intraoperative navigation. The unit they have developed offers additional advantages in relation to the original iMRI used by Dr. P. Black in Boston — mainly, the costs are reduced and the lower field permits standard instrumentation to be used closer to the device. However, the higher Tesla units provide superior resolution. Whichever system is employed, as with all new technologies, the experience of the team, the institutional support, and the surgical volumes all combine to enhance the results of surgery. Neuronavigation with image guidance is now state-of-the-art at tertiary medical centers. As the authors indicate, these iMRI systems allow maximal and safe resection of the tumors. Their article is important to the field as the newer technologies are integrated into neurosurgical practice.

Dr. Ivo W. Tremont-Lukats and Dr. Mark R. Gilbert provide a superb, comprehensive review of advances in translational and molecular therapies. They describe the discovery, rationale, current clinical trials, and potential value of a wealth of new approaches proposed for the treatment of malignant brain tumors. The small molecules that target intracellular signaling pathways include inhibitors of tyrosine kinase, farnesyltransferase, cyclooxygenase, and matrix metalloprotease. These inhibitors may find their ultimate clinical value in combination with

other biological therapies as part of a “cocktail” or in combination with oral chemotherapy (eg, temozolomide). They also provide a new approach as potential radiosensitizers to enhance the effects of radiation therapy. In general, the new agents are far less toxic than standard chemotherapy, and they offer hope to patients with brain tumors as chemopreventive agents or as a means to increase the time to tumor progression once the tumor is removed completely by the surgeon. The excellent review by these authors also illustrates the critical importance of the current NCI-sponsored brain tumor consortia, NABTC and NABTT, to bridge the gap from the laboratory to the bedside.

Dr. Yang Liu, Dr. Ka-yun Ng, and Dr. Kevin O. Lillehei provide an important summary of a promising area of brain tumor therapy: using the body’s immune system to reject the tumor. This review, from the University of Colorado where much progress has been made, reflects the authors’ expertise and ability to translate advances in molecular biology towards the development of a brain tumor vaccine. A number of approaches are being explored, including the use of dendritic cells, directed cytokine delivery, gene-based immunotherapy, and reversal of tumor-induced immunosuppression. Therapeutic manipulation of the immune system holds great promise for the future treatment of patients with brain tumors.

Dr. Brian Ragel and Dr. Randy L. Jensen apply the many new approaches to one of the most chal-

lenging problems facing neuro-oncologists — the patient with a “benign” tumor that is aggressive, inoperable because of its location, or actually undergoing malignant transformation. A surgical “cure” is often not possible, but the authors are active surgical scientists who are innovating medical therapy of these tumors. The rationale, pre-clinical experience, and immunohistochemical markers (eg, MIB-1 antibody) related to aggressive meningiomas are presented. The novel systemic treatment options are reviewed, including inhibitors of angiogenesis, growth factors, growth hormones, and signal pathways. Of great interest is the use of an inhibitor of the growth hormone receptor using pegvisomant.

A major problem not only in neuro-oncology but in the entire field of oncology is that of multidrug resistance to cytotoxic therapies. Several different agents can inhibit overexpression of P-glycoprotein, a phenomenon thought to be one of the major causes of increased efflux of chemotherapy from cancer cells. Dr. Hilary Thomas and Dr. Helen Coley review the clinical development of agents that can minimize this problem, and they present intriguing early results from clinical trials of the “third-generation” agents.

Steven Brem, MD, FACS

Professor of Interdisciplinary Oncology
and Neurosurgery
University of South Florida
Program Leader, Neuro-oncology
Chief, Neurosurgery
H. Lee Moffitt Cancer Center & Research
Institute
Tampa, Florida