

Tumor NEWS



Spring 2014

A A N S / C N S S e c t i o n o n T u m o r s

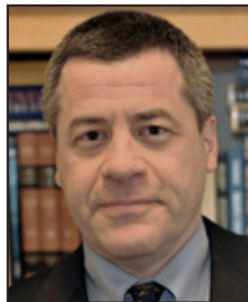
Editor: Jennifer Moliterno Gunel, MD • www.TumorSection.org • Follow us on Twitter: @Tumorsection



In This Issue...

- 1**
- From the Chair
- 3**
- Medical Neuro-Oncology
- 4**
- Tumor Section Awards
- 6**
- Clinical Trials
- 8**
- International Committee
- 9**
- Journal of Neuro-Oncology Report
- 10**
- Topic Review in Neuro-Oncology:
Isocitrate Dehydrogenase Mutant
Gliomas
- 12**
- Are We Still Finding Novel Treatments
in Nature?
An Update on Neuro-oncology and
Curcumin.

From the Chair



*Frederick G. Barker,
MD, FAANS
Chair, Section on Tumors*

Welcome to the spring 2014 Tumor Section newsletter! Section activities have continued at a brisk pace since last fall. I will start by offering thanks to Dr. Moliterno for putting together another informative newsletter issue, with many new features you will notice as you page

through.

Since the fall newsletter, the Section has held two very successful meetings. First, the Congress of Neurological Surgeons (CNS) 2013 meeting, for which the Section's activities were organized by Ian Parney, MD, PhD. A special seminar on "Novel Imaging in Brain Tumor Surgery" was the highlight of the meeting, along with the presentation of the second Abhijit Guha Award to Henry Brem, MD, FAANS,

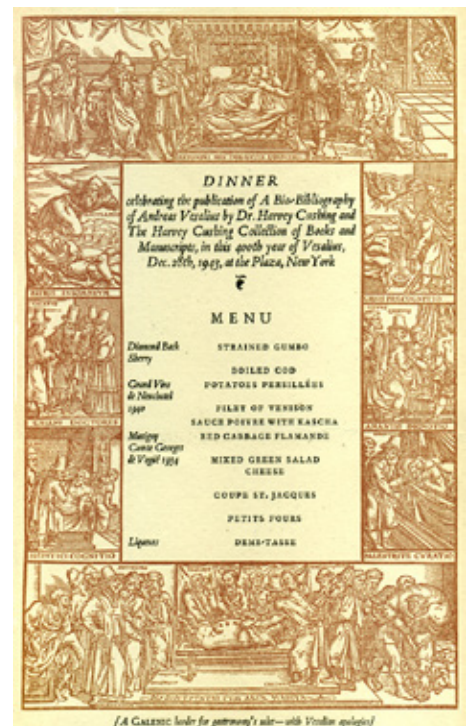
In November, many Section members traveled to Tel Aviv for a special joint meeting with the European Association of Neurosurgical Societies (EANS). The meeting was the first annual EANS meeting to focus on a single subspecialty within neurosurgery and the first joint meeting with the American Association of Neurological Surgeons (AANS) and the CNS Tumor Section. Of the 735 total participants representing 54 countries, the U.S. contingent was 100 strong — the second largest single nation attendance after the host country, Israel. Jeffrey Weinberg, MD, FAANS, and Zvi Ram, MD, represented the Tumor Section on the meeting's scientific committee, and about 30 travel fellowships were awarded to U.S. residents and fellows,

supporting travel to the meeting.

This spring the AANS will meet in San Francisco for the 82nd Annual Scientific Meeting. Dr. Moliterno has coordinated two exciting special seminars for the Section, "State of the Art Endoscopic Surgery," and "Interpreting the "New" Pathology Report: What the Tumor Surgeon Needs to Know for Clinical Applications." In addition, there will be a Young Neurosurgeons reception coordinated by Ian Dunn, MD, FAANS, featuring James Markert, MD, FAANS, as the speaker. I look forward to seeing many of you at the meeting.

The Section's website has been in need of an update, and a year-long effort by several members

continued on page 2



should finally be unveiled this spring. Fred Lang, MD, FAANS, and consultant Chas Haynes, the Executive Director of Society for Neuro-Oncology (SNO), have coordinated the construction of the new website, which will be taken over by Information Technology co-chairs Chris McPherson, MD, FAANS, and Dr. Weinberg. Look for information about the new website soon.

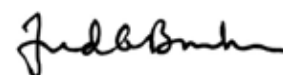
This year marks the 500th anniversary of the birth of Andreas Vesalius, the pioneering anatomist of the 16th century and favorite of Harvey Cushing. Cushing celebrated Vesalius' quartercentenary in a 1914 article, and published his landmark full scale bio-bibliography posthumously in 1943. Accompanying this article is a scan taken from a print struck from the original woodblocks that illustrated Vesalius' 1543 *De corporis humani fabrica*, believed to have been illustrated by Titian's pupil Jan van Calcar. The woodblocks were printed for the last time shortly before they were destroyed in World War II. Look for this print and others on the new website, and much more.

Finally, many members will be following closely as a controversy unfolds over the use of bevacizumab as first line therapy in glioblastoma. The Feb. 20, 2014, issue of the *New England Journal of Medicine* contains the primary reports of two large randomized clinical trials comparing initial glioblastoma treatment with or without bevacizumab, in addition to radiotherapy with concomitant temozolomide (RTOG 0825, a primarily North American trial, and the AVAglio trial, primarily conducted in Europe). Both trials showed no prolongation of survival with bevacizumab; both showed substantially longer progression-free survival with bevacizumab, although the RTOG investigators did not declare the difference statistically significant because of an unusually ambitious pre-specified P value for this endpoint. The crux of the issue, then, would seem to be patients' quality of life with or without bevacizumab, and here the trials surprisingly reported diametrically opposed results. The North American trial found worse neurocognitive and quality of life measures in patients receiving bevacizumab, while the European AVAglio trial

investigators reported superior health-related quality of life, longer maintenance of independent performance status and lower steroid requirements in the bevacizumab-treated group.

The solution to this apparent contradiction remains to be discovered. With the exception of one exploratory endpoint in the AVAglio study (time to deterioration by KPS), the quality of life and performance status results in both trials were recorded only in a minority of living patients about a year or so after treatment initiation. By design, patients with progressive disease were not assessed for these endpoints. Different patterns of patient dropout (perhaps because of differences in trial design and/or conduct) could possibly hold the key to the divergent results. The unfolding of this story over the next year or so is bound to influence the drug's potential approval in many national markets, and will be of intense interest to all neurosurgical oncologists.

Additional important results from a completed clinical trial are also expected later this spring, as the RTOG reports updated results from trial 9802. This randomized trial compared external beam radiation alone versus radiation plus subsequent PCV chemotherapy in patients with "high-risk" low-grade gliomas. New reports suggest the updated survival results from the trial now show a survival advantage in the patients treated with PCV chemotherapy; the trial had previously been reported to be negative for the survival endpoint. Subgroup analyses of this trial by molecular stratification (1p/19q, IDH) are anxiously awaited. 2014 should be an interesting year!



Fred Barker, MD, FAANS



Susan M. Chang, MD

The Radiation Therapy Oncology Group (RTOG), a clinical trials organization funded by the National Cancer Institute (NCI), part of NIH, and NCI reported on the long-term follow-up analysis of RTOG 9802 showing significantly longer survival for adult patients with newly diagnosed low grade glioma (LGG) who received chemotherapy in addition to radiation therapy. Between October 1998 and June 2002, 251 LGG patients were enrolled who were defined as “high-risk” because they were 40 years of age or older or had a less than complete surgical removal of their tumor if they were less than 40 years of age. After surgery, all patients started treatment with radiation therapy. Following completion of radiation therapy, patients were randomized 1:1 to either surveillance or six cycles of chemotherapy. Patients receiving chemotherapy were treated with three drugs: procarbazine (P); CCNU (C), which generically is known as lomustine; and vincristine (V). This chemotherapy, termed PCV, was given over 21 days and repeated every eight weeks for a total of six cycles.

Preliminary reports of this study were published in 2012 but at the time of that report only 35% of patients had died and the median follow up of patients still alive was 5.9 years.¹ With a median follow-up after initial enrollment of almost 12 years, a significant improvement in overall survival was noted for study participants who received PCV chemotherapy plus radiation therapy (13.3 years median survival time) compared to those receiving radiation therapy alone (7.8 years median survival time), a difference of 5.5 years. Analysis of clinical outcome based upon the molecular and genetic characteristics of the tumors (including mutations in the isocitrate dehydrogenase gene, and 1p19q codeletion status) is ongoing and should allow for the identification of patients who will, and who will not, benefit from chemotherapy, as has been shown for anaplastic oligodendroglioma patients.^{2,3} Full details from the analysis of RTOG 9802 are to be presented at scientific meetings in 2014 and in a peer-reviewed publication.

This report is practice changing and patients who are deemed appropriate candidates for radiation therapy should be encouraged to receive chemotherapy as well, taking into account both the potential benefits and risks. Ongoing clinical trials in LGG are assessing the role of temodar either as a single agent or in combination with radiation therapy.

References

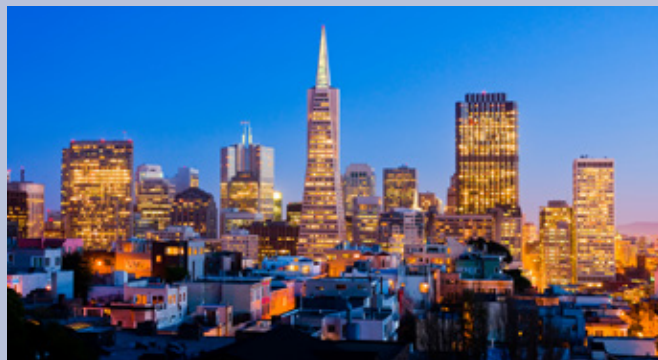
1. Shaw EG et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. *J Clin Oncol.* 2012 Sep 1;30(25):3065-70
2. van den Bent MJ et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013 Jan 20;31(3):344-50
3. Cairncross G et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol.* 2013 Jan 20;31(3):337-43

2014 AANS Meeting Preview

Jennifer Moliterno Gunel, MD

The American Association of Neurological Surgeons (AANS)/ Congress of Neurological Surgeons (CNS) Section on Tumors has several exciting events planned for the upcoming 2014 AANS Annual Scientific Meeting in San Francisco. We will have two special seminars — “State of the Art Endoscopic Surgery” will take place on Tuesday, April 8, 2014 (2:00-3:30 p.m.) and feature experts in the discipline describing the use of the endoscope for the resection of tumors located throughout the central nervous system, as well as a discussion of complication avoidance and reconstruction. Our second seminar, “Interpreting the “New” Pathology Report: What the Tumor Surgeon Needs to Know for Clinical Applications,” will be held on Wednesday, April 9, 2014 (2:00-3:30 p.m.), and will focus on understanding the modern day pathology report, specifically discussing the clinical utility of commonly identified molecular data for various adult and pediatric tumors. Following each session, the presentation of the highest scoring Original Science abstracts will take place. As part of the session on April 9th, we will host a face-off between experts in the field discussing the management of multiple metastases.

We look forward to seeing you in San Francisco!



Tumor Section Awards

Manish K. Aghi, MD, PhD, FAANS

The AANS/CNS Section on Tumors' Awards Committee will recognize 10 award winners and one awarded lectureship at the 2014 American Association of Neurological Surgeons (AANS) Annual Scientific Meeting in April. Most of the awards are limited to Section members and provide an additional incentive for membership. The award winners for the AANS Annual Scientific Meeting will be recognized at the Section's Plenary Session on Monday, April 7, 2014, from 2-5:30 p.m. The awards program encourages submission of the highest quality work in neuro-oncology.

Synthes Skull Base Award

The Synthes Skull Base Award is given to an attending neurosurgeon, resident or fellow in the Section who submits the best abstract related to skull base surgery. This award is given at the annual meetings of the AANS and CNS. Franco DeMonte, MD, chair of the Skull Base Committee, was largely responsible for obtaining this award through a generous contribution from the Synthes Corporation. The winner for the 2013 CNS meeting was Hideyuki Kano, MD, PhD, of the University of Pittsburgh for his presentation, "Chondrosarcoma Radiosurgery: Report of the North American Gamma Knife Consortium." The winner for the 2014 AANS Annual Scientific Meeting will be Arman Jahangiri, BS, of University of California, San Francisco, for his presentation, "Incidence of Headache as a Presenting Complaint in Over 1000 Patients with Sellar Lesions and Factors Predicting Postoperative Improvement." The award includes a \$1,000 honorarium.



Hideyuki Kano, MD, PhD, receives the Synthes Skull Base Award from Frederick G. Barker, MD, FAANS.

Preuss Award

The Preuss Award, sponsored by the Preuss Foundation, is given at each of the AANS and CNS annual meetings to a young scientist investigating brain tumors who is within 10 years of training and has submitted the best basic science research paper. The 2013 CNS winner was Peter Fecci, MD, PhD, of the Massachusetts General Hospital for his presentation, "Of Mice and Men: Matched Observations of Lymphopenia, Splenic Retraction, and the Bone Marrow as Harbor for Lost T-cells in Mice and Patients with Glioblastoma." The winner for the 2014 AANS Annual Scientific Meeting will be Loyola Veronique Gressot, MD, of Baylor College of Medicine, for her presentation, "Signal Transducer and Activator of Transcription 5b Promotes Malignant Progression In Glioma." This award has a \$1,000 honorarium.

National Brain Tumor Society Mahaley Award

The National Brain Tumor Society Mahaley Award is given at each of the AANS and CNS annual meetings to a neurosurgery resident, fellow or attending physician who submits the best clinical study

in neuro-oncology. At the 2013 CNS meeting the award was presented to Russell R. Lonser, MD, for his paper, "Natural History of Central Nervous System Hemangioblastomas in von Hippel-Lindau Disease." The winner for the 2014 AANS Annual Scientific Meeting will be John H. Sampson, MD, PhD, of Duke University, for his presentation, "Tetanus toxoid conditioning enhances migration and efficacy of dendritic cell vaccines in patients with glioblastoma." The award carries a \$1,000 honorarium.



Russell R. Lonser, MD, accepts the National Brain Tumor Foundation Mahaley Award from Frederick G. Barker, MD, FAANS.

Integra Foundation Award

The Integra Foundation Award, sponsored by the Integra Foundation, is given at each of the AANS and CNS annual meetings for the best research or clinical paper submitted investigating benign brain, spinal or peripheral nerve tumors. At the 2013 CNS meeting the winner was Arman Jahangiri, BS, of University of California, San Francisco, for his presentation, "Rate and Time Course of Improvement in Endocrine Function After Over 1000 Pituitary Operations." The winner for the 2014 AANS Annual Scientific Meeting will be Jason P. Sheehan, MD, PhD, FAANS, of University of Virginia, for his presentation, "Gamma Knife Radiosurgery for Sellar and Parasellar Meningiomas: A Multicenter Study of 763 Patients." The award carries a monetary honorarium of \$1,000.



Arman Jahangiri, BS, right, accepts the Integra Foundation Award from Frederick G. Barker, MD, FAANS.

Springer Journal of Neuro-Oncology Award

The *Journal of Neuro-Oncology* Award is sponsored by Springer Publishers and is presented at both the annual AANS and CNS annual meetings to a highly ranked abstract in either clinical or basic science as related to neuro-oncology. The 2013 CNS recipient was Jin-song Wu, MD, PhD, of Huashan Hospital for the paper entitled, "3.0T iMRI Guided Resection in Cerebral Glioma Surgery: Interim Analysis of a Prospective, Randomized, Triple-blind, Parallel-Controlled Trial." The winner for the 2014 AANS Annual Scientific Meeting will be Manish K. Aghi, MD, PhD, FAANS, of the University of California, San Francisco, for the presentation, "Replicating



Jin-Song Wu, MD, PhD, right, accepts the Journal of Neuro-Oncology Award from Frederick G. Barker, MD, FAANS.

Retrovirus Toca-511 Delivered using Convection-Enhanced Real-Time MRI Guidance for Recurrent Glioblastoma.” A \$500 award and a framed certificate are given to the winner.

Stryker Neuro-Oncology Award

The Stryker Neuro-Oncology Award is given to a high-ranking brain tumor clinical or basic science abstract submitted by a resident or medical student. The award is presented at the CNS and AANS annual meetings, and the senior author of the paper must be a member of the AANS/CNS Section on Tumors. The 2013 CNS recipient was Ranjith Babu, MS, of Duke University for the paper, “Spinal Cord Astrocytomas: A Modern 20-year Experience at a Single Institution.” The winner for the 2014 AANS Annual Scientific Meeting will be Javier Figueroa, BS, of MD Anderson, for the paper, “Mesenchymal Stem Cell Exosomes Enhance Glioma Stem Cell Viability and Stemness via Delivery of MicroRNA.” A monetary component of \$1,000 is included with an award certificate.



Ranjith Babu, MS, receives the Stryker Neuro-Oncology Award from Frederick G. Barker, MD, FAANS.

Leksell Radiosurgery Award

This award, presented at each AANS meeting, starting in 2009, is for the best paper on stereotactic radiosurgery related to brain tumors. The award comes with a monetary component of \$2,000. At the 2013 AANS Annual Scientific Meeting, the award was given to Hideyuki Kano, MD, PhD, from University of Pittsburgh for his presentation entitled, “The Role of Stereotactic Radiosurgery for Intracranial Hemangioblastomas: An International Multicenter Study.” At the 2014 AANS Annual Scientific Meeting, the award will be given to Isabelle M. Germano, MD, of Mount Sinai Hospital, for her presentation, “Clinical Outcome and Risk of Spine Deformity and Vertebral Compression Fracture after Spine Radiosurgery.”

Brainlab Community Neurosurgery Award

The Brainlab Community Neurosurgery Award is awarded at the annual meetings of the AANS and CNS. This award is given to a neurosurgeon practicing in a nonacademic or international setting with the best abstract related to central nervous system tumors. Previous AANS/CNS Section on Tumors chairs Michael McDermott, MD, FAANS; and Ronald Warnick, MD, FAANS, were instrumental in securing this award given through the generosity of Brainlab. No abstract was selected for this award at the 2013 CNS meeting. At the 2014 AANS Annual Scientific Meeting, the award will be given to Jan Coburger, MD, from the University of Ulm in Germany, for his presentation, “5-Aminolevulinic Acid Fluorescence Exceeds Gd-DTPA Enhanced Intraoperative MRI in Tumor Detection at the Border of Glioblastoma Multiforme: A Prospective Study based on a Histopathological Assessment.” The award carries a \$1,000 honorarium.

American Brain Tumor Association Young Investigator Award

Sponsored by the American Brain Tumor Association, the Young Investigator Award is given at each AANS and CNS annual meeting to a young faculty member involved in neuro-oncology research who has demonstrated outstanding potential for future basic science research. The applicant must have been out of training for less than six years. No abstract was selected for this award at the 2013 CNS meeting. At the 2014 AANS Annual Scientific Meeting, the award will be given to Eric M. Thompson, MD, of The Hospital for Sick Children and University of Toronto, for his presentation, “The Clinical Importance of Extent of Resection in Medulloblastoma is Dependent on Molecular Subgroup.” A \$2,000 honorarium accompanied this award.

Ronald L. Bittner Award

The Ronald Bittner Award is endowed by Mrs. E. Laurie Bittner in memory of her husband, Ronald L. Bittner. It is awarded to the Best Abstract Paper submitted to the AANS Annual Scientific Meeting on Brain Tumor Research by a resident or junior faculty member. This award includes a \$1,000 honorarium. At the 2013 AANS Annual Scientific Meeting, the award was given to Orin Bloch, MD, of University of California, San Francisco, (UCSF) for his presentation, “Glioma-Induced Immunosuppression Shortens Progression-Free Survival in a Trial of Immunotherapy for Glioblastoma.” At the 2014 AANS Annual Scientific Meeting, the award will be given to Shawn Hervey-Jumper, MD, of UCSF, for his presentation, “Awake Craniotomy to Maximize Glioma Resection: Methods and Technical Nuances with 561 Patients.”

Bittner Lecture

In addition to the Ronald Bittner Award, the Bittner Family Foundation sponsors an annual Bittner Lectureship awarded by the AANS at its Annual Scientific Meeting. The lectureship is awarded to an established investigator, to be presented during the main scientific program component of the AANS Annual Scientific Meeting. Selection of the Bittner Lecturer is made by the Senior Scientific Program Committee.. At the 2013 AANS Annual Scientific Meeting, the Bittner Lecture was delivered by Nino Chiocca, MD, PhD, FANNS of Brigham and Women’s Hospital. The Bittner Lecturer for the 2014 AANS Annual Scientific Meeting is Frederick F. Lang Jr., MD, FAANS.

The Abhijit Guha Award

The Abhijit Guha Award and Lecture are jointly sponsored by the Section on Tumors and the Society for Neuro-Oncology (SNO) and is given annually alternating between the SNO and Section meetings. The first annual award was given to James Rutka, MD, PhD, FAANS at the SNO meeting in 2012, and the second award was given to Henry Brem, MD, FAANS, at the 2013 CNS meeting. The 2014 award will be given at the SNO meeting in November, with the winner to be determined later this year.

The AANS/CNS Section on Tumors would like to thank the award sponsors for helping to encourage submission of the highest quality work in neuro-oncology. Congratulations to the 2014 AANS Annual Scientific Meeting award winners.

Each issue of the Tumor Section Newsletter will feature a more in-depth look into two clinical trials; one sponsored by the Alliance for Clinical Trials in Oncology and the other by the Radiation Therapy Oncology Group. The focus will be on those trials that may be of particular interest to neurosurgeons.

Natural History of Post-Operative Cognitive Function, Quality of Life and Seizure Control with Supratentorial Low Risk Grade II Glioma

Daniel Cahill, MD, PhD; and Michael Vogelbaum, MD, PhD

The Radiation Therapy Oncology Group (RTOG) is a National Cancer Institute (NCI)-funded cancer clinical cooperative group with eight brain tumor clinical trials currently open for recruitment (<http://www.rtog.org/ClinicalTrials/ProtocolTable.aspx>). As an important organizational note, in 2014 the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG) will progress toward unification as the cancer clinical cooperative group to be known as “NRG Oncology.” The three legacy groups have continued to carry out NCI-supported trials as independent but collaborative entities as planning for integration was underway in 2013. In the second quarter of 2014, the new cooperative group’s federal research activities will transition to management through the NRG Oncology Operations Center.

Here, we highlight one study for low-grade glioma (LGG) patients, RTOG 0925, which is an observational study of the natural history of postoperative cognitive function, quality of life, and seizure control in patients with supratentorial low-risk LGG. The protocol notes, “Optimal therapy for patients with low-risk, supratentorial grade II glioma remains a highly controversial issue in the neuro-oncology community. Recent phase II data from RTOG 9802 show that, although the two-year and five-year overall survival (OS) rates in low- (99 percent and 93 percent) versus high-risk (87 percent and 66 percent) LGG were significantly different ($P < 0.0001$), the progression-free survival (PFS) was not (82 percent and 48 percent vs. 73 percent and 50 percent, with $P = 0.13$) (Shaw 2008). Because none of the current treatment modalities have been shown to improve OS (van den Bent 2005; Shaw 2008) observation is usually recommended in this “low-risk” population, even with this high rate of progression over time. To better assess the clinical impact and meaning of tumor progression and whether observation is a reasonable strategy for low-risk LGG, this phase II trial will evaluate neurocognitive function (NCF), quality-of-life (QOL), and seizure control over time and after tumor progression in patients undergoing observation alone after newly diagnosed LGG. This study seeks to compare NCF, QOL, and seizure control over time in untreated patients who have radiographic progression versus no evidence of radiographic disease progression.”

This is a notable trial due to the fact that no therapeutic

intervention is planned for enrolled patients, however, it holds the potential to rigorously establish important baseline clinical outcome endpoints for patients with these tumors. This data will be particularly significant for the field as we enter the era of targeted therapeutics for LGGs (ie. IDH1-mutant directed agents). The key contribution of neurosurgeons for patient enrollment in this trial comes with the identification of LGG patients who may safely enter a period of observation after initial surgical resection establishes the diagnosis.

Report from the Alliance for Clinical Trials in Oncology

J. Bradley Elder, MD.

The previous report highlighted a surgical trial for recurrent glioblastoma entitled: A Phase II Randomized Trial Comparing the Efficacy of Heat Shock Protein-Peptide Complex-96 (HSPPC-96) (NSC #725085, ALLIANCE IND # 15380) Vaccine Given With Bevacizumab Versus Bevacizumab Alone in the Treatment of Surgically Resectable Recurrent Glioblastoma Multiforme (GBM). This trial remains open and accruing patients, and the PI is Andrew T. Parsa, MD, PhD, FAANS.

The trial highlighted in this report focuses on another common entity in neurosurgical oncology — brain metastases. Specifically, the trial highlighted in this report focuses on postoperative adjuvant radiation for patients who have undergone surgery for brain metastasis.

Clinical Trial: A Phase III Trial of Post-Surgical Stereotactic Radiosurgery (SRS) Compared With Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease NCT01372774 (Alliance ID: N017C)

This clinical trial includes patients with one to four brain metastases who undergo surgery for one of the metastases. Any unresected lesions must measure no more than 3 cm. After stratification based on age, number of lesions, extent of extracranial disease and histology, patients will be randomized to two treatment arms:

Arm 1: Patients receive WBRT daily, five days per week for three weeks
Arm 2: Patients receive SRS using gamma knife or linear accelerator

Primary objectives:

- Ascertain whether there is improved overall survival in patients who receive SRS to compare to patients who receive WBRT.

- Determine if patients who receive SRS demonstrate less neurocognitive progression at six months post-radiation compared to patients who receive WBRT.

Secondary objectives include comparing patients who receive SRS to the surgical bed to those who receive WBRT for:

- Improved quality-of-life
- Time to central nervous system (CNS) failure of disease control
- Duration of functional independence
- Long-term neurocognitive status
- Adverse events
- Time to local recurrence and local recurrence rates at six months
- Evaluate for differences in CNS failure patterns (local, distant, leptomeningeal)

Additional Exploratory outcomes to be measured include:

- Use MRI to evaluate radiation changes in the limbic system that may correlate with neurotoxicity
- Determine whether any of the following factors are predictors of neurocognitive decline or neuroprotection:
 - Apo E genotyping (e.g. Apo E2, Apo E3)
 - inflammatory markers (e.g. IL-1, TNF- α)
 - Oxidative stress biomarkers
 - Hormone and growth factors (e.g. cortisol, progesterone, IGF-1, neuronal growth factor)

This trial is open at 81 centers in the United States and Canada. The PI is Paul D. Brown, MD, at M.D. Anderson Cancer Center. Further information regarding this clinical trial can be obtained from allianceforclinicaltrialsinoncology.org or clinicaltrials.gov.

2013 Congress of Neurological Surgeons Highlights

Ian Parney, MD, PhD

The AANS/CNS Section on Tumors once again featured prominently at the 2013 CNS meeting in San Francisco this past October. An excellent Original Science oral presentation session was held on Oct. 21, 2013. A wide variety of topics in neurosurgical oncology were discussed, including the role of intra-operative MRI in the management of newly diagnosed malignant gliomas, the natural history of hemangioblastomas, the timeline for endocrine improvement after pituitary surgery and continuous dynamic intra-operative corticospinal tract monitoring. This was followed by poster presentations in the Section on Tumors Neurosurgical Forum. On Oct. 22, 2013, the Section on Tumors was honored to be able to present the Dr. Ab Guha Award to Henry Brem, MD, FAANS, of Johns Hopkins University. Dr. Brem's Guha Award Lecture was a tour de force recap of his accomplishments as a neuro-oncological neurosurgeon and clinician-scientist. His lecture was followed by a seminar in Novel Imaging in Brain Tumor Surgery featuring discussion of metabolic imaging (Linda Liau, MD, PhD, FAANS), MR spectroscopy (Sarah Nelson, MD), a randomized controlled trial of intra-operative MRI in malignant gliomas (Jinsong Wu, MD), and MRI-guided focused ultrasound-mediated nanoparticle delivery to brain tumors (James Rutka, MD, PhD, FAANS).

Tumor Section Membership Committee

Randy Jensen, MD, PhD, FAANS

Membership in the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors currently includes 2,227 members with a large resident and fellow contingent, and growing international group as part of our organization. We have approved membership applications for more than thirty new members since last fall's CNS meeting. In November, we partnered with the European Association of Neurological Surgeons (EANS) to co-host their annual meeting in Tel Aviv, Israel. This allowed many of the members of the EANS to renew old and start new friendships with Tumor Section attendees. This should also increase our international membership numbers. As has been our tradition, we will continue to collaborate with the Young Neurosurgeons Committee (YNC) to host receptions at each of the annual meetings of the AANS and CNS. We expect each of these events to bring new opportunities for collaboration, education and social interaction with residents, fellows, younger neurosurgeons, and our many colleagues from around the world with interest in neurosurgical oncology. We have reached out to the Section on Women in Neurosurgery (WINS) leadership and plan to invite all of their members interested in tumor work that are not already Section members to join our group.

International Committee



Isabelle M. Germano, MD, FAANS

The International Committee had a very active past six months. The American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors joined the European Association of Neurological Societies (EANS) Annual Meeting in Tel Aviv, Nov. 11-14, 2013. The meeting, co-chaired by Shlomi Constantini, MD, MSc, and Zvi Ram, MD, had a superb attendance with more than 900 participants from around the world. Several members of AANS/CNS Section on Tumors attended the meeting, including Executive Committee members Fred Barker, MD, FAANS; Manish K. Aghi, MD, FAANS; William T. Couldwell, MD, PhD, FAANS; Isabelle Germano, MD, FAANS; Roberta Glick, MD, FAANS; Randy Jensen, MD, PhD, FAANS; Michael McDermott, MD, FAANS; and Mark Rosenblum, MD, FAANS. The numerous other meetings and advances that occurred over the past six months and planned for the next quarter, are highlighted below. The contributions are kindly provided by the International Committee Members.

Japan

Fumio Yamaguchi, MD, PhD

The 72nd Annual meeting of the Japan Neurosurgical Society was held Oct. 16-18, 2013, at Pacifico Yokohama. The main theme was “The Challenges to Evolving Society, the Unknown and the Unexplored.” James I. Ausman, MD, PhD, FAANS(L), from University of California, Los Angeles, presented the special lecture “How to Refute Inaccurate Media and Government Reports in Medicine.” The lecture was informative for Japanese doctors due to the many false reports from the media and government currently in Japan.

The Prospective Multi-Institute Study of Gamma Knife Radiosurgery Alone Treatment for Patients with 1-10 Brain Metastases (JLGK0901) has been conducted by the Japan Leksell Gamma Knife Society and was accepted for the publication in the LANCET Oncology. This study showed equal benefit of GKS as sole treatment for patients with 5-10 brain metastases compared with those with 2-4 in terms of OS.

Future meetings:

- The 23rd Conference on Neurosurgical Techniques and Tools (CNTT 2013). Apr. 18-19, 2014, Fukuoka, Japan — <http://cntt2014.umin.ne.jp/>
- The 34th Annual Meeting of the Japanese Congress of Neurological Surgeons. May 16-18, 2014, Osaka, Japan — <http://www.jcns2014.jp/>
- The 32nd Annual Meeting of the Japan Society of Brain Tumor Pathology. May 23-24, 2014, Tokushima, Japan — <http://btp32.umin.jp/index.html>
- The 23rd Annual Meeting of the Japanese Society of Stereotactic Radiosurgery. June 27, 2014, Osaka, Japan — <http://jssr2014.umin.ne.jp/>
- The 10th Japan Photodynamic Neurosurgical Society. June 28-29, 2014, Hamamatsu, Shizuoka, Japan — <http://jpns2014.umin.jp/>
- The 19th annual meeting of the Japanese Congress for Brain Tumor Surgery. Sep. 12-13, 2014, Tokyo, Japan.
- The 73rd Annual Meeting of the Japan Neurosurgical Society. Oct. 9-11, 2014, Tokyo, Japan — <http://jns2014.umin.jp/>
- 32nd Annual Meeting of the Japan Society for Neuro-Oncology. Nov. 30-Dec. 2, 2014, Chiba, Japan — <http://jsno32.umin.jp/>

Italy

Francesco DiMeco, MD

Future meetings:

- The 11th Congress of the European Association of Neuro-Oncology will be held in Turin, Italy, Oct. 9-12, 2014. The meeting will cover several topics of the neuro-oncology field including biology and pathology, imaging, surgery, radiotherapy, chemotherapy, targeted therapies, supportive/palliative care and quality of life. The deadline for abstract

submission is March 23, 2014.

- The 63rd Congress of the Italian Neurosurgical Society (SINCh) will be held in Vicenza, Sept. 25-27, 2014.

Argentina

Alejandra T Rabadan, MD, PhD

Highlights

The Section of Neuro-oncology of the Argentine Society of Cancerology continues the organization and participation in Post-Graduated Courses and Meetings in the region.

The International Symposium “Controversies in Skull Base Meningiomas,” sponsored by the Skull Base Section of the Latin American Federation of Neurosurgical Societies (FLANC), the Section of Neurooncology (SAC) and the Argentine Association of Neurosurgery (AANC) was held in Buenos Aires on Oct. 24, 2013.

We support two tumor registries in the region: first is the South American Glioma Network (SAGN) with leadership from Ricardo Ramina, MD, of Brazil and the second is the Argentine Inter-hospitals Neuro-oncological Registry (RAHON) with leadership from M. Garcia Lombardi, MD, et al — more information can be found at www.rahon.org.

Future meetings

- FLANC is organizing CLAN 2014 in Isla Margarita, Venezuela, May 10-17, 2014.
- The Neuro-oncological Section organized the Symposium “Current Trends in Gliomas”, Aug. 7-8, 2014, in Buenos Aires, as part of the Biennial Meeting of the Argentine Society of Cancerology.
- “Brain Tumor Awareness Day” will be held on Oct. 28 2014, as part of IBTA. We appreciate the support of Denis Strangman, MD.

Journal of Neuro-Oncology Report

Linda Liau, MD, PhD, FAANS

Spring 2014

The *Journal of Neuro-Oncology* publishes 15 issues a year (including both regular and special issues), with an impact factor of **3.115**.

There will be four upcoming special issues of *the Journal of Neuro-Oncology* for 2014:

- **Guidelines for Recurrent/Progressive Glioblastoma** (Guest Editor: Jeffrey J. Olson, MD FAANS)
- **Special Topics in Pituitary Tumors** (Guest Editors: Marvin Bergsneider, MD, FAANS; Anthony Heany, MD; and John Lee, MD)
- **AANS/CNS Tumor Section 30th Anniversary Special Issue** (Guest Editors: Tony D’Ambrosio, MD; and Fred Barker, MD, FAANS)
- **Guidelines for Low-Grade Gliomas** (Guest Editor: Jeffrey J. Olson, MD, FAANS)

We would like to thank and congratulate our previous Associate Editors for their outstanding contributions to the *Journal of Neuro-Oncology* over the past years: James Rutka, MD, PhD, FAANS (now Editor-in-Chief of the *Journal of Neurosurgery*) and Patrick Wen, MD (now the Editor-in-Chief of *Neuro-Oncology*). Jeffrey Raizer, MD has taken Dr. Wen’s place as the Associate Editor for medical oncology, and Jeffrey Bruce, MD, FAAS, will remain as Associate Editor for surgical neuro-oncology.

We are very pleased to acknowledge and thank the following top-10 reviewers for their hard work and support of *Journal of Neuro-Oncology* by their review of articles for the journal:

Michael Sughrue, MD
Jonathan Sherman, MD, FAANS
Marc Chamberlain, MD
Gordon Li, MD
Nader Pouratian, MD, PhD
Michael Lim, MD, FAANS
Mark Linskey, MD, FAANS
Benjamin Ellingson, PhD
Gabriel Zada, MD
Eiji Kohmura, MD

Topic Review in Neuro-Oncology: Isocitrate Dehydrogenase Mutant Gliomas

Kimberly A Foster, MD; Christopher P. Deibert, MD; and Nduka M. Amankulor, MD

Malignant glioma is a genetically heterogeneous disease. Effective treatment of these tumors may require molecularly targeted therapies aimed at specific genetic alterations. The recent discovery of new driver mutations in cellular metabolism genes in low-grade gliomas and secondary glioblastoma offer potential avenues for molecular diagnostic tools and drug discovery.¹ Genome-wide sequencing of human glioma has revealed somatic mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2).^{2,3} These enzymes normally catalyze an oxidative reaction in which isocitrate is converted to α -ketoglutarate (α -KG). Point mutations in the IDH1/2 genes enables unique gain of enzymatic function that permits the conversion of α -KG to D-2-hydroxyglutarate (D-2HG).⁴ Accumulation of D-2HG or reduced α -KG levels are thought to contribute to oncogenesis in glioma.

IDH mutations in glioma are the hallmark of a distinct subset of tumors and studies suggest that IDH mutant gliomas characterize a group of tumors with molecular origins that are different from IDH wild-type tumors. IDH1 and IDH2 mutations are found more commonly in 70-80 percent of grade II and III glioma and ~90 percent of secondary glioblastoma, suggesting these mutations early drivers of tumorigenesis in IDH mutant gliomas.⁵ Common genetic alterations found in primary glioblastoma, including EGFR amplification, are less likely to occur in IDH mutant tumors, while IDH mutations often occur in association with TP53 mutations, 1p/19q co-deletions and MGMT promoter methylation. Patients with mutant IDH tumors have a different clinical course and natural history than those with IDH wild-type tumors, and tend to be younger, with two- to four-fold greater median survival.^{3,6}

Oncogenesis in IDH mutant gliomas

While the IDH enzyme family includes multiple isoforms, IDH1 and IDH2 mutations are currently implicated in glioma tumorigenesis. IDH1 protein functions in the peroxisome and cytoplasm, whereas IDH2 functions in the mitochondria as part of the citric-acid cycle (CAC). Wild-type IDH1 participates in lipid and glucose metabolism, mediates cellular metabolism (lipogenesis) in the hypoxic state and protects against radiation and reactive oxygen species (ROS),⁷ while IDH2 also functions to protect against oxidative stress and hypoxia by maintaining citrate levels. Preliminary studies of mutant IDH suggest that the loss of the enzyme's ability to convert isocitrate to α -KG is central to tumorigenesis.⁸ Further evaluation demonstrated that the mutations do not cause a loss of function, but, instead, neomorphic activity that allows for the production and accumulation of the oncometabolite D-2HG.⁴

The role of IDH mutations in the pathogenesis of human glioma has not been fully elucidated and multiple potential mechanisms exist. The most salient hypothesis is that overproduction of the oncometabolite D-2HG alters normal cellular differentiation

programs in IDH mutant cells. Dang et al. showed that IDH mutations result in a two- to three-fold increase in the levels of D-2HG compared to tumors with wild-type IDH or normal tissue.⁴ Evidence suggests that D-2HG shifts cells towards malignancy via alteration of important metabolic proteins and might also influence epigenetic modifications in glioma cells. D-2HG can compete with α -KG and bind to α -KG-dependent enzymes, many of which play a role in cellular genomic stability and differentiation. While the function of specific α -KG-dependent enzymes is beyond the scope of this review, their inhibition can lead to histone modifications, DNA hypermethylation, angiogenesis, and other steps critical to oncogenesis.^{9,10} Though our understanding of the role of IDH1/2 mutations in glioma formation has increased significantly over the last few years, the exact mechanisms by which IDH enzymes alter cancer metabolism needs further exploration.¹

Prognostic value of IDH1/2 mutations in glioma

IDH mutations are enriched in diffuse astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III) and secondary glioblastoma, and have also been documented in other glioma subtypes, including oligodendroglioma, oligoastrocytoma, ganglioglioma, and adult supratentorial primitive neuroectodermal tumor (PNET).¹¹ IDH mutations likely precede other mutations, and have been associated with the proneural subtype of astrocytoma, DNA hypermethylation, CpG island methylator (CIMP) phenotype and other features.¹²

These mutations have been established as a predictive biomarker in several cancers. In glioma, IDH1 mutation is associated with a better prognosis than non-IDH mutant gliomas.¹³ Chesnelong et al. suggest that downregulation of citric-acid cycle enzymes may actually give IDH mutant gliomas a *limited* glycolytic capacity and may explain the more indolent course of such tumors.¹⁴ In a multivariate analysis controlling for tumor grade, age, MGMT promoter methylation status and genomic profile, IDH1 mutations emerged as an independent favorable prognostic marker.¹³ Another study of uniformly treated anaplastic oligodendroglioma patients found that the presence of IDH1 mutations carried significant prognostic significance for overall survival.¹⁵ Two recent meta-analyses of IDH1 mutations in glioma have corroborated prognostic value of IDH mutations.^{16,17}

Other genetic abnormalities and mutations occurring in concert with IDH mutations may also allow for the stratification and prognostication of glioma. A recent meta-analysis of nearly 2,200 patients with WHO grade II-IV glioma found an association between IDH mutations and MGMT promoter methylation, 1p/19q codeletion and p53 mutations, but not EGFR amplification. While IDH mutation status alone was predictive of

overall survival and progression-free rate in grade II and grade III tumors, the combination of IDH mutation, 1p/19q codeletion and PTEN deletion may indicate a particular subtype of diffuse glioma with favorable prognosis. Of importance to neurosurgeons, a recent retrospective study showed that resection of maximal tumor volume (enhancing + non-enhancing tumor) may confer particular survival advantages for IDH mutant anaplastic gliomas and GBMs compared to non-mutant tumors. Thus, IDH mutant gliomas may benefit from tailored therapeutic strategies that place greater emphasis on extent of surgical resection and continued use of alkylating chemotherapy.

Detection of IDH mutations in glioma

Detection of IDH mutations has become standard clinical practice.¹⁸ The two main laboratory methods for the evaluation of IDH mutation include genotyping and immunohistochemistry (IHC). Genotyping, including allele-specific PCR techniques, is performed on the DNA isolated from brain-tissue samples, whereas IHC utilizes an antibody that specifically targets the mutated form(s) of IDH. Both techniques are widely available and allow glioma tissue to be distinguished from benign CNS lesions, reactive glial processes and other CNS tumor types, and can help classify primary and secondary glioblastoma. Moreover, D-2HG, serves an important biomarker that can be exploited by imaging techniques, and may be important in diagnosing IDH mutant tumors and assessing response to therapy. To date, magnetic resonance spectroscopy (MRS) is the only imaging modality that has allowed for specific imaging-based detection of IDH mutations in glioma. In the future, D-2HG imaging may be utilized to predict tumor type, guide biopsy procedures, define intraoperative tumor margins, monitor treatment responses and diagnose tumor recurrence.

IDH mutations as potential therapeutic targets

Pharmacological therapies aimed at the direct inhibition of IDH mutant enzymes and their products are currently being developed. Two novel drugs, AGI 5198 and AGI 6780, block mutant IDH1 and mutant IDH2, respectively, and are efficient inhibitors of D-2HG levels *in vitro* and *in vivo*.^{19, 20} AGI 5198 reduced the ability of mutant IDH1 to produce D-2HG, induced histone demethylation and promoted expression of genes responsible for glial differentiation. Targeting other enzymes involved in the pathway of D-2HG production may have therapeutic benefit. Decreasing the supply of α -KG, the substrate necessary for D-2HG production, can also be achieved through small molecule inhibitors and treatment with exogenous α -KG could block the inhibitory effect D-2HG has on many critical enzymes. Finally, recent studies suggest that FDA-approved epigenetic therapies can induce differentiation of IDH mutant gliomas and inhibit growth of these tumors *in vivo*. In sum, IDH mutant tumors display epigenetic aberrancies, and pharmacologic reversal of abnormal histone modification or DNA methylation could represent an avenue for therapeutic intervention.

Conclusions

We now know that IDH mutations play a role in gliomagenesis, but the exact mechanism by which this occurs remains to be

discovered. IDH mutations carry significant prognostic value and represent a subset of tumors with a less aggressive clinical course when compared to IDH wild-type gliomas. Current technologies permit the relatively simple diagnosis of IDH mutations in glioma tissue. Importantly, IDH mutations in human glioma may represent a promising therapeutic target.

References

1. Yan, H., et al. (2009). Mutant metabolic enzymes are at the origin of gliomas. *Cancer Res* 69, 9157-9159.
2. Parsons, D.W., et al. (2008). An integrated genomic analysis of human glioblastoma multiforme. *Science* 321, 1807-1812.
3. Yan, H., et al. (2009). IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 360, 765-773.
4. Dang, L., et al. (2009). Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 462, 739-744.
5. Kloosterhof, N.K., et al. (2011). Isocitrate dehydrogenase-1 mutations: a fundamentally new understanding of diffuse glioma? *Lancet Oncol* 12, 83-91.
6. Hartmann, C., et al. (2009). Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol* 118, 469-474.
7. Metallo, C.M., et al. (2012). Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature* 481, 380-384.
8. Zhao, S., et al. (2009). Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1 α . *Science* 324, 261-265.
9. Lu, C., et al. (2012). IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature* 483, 474-478.
10. Turcan, S., et al. (2012). IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature* 483, 479-483.
11. Balss, J., et al. (2008). Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol* 116, 597-602.
12. Watanabe, T., et al. (2009). IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathol* 174, 1149-1153.
13. Sanson, M., et al. (2009). Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *J Clin Oncol* 27, 4150-4154.
14. Chesnelong, C., et al. (2013). Lactate dehydrogenase A silencing in IDH mutant gliomas. *Neuro Oncol*.
15. van den Bent, M.J., et al. (2010). IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *Clin Cancer Res* 16, 1597-1604.
16. Zhang, C.B., et al. (2014). Correlation of IDH1/2 mutation with clinicopathologic factors and prognosis in anaplastic gliomas: a report of 203 patients from China. *J Cancer Res Clin Oncol* 140, 45-51.
17. Cheng, H.B., et al. (2013). IDH1 mutation is associated with improved overall survival in patients with glioblastoma: a meta-analysis. *Tumour Biol* 34, 3555-3559.
18. Agarwal, S., et al. (2013). Comparative study of IDH1 mutations in gliomas by immunohistochemistry and DNA sequencing. *Neuro Oncol* 15, 718-726.
19. Wang, F., et al. (2013). Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. *Science* 340, 622-626.
20. Rohle, D., et al. (2013). An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science* 340, 626-630.

Topic Review in Neuro-Oncology: Are We Still Finding Novel Treatments in Nature? An Update on Neuro-oncology and Curcumin

Tiffany L. Powell, MD

Consumers making health-conscious choices is on the rise. From the food people choose to eat, to the clothes they wear, the containers used to store their food and the cosmetic products they place on their bodies, people want to know “What is in this stuff and how will it affect me?” This is quite a change from 15 years ago when few of us, or our parents, took the time to read an ingredient label or research the components of the products we consumed. The question posed is — who makes up this population of health-conscious consumers? Data from a 2011 Harris Poll identifies it is potentially some of the patients we are treating in our neurological oncologic practices. The poll reveals individuals 66 years and older as the most likely age group to pay attention to nutritional facts and alter their behavior accordingly. Following closely is 58 percent of Baby Boomers (ages 47-65) and 50 percent of Generation X'ers (ages 35-46).

It is no surprise that health-conscious patients' concerns remain present when diagnosed with cancer of the central nervous system (CNS). With increasing frequency, patients and their families inquire about what they should be eating or avoiding in the pre and postoperative period to support the remainder of their oncologic treatments. Their questions go far beyond avoiding aspirins or supplements that increase bleeding. For this type of patient, simply referring them to an oncologist to gather information seems to fall short of the care we can provide.

Over the past two decades one compound has been increasingly present in cancer publications, both basic science and clinical trials — curcumin. Known more commonly in the culinary community simply as turmeric, curcumin is an organic chemical extracted from the herbaceous perennial plant, *curcuma longa*.

It is ubiquitously present in Asian dishes and has been highly regarded for many centuries for its medicinal properties [1,5]. It remains one of the most potent anti-inflammatory agents found in food [1]. In the last decade, its anti-cancer properties have been increasingly investigated. Laboratory studies have shown its ability to inhibit angiogenesis, and force brain, breast and lung neoplastic cells, among others, into apoptosis. Some of the most-cited early research identifying curcumin's anti-cancer properties came out of M.D. Anderson under the direction of Ved Aggarwal, MD et al. They identified curcumin's ability to induce cleavage of the proapoptotic protein BID via activation of caspase-8. [2] Since that time more than 100 clinical trials have been conducted to further investigate its properties. However its specific use and potential effects in supporting treatments for CNS malignancies has yet to be fully evaluated.

More recently a few *in vitro* studies aimed at identifying the anti-proliferative effects of curcumin on primary gliomas have been completed, but they remain limited. The first dose-dependent effect suppression of glioma cell proliferation *in vitro* was reported by Timiras et al. in 2003. Since then several studies have identified mechanisms for this suppression. Dhandapani et al.

noted curcumin induced cell death via independent activation of p53 and upregulation of caspase and noted decreased expression of IAP and Bcl family genes typically associated with chemoresistance [2,3]. They also found MGMT and other DNA repair enzymes were inhibited by curcumin [3]. Additionally, Aoki et al. have demonstrated curcumin's induction of autophagy via inhibition of the Akt/mTOR/p70S6K pathway [3]. These studies further support curcumin's anti-cancer properties but have identified serious limitations in its oral bioavailability in humans.

In early 2014, Prasad et al. published a review of the current research investigating the bioavailability and metabolism of curcumin, which appeared in *Cancer Research and Treatment*. The low bioavailability and early degradation of curcumin in humans remains the main disadvantage and challenge of this therapy. One of the promising experimental models to address this issue involves the use of piperine. Piperine, a major component of black pepper, has been shown to improve the oral bioavailability of curcumin by 2,000 percent at 45 minutes in humans when co-administered [3]. The study also cited experimental models investigating the biodistribution of [¹⁸F]-curcumin into several organs including the brain after intravenous injection in mice. The initial brain uptake of [¹⁸F]-curcumin was increased by 48 percent with the co-administration of piperine, however within one hour only traces remained. Dilnawaz et al. in 2013 showed synergistic cytotoxic effects of curcumin and temozolomide in human derived T98 glioblastoma cells when using a magnetic nanoparticle based drug delivery system. Currently research investigating curcumin-piperine nanoparticles as well as other formulations including liposomal and cyclodextrin encapsulation is currently underway [3].

Clinical trials investigating curcumin's effectiveness treating CNS malignancies are extremely limited and thus its full potential for aiding current therapies in gliomas or other CNS malignancies remains largely unknown. A small preclinical study aimed at evaluating the bioavailability of curcumin in glioblastoma patients by measuring the intratumoral concentration of curcumin at the time of surgery was completed in Frankfurt in 2013 however results are not yet published. There are a number of clinical trials investigating curcumin's effectiveness in other cancers including breast, lung and colon with some promising results but CNS malignancies remains untapped [4]. Given the *in vitro* discoveries in gliomas cells lines and the recent advances in biodelivery this remains an area worth investigating.

Looking to nature for potential cancer treatments is no new phenomenon. In the 1940s, research investigating the effects of folic acid on patients with leukemia lead to the first successful therapy inducing remission in children with acute lymphocytic leukemia. In the 1950s, the discovery of vinca alkaloid derived from a flowering plant endemic to Madagascar lead to the development of vincristine. However, the general public's interest

in the development and use of natural compounds to aid cancer treatments is relatively recent. So it remains no surprise when this more health-conscious patient population looks for information regarding natural elements to support their oncologic treatments or inquires about research involving such compounds. Remaining aware of the advances and limitations of this area of cancer research will help us continue to be a valuable resource to our oncologic patients and allow us to increase the research efforts in support of the most promising natural agents being investigated in patients battling gliomas and other CNS malignancies.

References

1. Servan-Schreiber, D., *AntiCancer: A New Way of Life* (New York: Penguin Group 2009).
2. Anto, R., et al., Curcumin (diferuloylmethane) induces apoptosis through activation of caspase-8, BID cleavage and cytochrome c release: its suppression by ectopic express of Bcl-2 and Bcl-xl. *Carcinogenesis*, 2002. 23(1): p.143-150.
3. Prasad, S., Tyagi, A., Aggarwal B., Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: the Golden Pigment from Golden Spice. *Cancer Research Treatment*, 2014. 46(1): p.2-18.
4. Gupta, S., et al., Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials. *Am Association of Pharmaceutical Scientists*, 2013. 15(1): p.195-218.
5. Lee, WH., et al., Curcumin and its Derivatives: Their Application in Neuropharmacology and Neuroscience in the 21st Century. *Current Neur Phar*, 2013. 11:p.338-378.
6. Bouchard M., Most Americans are Health-Conscious, But Behavior Varies By Age. *The Harris Poll*, April 2011. 52.

Stereotactic Radiosurgery Report

Jason Sheehan, MD, PhD, FAANS

The American Association of Neurological Surgeons (AANS) has formed a partnership with Brainlab to create a national stereotactic radiosurgery registry. The registry would build on previous successes by the NeuroPoint Alliance. The goals of the registry are to meet the quality care and research needs of those practicing radiosurgery. In addition, the registry will provide much needed information to national medical organizations, corporate partners, government agencies, and healthcare as well as consumer agencies. Eventual expansion of the registry to primary and maintenance of certification efforts is anticipated. Outcome will provide the analytical support for the registry.

The registry will be a multi-year effort with specific milestones being set for each year. The data dictionary is being refined to balance both comprehensiveness and practicality. Specific bridges will allow for semi-automated transfer of data from workstations associated with specific radiosurgical devices.

Individuals and respective centers interested in assisting in the development and piloting of the national SRS registry should contact me via email at jsheehan@virginia.edu for further information.

Skull Base Surgery Update

Michael J. Link, MD, FAANS

The past year has been very stimulating for the neurosurgical community interested in skull base surgery. The 24th Annual Meeting of the North American Skull Base Society (NASBS) just concluded at the Grand Manchester Hyatt in San Diego, Feb. 14-16, 2014. The meeting had more than 500 attendees, and included 12 breakfast seminars and three plenary sessions. The sessions featured Honored Guest presentations from Ossama Al-Mefty, MD; Ivo Janecka, MD, MBA, PhD; and Piero Nicolai, MD, to name just a few. Additionally, David Dravecky, a former Major League Baseball all-star pitcher who lost his left arm (and he was left-handed) to a recurrent desmoid tumor at the height of his career, gave an incredibly inspirational presentation about life's priorities and facing adversity. Also, there were six concurrent sessions covering 24 different topics exploring some of the most controversial issues in skull base surgery including 140 proffered paper oral presentations and 135 posters. The pre-meeting practical dissection course held at University of California, San Diego, Feb. 12-13, 2014, featured a direct comparison of endoscopic versus open skull base approaches with both a hands-on dissection experience and a lecture-only and viewing prosections track, to accommodate various budgets and levels of interest and expertise. Next year's meeting is scheduled for Feb. 18-22, 2015, in Tampa, Fla. More information is available at www.NASBS.org.

It has also been an active academic time in skull base surgery. The year 2013 saw 665 major publications on skull base surgery listed in *PubMed* (<http://www.ncbi.nlm.nih.gov/pubmed/>) compared to just 304 a decade ago. There continues to be several open trials currently enrolling patients with skull base tumors. A full list of available trials is available at www.clinicaltrials.gov. Briefly, there is a trial open through the National Cancer Institute exploring the role of bevacizumab in reducing central nervous system side effects in patients who have undergone radiation therapy for brain tumors including meningiomas (NCT00492089). The NYU group is doing a phase 0 study exploring the activity of RAD001 in vestibular schwannomas and meningiomas by administering the drug for 10 days prior to surgery and then measuring drug levels in serum and resected tumor specimen (NCT01880749). Also, the NINDS is enrolling patients to evaluate the ability of PET to predict which intracranial tumors in patients afflicted with NF2 will grow (NCT01222728), to highlight just a few.

The upcoming Tumor Section scientific sessions on April 7-9, 2014 at this year's AANS Annual Scientific Meeting in San Francisco also promise to have several interesting and informative presentations regarding skull base tumors. I'll look forward to seeing everyone there.

Young Neurosurgeons Committee

Kaisorn Chaichana, MD; Ian Dunn, MD, FAANS

The Young Neurosurgeons Committee (YNC) is the primary organizational voice of young neurosurgeons, focusing its efforts in education, public service, fundraising, medical student recruitment and organized neurosurgery. The Committee is now under the leadership of its new chair, Stacey Quintero-Wolfe, MD, FAANS, who assumed the reins from Edward Smith, MD, FAANS, this past year.

We are pleased to announce the continuation of the Tumor Section YNC reception, an opportunity for medical students, residents, fellows, and board-eligible neurosurgeons interested in neurosurgical oncology to interact with senior members of the field. Last year, we were fortunate to have Linda Liau, MD, PhD, FAANS, from UCLA, share her keys to success in becoming one of the field's pre-eminent clinician-scientists in neurosurgical oncology.

This year, we are delighted to host James Markert, MD, MPH, FAANS, Professor and Chair of Neurosurgery at the University of Alabama-Birmingham (UAB). Dr. Markert graduated with a MD and MPH from Columbia College of Physicians and Surgeons and received his neurosurgical training under Julian Hoff, MD, at the University of Michigan. Dr. Markert completed his research fellowship studying genetically-engineered HSV in glioma with Robert Martuza, MD, at the Massachusetts General Hospital. Dr. Markert was appointed Chief of the Division of Neurosurgery at UAB and among many accomplishments, was the founding Chair of the UAB Department of Neurosurgery and Co-Director of the UAB Brain Tumor SPORE. He will join the YNC Tumor Section reception being held at the AANS Annual Scientific Meeting in San Francisco on April 8, 2014, from 5:30-7:30 p.m.

Guidelines Committee

Steven N. Kalkanis MD, FAANS

The Section on Tumors' Guidelines Committee is proud to announce the upcoming release of the Progressive Recurrent Glioblastoma Guidelines, to be published soon in the Journal of Neuro-oncology. The progressive/recurrent glioblastoma guidelines project, expertly led by Jeff Olson, MD, FAANS, along with Tim Ryken, MD, FAANS, and with major support from Laura Mitchell and the Congress of Neurological Surgeons (CNS) national guidelines committee, received final approval and endorsement from the American Association of Neurological Surgeons (AANS)/CNS Joint Guidelines Committee and has been accepted for publication. We would like to especially thank the senior authors of each of the major chapters, including Dr. Ryken, Dr. Olson, Dr. Kalkanis, Daniel Brat, MD, PhD; Samuel Ryu, MD; Patrick Wen, MD; Lakshmi Nayak, MD; John Buatti, MD; Johnathan Morris, MD, and many others in our writing groups from the Section. We would also like to thank those from our multidisciplinary collaborations in radiation oncology, medical oncology, neuro-oncology, neuroradiology and neuropathology. This guideline initiative focuses on the difficult questions asked in tumor boards across the country: how best to treat GBM at recurrence? Specific chapters address the following questions in the clinical management and treatment of progressive GBM: Outcome assessment and Neurocognition; Role of Neuro-imaging (progression vs. radiation change); Role of Biopsy; Role of repeat Cytoreductive Surgery; Role of Radiotherapy Techniques (re-irradiation, stereotactic radiosurgery, brachytherapy); Role of Chemotherapy; and Future Innovations. We would especially like to acknowledge editor Linda Liau, MD, PhD, FAANS for agreeing to expedite the publication of these guidelines.

We are also pleased to report that the clinical practice guidelines for Low Grade Glioma, spearheaded by Dr. Olson and being co-led by Mark Linskey, MD, FAANS; Dr. Ryken and Dr. Kalkanis, are now in final draft form. All writing and internal revisions have been completed, and we are awaiting final approval and endorsement from the Joint Guidelines Committee. Low grade glioma guidelines chapters include: Role of Imaging (Sarah Jost Fouke, MD, FAANS), Role of Biopsy (Brian Ragel, MD, FAANS), Role of Surgical Resection (Manish Aghi, MD, FAANS), Neuropathology and Molecular Markers (Daniel Cahill, MD, PhD, FAANS), Role of Radiation (Ian Parney, MD, PhD), Role of Chemotherapy (Mateo Ziu, MD), Options for Recurrent Low Grade Glioma (Brian Nahed, MD) and Emerging Therapies for LGG (Andrew Sloan, MD, FAANS).

The multidisciplinary pituitary adenoma management guideline, now being led by Dr. Aghi along with Chirag Patil, MD, FAANS, and Zack Litvack, MD, continues in the writing stage with final drafts expected this spring.

We welcome all participants, and anyone interested in working on guidelines projects is strongly encouraged to contact me via email at skalkan1@hfh.org.

AANS/CNS Section on Tumors Executive Committee

Chair: Fred Barker

Secretary-Treasurer: Andrew Parsa

Past-Chair: Fred Lang

Advisory Board

Gene Barnett
Jeff Bruce
Ennio Chiocca
Roberta Glick
Jim Markert
Michael McDermott
Joseph Piepmeier
Mark Rosenblum
Raymond Sawaya
Ronald Warnick

COMMITTEES

Awards: Manish Aghi

Bylaws: Jason Heth

Clinical Trials: Ian Parney

Alliance: Brad Elder

RTOG: Daniel Cahill

Community Collaborative Initiative:

Aaron Cohen-Gadol

Development: William T. Curry Jr. (Co-chair)

Allen Waziri (Co-chair)
Orin Bloch
Chris Farrell
Daniel Prevedello
Michael Lim
Nader Sanai
Isaac Yang

Education (Continuing): Mark Linskey

Education (Meetings): Jonas Sheehan

Guidelines:

Steven Kalkanis (Chair)
Jeffrey J. Olsen

History: Anthony L. D'Ambrosio

IT/Website: Chris McPherson

Jeff Weinberg

International: Isabelle Germano (Chair)

Ricardo J. Komotar (Co-Chair)
Dominik Cordier (Switzerland)
Francesco DiMeco (Italy)
Hossam El Huseiny (Egypt)
M. Sam Eljamel (Scotland)
Nitin Mukerji (England)
Alejandra Teresa Rabadan (Argentina)
Zvi Ram (EANS)
Charles Teo (Australia)
Ugur Ture (Turkey)
Jose Valerio-Pascua (Central America)
Yonggang Wang (China)
Manfred Westphal (Germany)
Fumio Yamaguchi (Japan)

Journal of Neuro-Oncology: Linda M. Liau

Matrix: Ennio A. Chiocca (Chair)

Medical Neuro-Oncology: Susan Chang

Membership: Randy Jensen

NeuroPoint Alliance:

Mark E. Linskey (Chair)
James Bradley Elder

Newsletter: Jennifer Moliterno Gunel

Nominating: Fred Lang

Pediatrics: Richard Anderson

Programs:

Jennifer Moliterno Gunel (AANS '14)
John Kuo (CNS '14)
Clark Chen (AANS '15)
Michael Sughrue (AANS '15)
Michael Lim (CNS '15)
Gavin Dunn (Satellite '15)
Orin Bloch (Satellite '15)

Radiosurgery: Jason P. Sheehan

SANS: Sarah Jost Fouke (Chair)

Viviane Tabar

Skull Base: Michael Link

SNO: Michael Vogelbaum

Spine: Laurence D. Rhines

Washington: Andrew E. Sloan (Chair)

Brian Nahed

Young Neurosurgeons: Kaisorn Chaichana

Ian Dunn