



## In This Issue...

- 4**  
ACTION: Alliance for Clinical Trials in Oncology
- Academic Community Alliance (ACA) Initiative
- 5**  
Case Review in Neuro-Oncology: Craniopharyngioma
- Self-Assessment in Neurological Surgery (SANS)
- 6**  
CNS 2012 Meeting: Tumor Program Highlights
- North American Skull Base Society Course and Annual Meeting
- 2011 AANS/CNS Section on Tumors Biennial Tumor Satellite Symposium
- 7**  
Tumor Section Guidelines Committee
- 8**  
Section on Tumors: Education and Awards
- 9**  
The First Joint Neurosurgery and Radiation Oncology Resident Course in Stereotactic Radiosurgery
- Medical Neuro-Oncology/Society for Neuro-Oncology Update
- ABTA Clinical Research Grant
- 10**  
European Association of Neurosurgical Societies (EANS) Meeting
- 11**  
International Neurosurgical Updates
- 12**  
New Feature: Topic Review in Neuro-Oncology Genetics of Glioma: An Update for Neurosurgeons
- 14**  
Clinical Trials in Neuro-Oncology
- 15**  
AANS/CNS Section on Tumors Executive Committee

## From the Chairman



Frederick F. Lang, MD, FAANS, FACS

Welcome to the fall edition of the AANS/CNS Section on Tumors newsletter. I want to thank Jonas Sheehan, MD, FAANS, FACS, for his continuing efforts to publish this newsletter. The content has evolved over time, and Dr. Sheehan has added a new feature, “Case

Review in Neuro-oncology: Craniopharyngioma,” in which an interesting case is presented and discussed. This format has been in the newsletter before, but with Internet technology, we now have modified this feature so that Section members can provide input about the case via an online survey and discussion at the Section’s website, [www.tumorsection.org](http://www.tumorsection.org). We hope this is a fun and interesting way to foster discussion among members about common or complex clinical problems. It also has highlighted the need for us to spruce up our website — one of our goals in the next few months is enhance its quality. In addition, a second new feature, Topic Review in Neuro-oncology, debuts in this newsletter with a review of clinically significant glioma genetics for neurosurgeons.

As always, the Section on Tumors is actively engaged in continuing educational experiences for our members, so I am highlighting several important upcoming events.

First, in a few weeks, we will be gathering for the CNS Annual Meeting in Chicago. Members of the Section on Tumors have worked hard reviewing abstracts, and selecting the oral presentations and awards for this meeting. We are indebted to Viviane Tabar, MD, FAANS, who organized the

educational program, which includes a symposium entitled “Primary Spinal Neoplasms: Treatment and Science Updates.” This symposium partners the Section on Tumors with the Spine Section via our representative, Laurence Rhines, MD, FAANS. The goal of this symposium is to comprehensively review current strategies in the management of tumors of the spinal axis. We also are privileged to have Jay Loeffler, MD, chief of radiation oncology at Massachusetts General Hospital and Harvard Medical School, present a keynote address entitled “Proton Beam Therapy: Biology and Applications.” Dr. Loeffler is a pioneer in the clinical use of proton beam therapy and will share his experience with us.

Second, the Section on Tumors will be hosting its **10th Biennial Satellite Tumor Symposium** April 26-28, 2013, in New Orleans at the Hilton New Orleans Riverside just prior to the **2013 AANS Annual Scientific Meeting**. For the first time, this meeting will be held on Friday and Saturday so that Section members can attend both the Satellite Symposium and the AANS Annual Scientific Meeting, without overly extending their time away from home. Nadar Sanai, MD; and Isaac Yang, MD, are in the process of organizing the scientific program for this meeting, which will include abstract-driven presentations and educational sessions. In addition, the Society for Neuro-Oncology will co-sponsor a Special Symposium on Meningiomas, which will be a half-day event in which basic scientists, medical oncologists, radiation oncologists and neurosurgeons will discuss the most recent advances in the basic biology and treatment of meningiomas. Andrew Parsa, MD, PhD, FAANS, also has organized several industry-sponsored seminars that should be of great interest to members of the Section on Tumors. The Abstract Center for this meeting is now

*continued on page 3*



American  
Association of  
Neurological  
Surgeons



## SECTION ON TUMORS

*A Section of American Association of Neurological Surgeons and Congress of Neurological Surgeons*

July 18, 2012

Dear Colleagues:

One of my goals as Chair of the AANS/CNS Section on Tumors has been to increase the role of our members in the design and implementation of clinical trials, particularly National Cancer Institute funded cooperative group clinical trials. In this context, I have asked Michael Vogelbaum who heads the neurosurgical committee for RTOG, and Ian Parney, who is the AANS/CNS Tumor Section representative for a new clinical trial consortium called the ALLIANCE, to each highlight one current trial whose success would greatly benefit from the enthusiastic participation of neurosurgeons. They have each outlined such a trial below. The RTOG trial is an observational study of patients with low grade gliomas undergoing surgery. The ALLIANCE study is a randomized trial for metastases patients. If you are interested in participating in these trials, please feel free to contact Mike or Ian.

### RTOG TRIAL

RTOG 0925 is an observational study of patients with low risk low grade glioma (LGG). Patients eligible for this trial include those that have had an imaging complete resection or a biopsy of a LGG. This trial does not proscribe any adjuvant therapy, but instead it is designed to better understand the relationship between non-radiological (i.e. neurocognitive) and radiological progression in this group of fairly young patients who have a good prognosis. The primary endpoint is neurocognitive progression; clinical progression, deterioration in health-related quality of life (HRQOL), and seizure progression are secondary endpoints. Also, we will analyze tumor tissue for molecular markers (1p, 19q, MGMT, IDH1) and these will be correlated with the clinical outcome data.

There is a 12 week time-window allowed between the time of surgery and registration onto the study. Because most of these patients will not be seen by a radiation oncologist, it is essential that neurosurgeons take the initiative to present this trial to their eligible patients in order for it to be successful. Enrollment in this trial does not limit a patient's treatment options at time of recurrence; all subsequent treatment is at the discretion of the patient's clinical team.

The trial is being chaired by Randy Jensen, Department of Neurosurgery, University of Utah (801-581-6908, [randy.jensen@hsc.utah.edu](mailto:randy.jensen@hsc.utah.edu)) and Ali Choucaire, Department of Neurology, Norton Cancer Institute (Louisville, KY) (502-909-2315, [ALI.CHOUCAIR@nortonhealthcare.org](mailto:ALI.CHOUCAIR@nortonhealthcare.org)).

#### CHAIR

Frederick F. Lang, MD, FAANS  
M.D. Anderson Cancer Center  
Email: [flang@mdanderson.org](mailto:flang@mdanderson.org)

#### SECRETARY-TREASURER

Fred G. Barker II, MD, FAANS, FACS  
Massachusetts General Hospital  
Email: [barker@helix.mgh.harvard.edu](mailto:barker@helix.mgh.harvard.edu)

#### PAST CHAIR

Jeffrey N. Bruce, MD, FAANS, FACS  
New York Neurological Institute  
Email: [jnb2@columbia.edu](mailto:jnb2@columbia.edu)

#### MEMBERSHIP CHAIR

Allen Waziri, MD  
University of Colorado Hsc/Neurosurgery  
12631 E 17th Ave # Cbc-307  
Aurora, CO 80045-2527  
Email: [allen.waziri@ucdenver.edu](mailto:allen.waziri@ucdenver.edu)

ALLIANCE TRIAL

N107C is a phase III randomized trial of post-surgical stereotactic radiosurgery (SRS) compared with whole brain radiation (WBRT) for resected metastatic brain disease. This multi-center trial is being conducted through the Alliance for Clinical Trials in Oncology and seeks to determine how well SRS works compared with WBRT for brain metastases that have been surgically removed. This is a trial for adults ( $\geq 18$  years) with 1 – 4 brain metastases who have undergone surgery to remove at least one of the metastases. The maximum diameter of the resection cavity must be  $< 5$  cm and the maximum diameter of any unresected metastases must be  $\leq 3$  cm. Patients will be randomized to receive either SRS to the resection cavity or WBRT. All unresected metastases will receive SRS, regardless of study arm. Primary outcomes include overall survival and neurocognitive outcome at 6 months. Secondary outcomes include quality of life and functional independence, local recurrence, and distant central nervous system failure. Projected enrollment is 192 patients. The trial is currently open at 19 centers in the United States and 4 centers in Canada. For further information, please contact Dr. Ian F. Parney (Study Co-Chair for Neurosurgery; Dept. of Neurological Surgery, Mayo Clinic Rochester, 507-284-8167) or Dr. Paul Brown (Study Chair; Dept. of Radiation Oncology, M.D. Anderson Cancer Center, 713-563-2415).

Please feel free to contact Mike or Ian with any questions about these trials. Thank you for your support of these important clinical trial efforts.



Frederick F. Lang M.D.  
Chair, Tumor Section of the AANS/CNS

open through the AANS Abstract Center at <https://myaans.aans.org/MyAANS.aspx>; all Section members are encouraged to submit their work for presentation at this meeting.

Third, thanks to the efforts of Section on Tumors international member Zvi Ram, MD, from Israel, we have partnered with the European Association of Neurological Societies (EANS) to host an international neurosurgical oncology meeting, which will be held Nov. 11-14, 2013, in Tel Aviv. This meeting will bring together neurosurgical oncologists in all subspecialties (glioma, metastases, spine, skull base, radiosurgery, pediatrics, peripheral nerve) from the U.S. and all parts of Europe. We hope that all members of the Section on Tumors plan on attending this historic meeting, which we envision to be the first of many international collaborative meetings co-sponsored by the Section on Tumors and EANS. Please stay tuned for more information on this meeting.

As all of you are aware, the Section on Tumors Executive Committee recently decided to create a new award, The Guha Award & Lecture. This award is co-sponsored by the Society for Neuro-Oncology and named in honor of Abhijit Guha, MD, FAANS, who recently passed away after a valiant struggle against leukemia. Dr. Guha was a leader in the Section on Tumors and the sixth president of the Society for Neuro-Oncology; he maintained an active research laboratory, and trained numerous post-doctoral fellows, residents and students in neuro-oncology research. The Guha Award recognizes an accomplished investigator who is achieving significant results both in the laboratory and the clinic — a “lifetime achievement award,” if you will. Through a very rigorous vetting process conducted by the Section on Tumors Executive Committee and the Society for

Neuro-Oncology, it is my pleasure to announce that the winner of the first Ab Guha Award & Lecture is James Rutka, MD, PhD, FAANS, professor and chairman of the Department of Surgery, University of Toronto. Dr. Rutka has served as Chair of the Section on Tumors as well as president of the AANS. He is co-director of the Arthur and Sonia Labatt Brain Tumor Research Centre at the University of Toronto. He has been a thought-leader in neuro-oncology for the past 20 years, a consummate surgeon and a mentor to many of us. I cannot think of a more deserving honoree than Dr. Rutka. He will present his lecture at the 2012 Society of Neuro-oncology Annual Meeting, to be held Nov. 15-18, 2012, in Washington, D.C.

Let me close with a comment about clinical research and the Section on Tumors. One of my goals as chair of the AANS/CNS Section on Tumors has been to increase the role of our members in the design and implementation of clinical trials. I recently sent a letter out to members encouraging them to participate in two clinical trials that the Clinical Trials Committee has deemed worthwhile and that are being conducted by Section on Tumors members. A copy of this letter is printed on page 2 of this newsletter. I encourage all Section members to read this letter in order to learn about the current trials. Please contact the principal investigators if you are interested in participating.

Sincerely,



Frederick F. Lang, MD, FAANS, FACS

# ACTION: Alliance for Clinical Trials in Oncology

Ian Parney, MD, PhD

The Neuro-Oncology Committee of the Alliance for Clinical Trials in Oncology (ACTION or the Alliance; [www.alliance-website.org](http://www.alliance-website.org)) met again on June 30, 2012, in Chicago. The Alliance represents an amalgamation of three separate cancer cooperative groups: Cancer and Leukemia Group B, the North Central Cancer Treatment Group and the American College of Surgeons Oncology Group. The meeting featured excellent multidisciplinary participation, including contributions from several members of the AANS/CNS Section on Tumors. Highlights relevant to the Section include the multicenter opening of N107c (“A Phase III Trial of Post-Surgical Stereotactic Radiosurgery Compared with Whole Brain Radiotherapy for Resected Metastatic Brain Disease”).

This study for patients with up to four metastases (one of which has been resected) compares whole brain radiation to radiosurgery to the surgical cavity. All unresected metastases will be treated with radiosurgery. In addition, Section on Tumors member Andrew Parsa, MD, PhD, FAANS’ trial, “A Phase 2 multicenter randomized, double blind, placebo-controlled trial comparing efficacy of heat shock protein-peptide complex-96 (HSPPC-96) vaccine or placebo in combination with bevacizumab (Avastin) in the therapy of Recurrent Glioblastoma Multiforme (GBM)” has

been presented to the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute. This neurosurgically-driven study is the first clinical trial of any sort to be taken forward by the new Neuro-Oncology Committee. It reflects both the strong science leading up to the study and the strong commitment of the Neuro-Oncology Committee to neurosurgical clinical trials.

Finally, the Section on Tumors has agreed on a novel mechanism to facilitate neuro-oncology clinical trial development by neurosurgeons. Draft clinical trial protocols will be solicited from Section members at regular intervals throughout the year for multidisciplinary review and feedback. This effort will be headed up by Manish Aghi, MD, FAANS. After feedback, these studies may be referred on to ACTION or other cooperative groups as appropriate. Neurosurgical investigators from institutions that are members of the Alliance (or prior members of CALGB, NCCTG or ACOSOG) should e-mail Fred Barker, MD, FAANS, FACS, at [barker@helix.mgh.harvard.edu](mailto:barker@helix.mgh.harvard.edu); or Ian F. Parney MD, PhD, FRCSC, at [parney.ian@mayo.edu](mailto:parney.ian@mayo.edu) to discuss possible opportunities for neurosurgeons in this newly formed trials group.

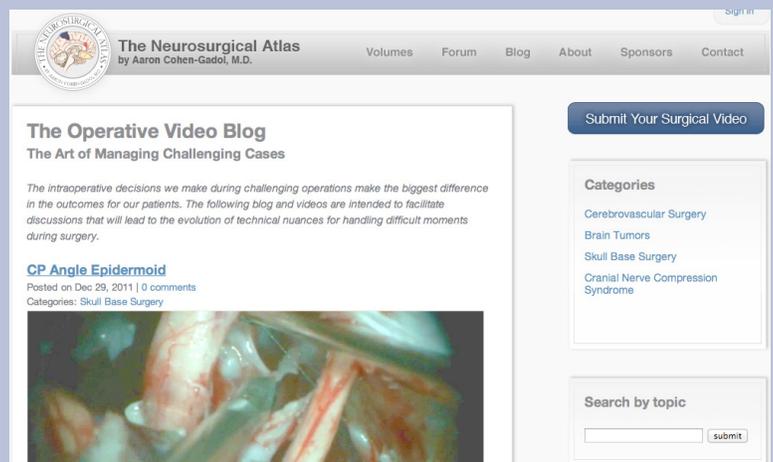
## Academic Community Alliance (ACA) Initiative

Brian T. Ragel, MD, FAANS; and Aaron Cohen-Gadol, MD, FAANS

The Academic Community Alliance (ACA) committee is charged with creating a dialogue between community and academic neurosurgical oncologists. This two-way conversation is meant to provide up-to-date treatment information, as well as surgical opinions on difficult cases.

In the fall of 2011, a neurosurgical blog was developed so neurosurgeons can solicit as well as give advice on challenging tumor cases (<http://www.neurosurgicalatlas.com/index.php/blog/>). This neurosurgery-specific blog allows users to submit difficult cases for opinion (see right).

Since inception, 300 viewers from around the world have visited this site. Currently, a mobile device application is being developed that will allow users to blog difficult cases from their smart phones. Ultimately, the ACA committee wishes to open a dialogue between neurosurgeons for the benefit of our patients.



The screenshot displays the Neurosurgical Atlas website. At the top, there is a navigation menu with links for Volumes, Forum, Blog, About, Sponsors, and Contact. The main content area features a blog post titled "The Operative Video Blog" with the subtitle "The Art of Managing Challenging Cases". Below the title is a short paragraph of text and a video thumbnail. To the right of the main content, there is a sidebar with a "Submit Your Surgical Video" button, a "Categories" list including Cerebrovascular Surgery, Brain Tumors, Skull Base Surgery, and Cranial Nerve Compression Syndrome, and a "Search by topic" search box with a submit button.

# Case Review in Neuro-Oncology: Craniopharyngioma

**Christopher McPherson, MD, FAANS**

A 56-year-old African-American female with a history of chronic schizophrenia was admitted to the hospital with a two-month decline in mental status and gait. On exam, she is confused, oriented only to name. She is only able to follow simple commands with prompting. She has psychomotor slowing with mixed expressive/receptive aphasia. She has mild right hemiparesis with a mild right pronator drift. Her gait is very unsteady, and she is only able to ambulate with full assistance. Her pupils are equal, round and reactive to light. On formal visual exam, her visual acuity is 20/50 in the right eye and 20/100 in the left eye, with bitemporal hemianopsia on visual field exam.

An MRI scan was obtained (see the three images below).

**Question #1: After discussion with the family, surgery is recommended, and the family agrees and provides consent. What would be your primary surgical plan?**

## Self-Assessment in Neurological Surgery (SANS)

Sarah Jost Fouke, MD; and Jason Sheehan, MD, PhD, FAANS

In early 2012, the Self-Assessment in Neurological Surgery (SANS) committee began its annual rolling update. For this update, 25 percent of the questions for maintenance of certification- (MOC-) compatible SANS products such as the general, spine and pediatrics examinations are new. The AANS/CNS Section on Tumors, specifically, has reviewed its active question bank and identified categories of question topics that are well represented, as well as those that are relatively under-represented. SANS aims to cover pre-clinical and clinical tumor biology, primary and metastatic tumors, and both benign and malignant tumor types.

At the Congress of Neurological Surgeons' 2012 Annual Meeting, SANS will be front and center, as spine and tumor programs provide an opportunity for participants to receive additional CME credit by completing SANS questions linked to related presentations at the meeting. With specific relevance to members of the Section on Tumors, the session focusing on vestibular schwannomas will be a highlight of the utilization of this technology. We encourage section members to explore this feature of the 2012 CNS Annual Meeting.

On an annual basis, members of the Section on Tumors who have expressed interest in participating in SANS are approached to contribute questions to the bank. This year, several members contributed a significant number of questions, and these efforts are greatly appreciated. Despite these excellent individual efforts, we are always looking for additional SANS question contributors. If you are interested in serving on the SANS committee, please contact one of us directly.

- Pterional craniotomy for resection of the tumor and drainage of the cyst
- Transsphenoidal resection of the tumor
- Stereotactic aspiration of the cyst with possible placement of Ommaya reservoir
- Craniotomy for transventricular resection of the cyst and the tumor

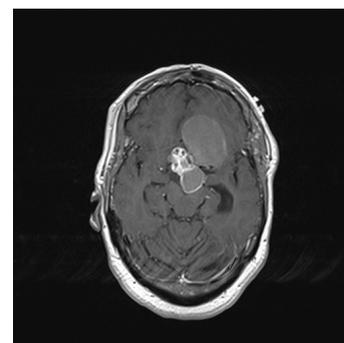
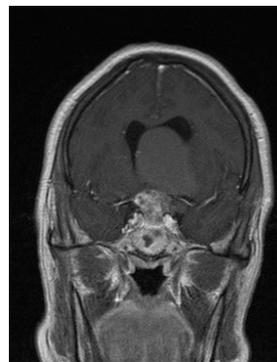
**Question #2: A stereotactic aspiration of the cyst was performed with placement of an Ommaya reservoir. The patient significantly improves in terms of her mental status, back to baseline, but visual function remains unchanged. What would be your management at this point?**

- Fractionated radiotherapy
- Craniotomy for resection of the tumor
- Transsphenoidal resection of the tumor
- No further treatment
- P-32 placement through Ommaya

**Question #3: Further surgery is planned. What would be your goal for surgery and plan for postoperative management?**

- Planned gross total resection and observation
- Planned gross total resection and postoperative radiation
- Planned subtotal resection and observation of residual
- Planned subtotal resection and postoperative radiation

Visit our website at [www.tumorsection.org](http://www.tumorsection.org) to see responses from the AANS/CNS Section on Tumors Executive Committee Members and to post your own responses.



# CNS 2012 Meeting: Tumor Program Highlights

**Viviane Tabar, MD, FAANS**

The Section on Tumors has selected the topic of primary spinal neoplasms as the theme of its 2012 Congress of Neurological Surgeons (CNS) symposium. Spinal tumors have not been covered comprehensively by the Section on Tumors at either the CNS' or the American Association of Neurological Surgeons' (AANS') meetings for more than 10 years, with the exception of extramedullary tumors in 2009. Tumors of the spine are an extraordinarily heterogeneous group of neoplasms. Recent years have witnessed important advances in our understanding of the biology of some of these tumors. Ongoing work has led to the classification of infratentorial ependymomas into transcriptionally, genetically and clinically distinct groups, paving the way for more individualized therapeutic strategies. Chordomas also have been the subject of ongoing molecular analysis leading to the wide confirmation of brachyury as a distinct marker and the identification of novel therapeutic targets. Concurrently, technological developments in radiation oncology now allow the delivery of radiation beams with greater precision and target conformity, as well as concomitant image guidance. This has led to wider applications, including the use of image guided radiation therapy (IGRT), intensity modulation radiation therapy (IMRT) and even single-dose stereotactic radiosurgery for the management of various spine tumors.

The symposium will cover advances in the clinical management, as well as the biology of the main spine tumor groups. George Jallo, MD, FAANS, from Johns Hopkins University will discuss

intramedullary tumors, followed by Paul McCormick, MD, MPH, FAANS, immediate past president of the AANS, who will share his expertise in the management of intradural extramedullary tumors with a focus on schwannomas and neurofibromatosis. Laurence Rhines, MD, FAANS, will end the symposium with an overview of primary spine neoplasms and a thorough discussion of chordomas. As a special guest, Jay Loeffler, MD, chief of radiation oncology at Massachusetts General Hospital, will discuss radiotherapy for spine tumors, as well as provide an update on the use of proton beam therapy in a special lecture that ends the Section on Tumors program that day. There is growing interest in proton beam therapy and its promise of dose escalation and exquisitely conformal targeting as a means of pushing the limits of the therapeutic window of radiation therapy. As a leading figure in radiation oncology, Dr. Loeffler will deliver a lecture followed by a discussion that will be of great interest to a wide CNS audience.

## North American Skull Base Society Course and Annual Meeting

**Nick Levine, MD**

The North American Skull Base Society (NASBS) held a three-day resident course in open and endoscopic skull base dissections July 27-30, 2012, at Louisiana State University (LSU) in New Orleans. Thirty senior neurosurgery residents, head and neck fellows, and neuro-otology fellows attended.

The NASBS Annual Meeting will be held Feb. 15-17, 2013, at Doral Golf Resort and Spa in Miami. A pre-meeting endoscopic course will be offered on Feb. 13 and an open skull base dissection course on Feb. 14. The meeting's theme will be "The complexity of measuring true quality in skull base surgery."

The NASBS research committee currently is establishing a patient registry for rare skull base pathologies and hopes that it will be operational next year.

## 2011 AANS/CNS Section on Tumors Biennial Tumor Satellite Symposium

**Nader Sanai, MD**

The AANS/CNS 10th Biennial Satellite Tumor Symposium is scheduled for April 26-27, 2013 — in conjunction with the 2013 AANS Annual Scientific Meeting — and will be held at the Hilton New Orleans Riverside Hotel in New Orleans. The Scientific Program Committee encourages you to submit an abstract for possible selection for oral presentation through the AANS Annual Scientific Meeting [submission process](#). The abstract submission deadline is Jan. 4, 2013. Accepted submissions will be published in the [Journal of Neuro-Oncology](#).

This special symposium aims to provide a forum for presentation and discussion of leading-edge innovations in modern brain and spine tumor management. Experts from all disciplines of neuro-oncology — including neurosurgeons, neuro-oncologists, medical oncologists, neuropathologists, radiation oncologists, neuroradiologists, laboratory scientists and allied health professionals — will be participating to discuss the research, diagnosis, care and treatment of central nervous system tumors. This year's program includes exhibits, scientific sessions, specialized symposia, and receptions that highlight the most significant clinical and scientific paradigms emerging for specialists in neuro-oncology. Additionally, this year the [Society for Neuro-Oncology](#) will join the AANS/CNS Section on Tumors in hosting a special symposium on meningiomas. Taken together, the multidisciplinary nature of this biennial event will provide an exceptional opportunity to share and discuss fundamental advances in neuro-oncology and neurosurgical oncology.

# Tumor Section Guidelines Committee

**Steven N. Kalkanis, MD, FAANS**

The Section on Tumors continues to generate very topical guidelines initiatives addressing critical knowledge and practice gaps in our profession. As one of the most integral and active delegations to the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee (JGC), the Section on Tumors guidelines group has completed the initial writing and review stage for both of our current projects: the metastatic spine guidelines and the progressive/recurrent glioblastoma multiforme (GBM) guidelines. Final revisions and submission for endorsement are scheduled to occur for both projects by the end of this year and slated for publication in 2013.

The chapters on brain metastases clinical practice guidelines, published in the *Journal of Neuro-oncology* in 2010, continue to receive significant worldwide citations; this year, they garnered a retroactive formal endorsement from the American Society for Radiation Oncology (ASTRO). Our newest guidelines effort addressing the management of pituitary adenoma launched this summer and was led by Chirag Patil, MD. Dr. Patil's multidisciplinary working group has completed the initial evidentiary table generation and literature review, and currently is in the writing stage, with a completion goal of Spring 2013.

2012 also marks the first year of the new comprehensive national guidelines initiative sponsored by the CNS, whereby the organization has created an internal infrastructure for scientific medical evidence guidelines development, including the hiring of high-level expert professional staff, with an initial annual investment of \$250,000. I am honored to lead this effort, and I look forward to working closely with Timothy Ryken, MD,

FAANS, the chair of the Joint Guidelines Committee, and the entire JGC leadership team. Laura Raymond — the new project manager for the CNS Guidelines Committee — as well as working with anyone interested in sponsoring and generating new guidelines projects in the future. We anticipate a fast-tracked set of new publications in both spine metastases and progressive/recurrent GBM in the coming year.

Jeff Olson, MD, FAANS, is leading the multidisciplinary effort on the recurrent GBM guidelines project. Completed and published in 2008, the guidelines project for the treatment of GBM at initial presentation, also led by Dr. Olson, will be updated soon. In the meantime, this new initiative focuses on the difficult questions posed in tumor boards across the country, including how best to treat GBM at recurrence. In managing recurrent or progressive malignant glioma, guidelines chapters are in the final stages of review and will address the following topics: outcome assessment and neurocognition; role of neuro-imaging (progression vs. radiation change); role of biopsy; role of cytoreductive surgery; role of radiotherapy techniques (re-irradiation, stereotactic radiosurgery, brachytherapy); role of chemotherapy; and future innovations.

Dr. Ryken is spearheading the metastatic spine disease guidelines. This guidelines project has proven to be an excellent opportunity for collaborating with other sections (Spine and Tumor Sections), as well, and final drafts are being reviewed this month. Chapters for this project include the following:

- radiographic assessment
- medical management
- indications for surgery
- radiotherapy and combination treatments
- implantable devices including pain pumps
- vertebral augmentation (kypho/vertebroplasty)
- pre-operative embolization
- pathology-specific recommendations

We welcome all participants. Anyone interested in pursuing any of these guidelines topics — or new projects — is strongly encouraged to contact me at [skalkan1@hfh.org](mailto:skalkan1@hfh.org)

# Section on Tumors: Education and Awards

**Andrew T. Parsa, MD, PhD, FAANS**

## **Education: Practical Courses**

The practical courses related to tumor continue to be among the most popular and well-attended at the annual meetings. The American Association of Neurological Surgeons (AANS) now features an update course exclusively devoted to malignant tumors, including relevant topics of interest such as new molecular classifications that have prognostic significance, anti-angiogenic therapies and guidelines for treating brain metastasis. The Congress of Neurological Surgeons (CNS) features a day-long course focusing on benign tumors in the morning and malignant tumors in the afternoon. Due to an outstanding faculty, attendance continues to be excellent for all of the courses.

## **Awards**

The Section on Tumors Awards Committee continues to present 10 awards and one research grant award. Most of the awards are limited to Section members, providing an additional incentive for membership. Support for the awards program encourages the submission of high-quality neuro-oncology work to our meetings. These awards are presented during the annual meetings for the AANS (held this past April) and the CNS, which takes place Oct. 6-10, 2012, in Chicago.

## **Springer Journal of Neuro-oncology Award**

The *Journal of Neuro-Oncology* Award is sponsored by Springer Publishers, and presented at both the annual AANS and CNS meetings to a highly ranked abstract in either clinical or basic science as related to neuro-oncology. The 2012 AANS recipient was Arthur Po-Fei Chou, MD, PhD, of the University of California, Los Angeles (UCLA) for his paper titled "Identification of Retinol Binding Protein 1 (RBP1) Methylation as a Marker of IDH1 and IDH2 Mutation in Gliomas." A \$500 award and a framed certificate were presented to the Dr. Chou.

## **Bittner Award**

The Bittner Award is sponsored by Mrs. E. Laurie Bittner in memory of her husband, Ronald Bittner, and is awarded each year at the AANS Annual Scientific Meeting to the resident or junior faculty member for his or her work on an abstract. The 2012 winner of the Bittner Award was Daniel P. Cahill, MD, PhD, from Massachusetts General Hospital for his submission titled "IDH1 Status Determines the Survival Benefit of Surgical Resection for Malignant Astrocytomas." This award includes 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 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. The 2012 AANS winner was Isaac Yang, MD, from UCLA for his abstract titled "Bevacizumab Treatment in Glioblastoma

Patients is Associated with an Increased Development of Secondary Gliosarcoma." A \$2,000 honorarium accompanies this award.

## **Leksell Award**

The Leksell Award is given each year at the AANS Annual Scientific Meeting for the best submission related to stereotactic radiosurgery and includes a \$2,000 honorarium. The 2012 AANS Leksell Award winner was Edward A. Monaco, MD, PhD, from the University of Pittsburgh for his abstract titled "Impact of Triple Negative Phenotype on Prognosis of Patients with Breast Cancer Brain Metastases following Gamma Knife Surgery."

## **BrainLAB Community Neurosurgery Award**

The BrainLAB Community Neurosurgery Award is awarded at both the AANS and CNS annual meetings. This award is given to a neurosurgeon practicing in a non-academic setting with the best abstract related to central nervous system tumors. There were no eligible recipients for this award at the AANS Annual Scientific Meeting this year.

## **Preuss Award**

The Preuss Award, sponsored by the Preuss Foundation, is given at each of the AANS and CNS meetings to a young scientist investigating brain tumors, within 10 years of training, who has submitted the best basic science research paper. The 2012 AANS winner was Michael Lee Mumert, MD, of The University of Utah for his presentation "Identifying Genes that Promote Spinal Metastasis in Sonic Hedgehog-Dependent Medulloblastoma in Mice." This award includes a \$1,000 honorarium.

## **Integra Award**

The Integra Foundation Award, sponsored by the Integra Foundation, is given at each of the AANS and CNS meetings for the best research or clinical paper. At the 2012 AANS Annual Scientific Meeting, the winner was Andrew Parsa, MD, PhD, FAANS, from the University of California, San Francisco (UCSF) for his presentation "A Phase 2 Multicenter Trial of Autologous Heat Shock Protein-Peptide Vaccine (HSPPC-96) for Recurrent Glioblastoma Multiforme (GBM) Patients Shows Improved Survival Compared to a Contemporary Cohort Controlled for Age, KPS and Extent of Resection." The award includes a monetary component of \$1,000.

## **National Brain Tumor Society Mahaley Award**

The NBTS Mahaley Award is given at each of the AANS and CNS meetings to a neurosurgery resident, fellow or attending who submits the best clinical study in neuro-oncology. At the 2012 AANS Annual Scientific Meeting, the award was given to Frederick F. Lang, MD, FAANS, from MD Anderson Cancer Center in Houston for his talk titled "A Prospective Randomized Trial of Seizure Prophylaxis in Patients Undergoing Surgery for Supratentorial Intraparenchymal Tumors." In addition, Dr. Lang was awarded a \$1,000 honorarium.

### **Stryker Neuro-Oncology Award**

The Stryker Neuro-Oncology Award is given to a resident or medical student who submits a high-ranking brain tumor clinical or basic science abstract. The award is presented at the CNS and AANS annual meetings, and the senior author on the paper must be a member of the Section on Tumors. The 2012 AANS recipient of this award was Phiroz Tarapore, MD, of UCSF for his paper titled "Preoperative Multi-modal Motor Mapping: A Comparison of Magnetic Source Imaging, Navigated Transcranial Magnetic Stimulation, and Direct Cortical Stimulation." The award included a monetary component of \$1,000.

### **Synthes Skull Base Award**

Presented at the AANS and CNS annual meetings, the Synthes Skull Base Award is given to an attending neurosurgeon, resident or fellow within the Section on Tumors who submits the best abstract related to skull base surgery. The winner for the 2012 AANS meeting was Robert M. Starke, MD, from the University of Virginia for his presentation "Gamma Knife Radiosurgery of Skull Base Meningiomas." The award includes a \$1,000 honorarium.

### **The First Joint Neurosurgery and Radiation Oncology Resident Course in Stereotactic Radiosurgery**

**Jason Sheehan, MD, PhD, FAANS**

The American Association of Neurological Surgeons (AANS) and the American Society for Radiation Oncology (ASTRO) recently hosted the first-ever joint resident course in stereotactic radiosurgery. I had the opportunity to direct this course with John Suh, MD.

Held in Evanston, Ill. from Aug. 3-5, 2012, the course was offered to senior residents in neurosurgery and radiation oncology. Residents were nominated by program directors and then selected by the sponsoring societies. More than 30 residents from around the country participated in the course, which lasted more than two-and-a-half days and included lectures as well as practical, hands-on instruction with various radiosurgical platforms. Intracranial and spinal radiosurgery were the focuses of the lectures.

Radiation oncologists, medical physicists and neurosurgeons comprised the faculty. In addition to the course directors and local host, faculty included John Buatti, MD; Eric Chang, MD; Steven Chang, MD, FAANS; Antonio DeSalles, MD, PhD; Peter Gerszten, MD, MPH, FAANS; Minesh Mehta, MD; Samuel Ryu, MD, FAANS; David Schlesinger, PhD; Kris Smith, MD, FAANS; Jason Weaver, MD, FAANS; and Yoshiya Yamada, MD. The course was made possible through unrestricted educational grants from Accuray, Brainlab, Elekta, Medtronic, Mevion, Siemens and Varian. Thank you to the faculty members, corporate sponsors and professional societies for making this multidisciplinary resident course in radiosurgery a tremendous success.

### **Medical Neuro-Oncology/Society for Neuro-Oncology Update**

**Susan M. Chang, MD**

The annual Society for Neuro-Oncology meeting will be held Nov. 15-18, 2012, in Washington, D.C. The scientific chair for the meeting is Ennio Chiocca, MD, PhD, FAANS. In determining the meeting's subject matter, several members of the Section on Tumors served on the scientific committee to enhance the multidisciplinary representation of topics. The meeting will highlight advances in the field over the last year and include initial clinical outcome results for the international randomized trial of the bevacizumab drug for the treatment of newly diagnosed glioblastoma (AVAglio). Additional topics include targeted therapies, immunotherapy, and biological and stem cell mediated therapies. A session on quality of life and a course on the basics of biomarkers also will be featured. There will be several sessions of special interest to members of the Section on Tumors, including an update on brain metastases, pituitary tumors, Neurofibromatosis type II (NF2) and hearing preservation. During the meeting, James Rutka, MD, PhD, FAANS, will be honored with the Abhijit Guha Award for his significant career in neuro-oncology.

### **ABTA Clinical Research Grant**

**Howard Weiner, MD, FAANS**

The American Brain Tumor Association (ABTA) Clinical Research Grant was initiated in 2007 and is designed to provide support to early-stage clinical research projects in hope of developing successful projects that would go on to full-scale funding from the National Institutes of Health, American Cancer Society, and other major funding sources. The grant initially was approved as a one-year grant with \$50,000 dedicated in support. In 2008, the first grant was awarded to John Sampson, MD, PhD, FAANS, of Duke University for his project entitled, "A Pilot Study of in vivo PET Imaging of Gene Expression and Tumor Localization of RNA-modified T cells in Patients with Glioblastoma." Due to this initial success, the grant was extended to a two year \$100,000 grant. In 2009, Andrew Parsa, MD, PhD, FAANS, of the University of California, San Francisco was awarded the grant for his project entitled, "HSP Immunotherapy for Recurrent Glioma Patients: PI(3) Kinase Activation Predicts Poor Clinical Outcomes." The goal of this grant was to identify if PI(3) kinase activation correlates with poor response to brain tumor immunotherapy using the heat shock protein immunotherapy model. The 2011 two-year ABTA Clinical Research Grant was awarded this past spring to Linda Liau, MD, PhD, FAANS, of the University of California, Los Angeles. The next two-year cycle of grant applications will have an anticipated due date in 2013.

# European Association of Neurosurgical Societies (EANS) Meeting

**Zvi Ram, MD**

For the first time, the European Association of Neurological Societies (EANS) will co-host its meeting with the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors, and the Annual International Neuro-Oncology Updates, bringing together the best of two continents. The meeting will focus on neuro-oncology's major topics, including issues pertaining to spine, peripheral nerves, adult and pediatric cases, and more. It is our pleasure to invite you to the EANS Annual Meeting 2013, which will take place Nov.11-14, 2013, in Tel Aviv, Israel.

The meeting will bring together neurosurgeons with interest and expertise in neuro-oncology from Europe, North America and the entire world. The stimulating scientific program will highlight the latest scientific achievements, enhance existing knowledge, and lead to improved diagnosis, prevention and treatment of neoplastic central nervous system disorders. The program will include state-of-the-art plenary lectures, selected presentations from submitted abstracts and ample opportunity for interactive discussions, as well as meet-the-expert sessions with the world's leading neurosurgeons, neuro-oncologists and scientists.

For registration information, visit [www.kenes.com/eans2013](http://www.kenes.com/eans2013).



THE EUROPEAN ASSOCIATION  
OF NEUROSURGICAL SOCIETIES

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EANS Tumor Section  
AANS/CNS Section on Tumors  
Annual International Neuro-Oncology Updates

**Tel Aviv, Israel, 11-14 November, 2013**



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# International Neurosurgical Updates

**Randy Jensen, MD, PhD, FAANS, Chair**

## **Scotland: Sam Eljamel, MD, FRCS**

The Scottish Department of Health and Wellbeing had an initiative to develop Quality Performance Indicators (QPI) for brain cancer. We are working on developing specific, relevant, achievable and measurable QPIs in this field, including one on the extent of surgical resection in malignant gliomas, postoperative imaging of malignant gliomas, the use of gliadel, etc. The National Scottish Brain Tumor convention and the board will be in Edinburgh later this year. The [Society of British Neurological Surgeons \(SBNS\)](#) will meet Sept. 26-28, 2012, in Leeds, England.

## **Japan: Fumio Yamaguchi, MD, PhD**

On Aug. 18, 2012, the 2012 Current Trends in the Management of Malignant Gliomas meeting was held in Tokyo. A wide variety of topics was lectured and discussed, including the results of clinical trials on newly diagnosed or recurrent glioblastoma multiforme performed in Switzerland, Canada, Japan and the U.S.

Brain tumor-related epilepsy is becoming the topic of discussion after the approval of new generation antiepileptic drugs (AED) in Japan. Treatments with drugs such as levetiracetam and lamotrigine are increasing for symptomatic epilepsies in brain tumor patients due to less interaction with chemotherapeutic agents. The next step for AED will be a monotherapy of these drugs that is currently not approved by the government.

## **Future meetings for neurosurgery and neuro-oncology in Japan:**

- 13th Annual Meeting of the Japan Society of Molecular Neurosurgery  
Sept. 20-21, 2012, in Kumamoto, Japan | <http://jsmn.umin.jp>
- 71st Annual Meeting of the Japan Neurosurgical Society  
Oct. 17-19, 2012, in Osaka, Japan | <http://www.jns2012.jp/>
- 30th Annual Meeting of the Japan Society for Neuro-Oncology  
Nov. 25-27, 2012, in Hiroshima, Japan
- 22nd Conference on Neurosurgical Techniques and Tools (CNTT)  
Apr. 12-13, 2013, Matsumoto, Japan
- 33rd Annual meeting of the Japan Congress of Neurological Surgeons  
May 10-12, 2013, in Osaka, Japan
- 4th International MASSIN Congress  
Sept. 4-6, 2013, in Kobe, Japan | <http://www.massin2013.jp>

## **Argentina: Alejandra T Rabadán, MD**

The Advances in *Brain Tumors* meeting, organized by the Section of Neuro-Oncology of the Argentine Society of Cancerology, will be held in Buenos Aires in October 2013.

We are organizing the 5th Symposium of the Society of Cancerology and Congress of the Federation of Societies of Cancerology (MERCOSUR) to be held in Buenos Aires in August 2014. The main topics include controversies in the management of brain metastases and low grade tumors.

The next Latino-American Meeting, CLAN - 2013, will be held in Venezuela (Isla Margarita) in October 2013. The Neuro-oncological Section of the Latin-American Federation of Neurosurgical Societies (FLANC) now is working in the scientific program of the FLANC Neuro-oncological Section.

## **China: Yonggang Wang, MD**

The seventh annual meeting of the Chinese Congress of Neurological Surgeons was held on May 26-27, 2012, in the city of Nanning, located in the Guangxi province. As one of two major Chinese national neurosurgical meetings, more than 1,000 neurosurgeons from all over the China attended this meeting. Many international neurosurgical experts also were invited to give wonderful lectures.

## **Upcoming meetings in China include the following:**

- 1st Microinvasive Neurosurgery Meeting and 2nd Spinal Neurosurgery Meeting  
Sept. 27-29, 2012, in Chengdu, China | <http://www.ccnsnet.org/?action-viewnews-itemid-1189>
- Chinese Neurosurgical Society Annual Meeting  
October 11-13, 2012, in Hangzhou, China | <http://www.cnsmeeting.com/2012/cn/>
- 11th AOSBS Asian-Oceanian International Congress on Skull Base Surgery  
October 27-28, 2012, in Beijing, China | <http://www.aosbs2012.org/>
- 5th Academic Congress of International Chinese Neurosurgical Sciences  
Nov. 2-4, 2012, in Tainan, Taiwan | <http://icfns.cnming.com/>

# New Feature: Topic Review in Neuro-Oncology Genetics of Glioma: An Update for Neurosurgeons

Jennifer Moliterno Gunel, MD; and Cameron Brennan, MD

Cancer is a disease of the genome, and there is hope that identifying underlying genetic mutations of an individual tumor can serve as a roadmap for rational, personalized therapy. For some tumor types, the discovery of genomic mutations in cancer has translated rapidly to clinical practice. To date, the most notable successes have been where mutations in growth factor receptors appear to be abnormally driving pro-growth pathways upon which the tumor depends: HER2 mutation in breast cancer predicts response to the HER2 inhibitor trastuzumab (Herceptin); EGFR mutation in non-small cell lung cancer (NSCLC) is treated by EGFR inhibitors such as erlotinib or gefitinib; gastrointestinal stromal tumors arising from mutation of *c-Kit* or *PDGFRA* respond to imatinib. The translation from discovery to clinical practice can move rapidly: Discovery of the *EML4-Alk* gene fusion in non-small cell lung cancer led to positive clinical trials of the *Alk* inhibitor within just three years. For other tumor types such as glioblastoma, the story has been very different and marked by frustration.

## Receptor Tyrosine Kinases and Primary Glioblastoma

Glioblastoma multiforme (GBM) long has been known to harbor mutations in growth factor receptors present in over more than half of all cases. Clinical trials of inhibitors to these genes have failed to show efficacy, at least as a single therapy. One hypothesis to explain this failure has been that these tumors are quite heterogeneous, with the co-existence of multiple mutations consequently rendering GBMs largely unresponsive to single inhibitors. The hunger to find these other mutations has been answered by The Cancer Genome Atlas (TCGA). This joint NCI/NHGRI pilot project started in 2006 and was intended to demonstrate the feasibility of characterizing a cancer genome at unprecedented detail and breadth. GBM was selected to be the first tumor for evaluation, and the project has completed its goal of analyzing more than 500 GBM tumors, generating hundreds of terabytes of data that now are in the public domain (<http://tcga-data.nci.nih.gov/tcga>).

To date, TCGA has revealed a familiar picture of GBM, but in much greater detail. Genomic analyses of primary GBM samples revealed a high incidence of TP53, RB and receptor tyrosine kinase (RTK)/phosphoinositide 3-kinase (PI3K) pathway dysregulation. Overall, 74 percent of the samples harbored at least one aberration in all three of these major cancer target pathways. Impairment of p53 signaling was found in 87 percent of GBM samples through *CDKN2A* deletion (49 percent), *MDM2* (14 percent) and *MDM4* amplification and mutation/deletion of TP53 (35 percent). Likewise, Rb signaling was mutated in 78 percent of the samples, and RTK/RAS/PI3K activation was found in 88 percent of tumors, including newly-identified contributions from mutations in *NF1* and *PI3K* subunits.

While sequencing technology has reached a level that enables genome-wide cataloging of the driver mutations in a patient's

GBM, the promise of personalized therapy has not yet been realized. EGFR remains a target of particular interest given its amplification in roughly half of primary GBMs and in light of the success treating EGFR-mutant NSCLC with EGFR inhibitors. It turns out, however, that EGFR mutations in GBM commonly target a different region of the protein than the mutations seen in lung cancer. A recent report by Vivanco et al. describes how EGFR mutations in GBM leave the protein in a distinct conformation that is more susceptible to a subset of EGFR inhibitor drugs, so-called type II inhibitors, which have not yet been rigorously tested in brain tumors. Clinical trials are underway using these inhibitors in a pulsatile high dose regimen designed to drive drug across the blood-brain barrier. This pulsatile dosing strategy has been effective in treating EGFR-mutant NSCLC brain metastases using Type I inhibitors and can rescue patients who have had CNS progression on standard daily dosing.

The renewed interest in targeting EGFR and other RTKs with better drugs must be tempered by another important recent finding: Several studies in the last year have revealed a degree of genomic diversity in individual GBM tumors that has never been seen in other cancers. Indeed, amplifications of the RTKs EGFR, *PDGFRA* and *MET* have been found in variable proportions across a single tumor specimen, typically in a pattern of independent tumor cell subpopulations each harboring a dominant RTK. If this is undetected prior to treatment, therapy with a single drug may be doomed to failure. This is particularly relevant for current clinical trials of *PDGFR* inhibitors. Among patients whose GBM is reported to harbor *PDGFRA* amplification by conventional molecular diagnostics, as many as 40 percent may have a second population of tumor cells harboring EGFR or *MET* amplification.

Together, these recent findings inform new rational approaches to targeting the most common “druggable” mutations in primary GBM, incorporating measures of intratumoral heterogeneity into molecular diagnostics and potentially using combinations of inhibitors where the safety profile allows. Additionally, the unprecedented degree of heterogeneity found in GBM suggests that the genetic composition of an individual tumor will change with time depending on prior treatment. Tumor resampling and resequencing may be particularly important for GBM to optimize treatment at different time intervals, particularly during progression or recurrence.

## IDH and Low-grade/Secondary GBM

The initial TCGA study focused on investigating primary GBM, the most common form of which appears to arise *de novo* in older patients. Meanwhile, a complimentary genomic story has been found in secondary GBM that arise from lower-grade gliomas through step-wise progression from lower-grade astrocytomas (WHO II/III). To date, the most prevalent signature mutation

in these tumors involves isocitrate dehydrogenase (IDH). The responsible genes — IDH1 and IDH2 — have been found to be mutated in more than 70 percent of secondary GBM, lower-grade astrocytomas and oligodendrogliomas. This suggests that IDH mutation is an early and powerful event in this form of gliomagenesis. While its exact role in oncogenesis has yet to be fully elucidated, mutations of IDH1 and IDH2 also have been found in a subset of acute myeloid leukemias, as well as other cancers, including melanomas, prostate colon and thyroid cancers.

Isocitrate dehydrogenases normally function in the citric acid cycle to catalyze the conversion of isocitrate to alpha-ketoglutarate (a-KG). IDH1 mutation in glioma occurs at codon 132, which leads to a switch from arginine to a histidine; mutations of IDH2 are far less common, but are at a matching location. These mutations lead to a modified enzymatic function that converts a-KG into an aberrant metabolic product, 2-hydroxyglutarate (2-HG). How 2-HG might promote gliomagenesis remains unclear, but several recent observations have been illuminating. 2-HG is structurally similar to a-KG and can competitively inhibit the activity of enzymes that normally use a-KG as a co-factor. Among such enzymes are important epigenetic “writers” that function to add and remove methyl groups to DNA, and, thereby, regulate what part of the genome is transcribed into RNA. These epigenetic writers are thought to be a critical mechanism by which normal glioneuronal precursor cells transition to their final differentiated state as mature astrocytes and oligodendrocytes. Recent reports show that IDH1 mutation leads to widespread DNA hypermethylation and deregulation of gene expression, and that this is associated with loss of cellular differentiation. Targeting the effects of IDH mutation, either by inhibiting 2-HG production directly or by modulating DNA methylation, may potentially serve as a significant druggable opportunity in low-grade gliomas and secondary GBM.

While the effects of IDH mutation are being actively investigated, it has become increasingly apparent that the mutation is a powerful and independent prognostic marker in high-grade gliomas. GBMs with IDH mutation appear to fare at least as well as non-mutated anaplastic astrocytomas with regard to overall survival and time to progression. In fact, IDH status appears to be a stronger predictor of survival than histologic grade, age or MGMT status alone among high-grade gliomas. IDH mutation also may be prognostic in low-grade (WHOII) astrocytomas and oligodendrogliomas, but there is no consensus to date on whether this is independent of other prognostic factors. A commercial antibody to detect the R132H mutation by immunohistochemistry is available, and there has been increasingly widespread adoption of the diagnostic among neuropathologists.

## Conclusion

In recent years, significant advances have been made in genomic sequencing technologies, and we are now equipped to better understand the complex molecular make-up of gliomas. For instance, non-biased genome-wide sequencing is the only way IDH mutations would have been discovered, since metabolic enzymes were not initially thought to be key contributors to cancer. This pivotal finding has led to a rapid adoption of a new prognostic

biomarker that may indeed supplant conventional histologic grading in the management of glioma. This profound effect underscores the importance of using next generation sequencing in the study of gliomas. Such techniques were not available to the TCGA in 2006, but have been since added to the pipeline. New genome-wide sequencing results for nearly 300 primary GBM samples are anticipated to be released before the end of the year. A TCGA project in low-grade gliomas currently is underway and has accrued nearly 150 tumors thus far.

This is an exciting time in glioma research, and neurosurgeons are assuming an increasingly important role in this process. The complex intratumoral heterogeneity of GBM presents a significant barrier to effective, durable treatment and the need for precise sampling of tumors is increasingly apparent. Modern clinical trials of targeted inhibitors routinely incorporate surgical arms to biopsy patients on the investigational drug and obtain critical confirmation that the target has been hit. The continued effort to better catalog the underlying genomic alterations in glioma is producing an atlas against which an individual's tumor can be compared and mapped so that more information can be inferred from the individual's sample. The initial failure of therapy aimed at genomic targets in GBM has been sobering, but a closer look at the tumor genome is beginning to shed light on why those initial trials may have failed and how new trials should be designed.

## Suggested Readings

1. The Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. 2008; 455: 1061-1068.
2. Dunn GP, Rinne ML, Wykosky J, et al. Emerging insights into the molecular and cellular basis of glioblastoma. *Genes Dev*. 2012 Apr 15; 26(8): 756-84.
3. Vivanco I, Robins HI, Rohle D, et al. Differential sensitivity of glioma- versus lung cancer-specific EGFR mutations to EGFR kinase inhibitors. *Cancer Discov*. 2012; 2(5): 458-71.
4. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH-1 mutated glioblastomas, and IDH-1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol*. 2010; 120 (6): 707-18.
5. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008; 321(5897): 1807-12.
6. Szerlip NJ, Pedraza A, Chakravarty D, et al. Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response. *Proc Natl Acad Sci*. 2012; 109(8):3041-6.
7. Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature*. 2012; 483(7390):479-83.
8. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature*. 2012; 483(7390):474-8.

# Clinical Trials in Neuro-Oncology

**Manish K. Aghi, MD, FAANS; Costas G. Hadjipanayis, MD, PhD, FAANS;  
and John A. Boockvar, MD, FAANS**

The clinical trials subcommittee of the AANS/CNS Joint Section on Tumors Executive Committee is a recently formed group dedicated to increasing the involvement of neurosurgeons in brain tumor clinical trials. The subcommittee is interested in increasing the involvement of neurosurgeons in trials of all kinds, including observational trials and trials for every type of brain tumor. The simple goal of increasing patient enrollment into trials and registries allows all neurosurgeons to contribute to the advancement of the field of neuro-oncology. The Section on Tumors has provided a complete list of clinical trials in neuro-oncology with a brief description of each trial's rationale at [www.tumorsection.org](http://www.tumorsection.org).

The section also would like to report a recently completed trial with impactful results that was presented at the June 2012 American Society of Clinical Oncology (ASCO) meeting by Martin J. van den Bent, MD, PhD. The abstract by the European Organization for Research and Treatment of Cancer (EORTC), entitled "Long-term follow-up results of EORTC 26951: A randomized phase III study on adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors (AOD)," describes the striking difference in the primary endpoints of overall survival (OS) and progression-free survival (PFS) for patients receiving chemotherapy in combination with radiation therapy over the 17-year trial period. The study included 368 patients between 1996 and 2002 with newly diagnosed, previously untreated anaplastic oligodendroglioma, or oligoastrocytoma randomized to treatment with 59.4 Gy of fractionated radiotherapy alone or followed by six cycles of the chemotherapy regimen known as PCV (procarbazine (Matulane), CCNU (lomustine, CeeNU) and vincristine (Oncovin, Vincasar)). Chromosomal 1p/19q, IDH, and MGMT

promoter methylation status were determined in 300, 167 and 186 patients, respectively. The addition of chemotherapy improved OS by 11 months in the entire intent-to-treat population (median 42 vs. 31 months). PFS nearly doubled with chemotherapy to a median of 24 months in comparison to 13 months after radiation therapy alone. Of particular note, three-quarters of the patients in the radiotherapy group received chemotherapy after disease progression, confirming the need for early chemotherapy after radiation. The increase in OS and PFS was found almost exclusively in the subgroup of patients with the chromosomal co-deletions of 1p and 19q. Seventy-six of 300 patients tested were found to have the 1p/19q co-deletion. Their risk of death was 44 percent lower when those patients received chemotherapy following radiotherapy with a gain of 28 months in median OS. In the 1p/19q group, the median OS for those patients undergoing radiotherapy and chemotherapy was not reached after more than 11 years (140 months) of follow-up compared with a median OS of approximately nine years (112 months) in the patients receiving only radiation therapy. In the 224 patients without the 1p/19q co-deletions, the difference in OS was non-significant. There was a slight trend towards improved OS in MGMT methylated and IDH mutated tumors versus unmethylated and IDH wild-type tumors. The seminal trial by Van Den Bent et al. highlights the need for early chemotherapy after radiation for patients with malignant oligodendroglial tumors. Those patients with 1p/19q co-deletion should be the main candidates for chemotherapy after radiation. The PCV chemotherapy regimen has largely been replaced with the oral agent temozolomide (Temodar) due to the associated side effects.

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