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From the Chairman



Frederick F. Lang, MD, FAANS, FACS

With this newsletter, I approach the end of my two-year tenure as chair of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors. During these two years, it has become increasingly evident to me that the Section on Tumors is the premier neurosurgical-oncologic organization in the world. The members of this Section, and especially the executive committee, have shown that they are dedicated to excellence and to selfless volunteerism. The chairs of each of the committees have done superior jobs. The international members have represented their countries well. The advisory board has consistently provided sage advice. The staff and leadership in the AANS and CNS have been a tremendous help.

Secretary/Treasurer Frederick Barker, MD, FAANS, FACS, has done yeoman's work and has been an outstanding partner throughout the past two years. Past Chair, Jeffrey Bruce, MD, FAANS, FACS, has been a great source of guidance. So, as my term approaches its end, I extend my most sincere thanks to the executive committee and to all the members of the Section on Tumors for making my time as chair so enjoyable and rewarding.

I encourage all members of the Section on Tumors to support the Section by attending our flagship meeting, namely, the 10th Biennial Satellite Tumor Symposium, which will be

held in New Orleans, from April 26-28, 2013, at the Hilton New Orleans hotel just prior to the AANS 81st Annual Scientific Meeting. We have arranged for this meeting to be held on Friday and Saturday so Section members can attend both the Satellite Symposium and the AANS Annual Scientific Meeting without over-extending their time away from home. Scientific Program Chairs Nadar Sanai, MD, and Isaac Yang, MD, have put together an amazing program, including oral presentations of the best original research selected from more than 200 abstract submissions. In addition, they have arranged two outstanding keynote lectures, one from Eric Holland, MD, PhD, who will speak on "Mouse Models of Glioma Subtypes," and the other by Linda Liau, MD, PhD, FAANS, who will present her work on "Imaging Paradigms to Characterize Tumor Genetics." Equally exciting, we have partnered with the Society for Neuro-Oncology to organize the first-ever "Special Symposium on Meningiomas," which will be a full-day event focusing on the most recent advances in the basic biology and treatment of meningiomas, including oral presentations of selected meningioma abstracts. In addition, Mike Vogelbaum, MD, PhD, FAANS, has organized an outstanding line-up of speakers from all disciplines who will focus on meningiomas from the perspectives of neurosurgery, neuro-oncology, radiation oncology, pathology, radiology and basic science. Rounding out each evening, Andrew Parsa, MD, PhD, FAANS, has organized several industry-sponsored seminars that should be of great interest to Section members, including seminars on the "Latest Advances in Immunotherapy" and "Surgical Adjuncts to

continued on page 2

Optimize Tumor Resection.” Finally, the meeting will end with a reception celebrating the 10th anniversary of the Biennial Satellite meeting, with a special presentation to this year’s winner of the Wilson Award. I encourage all members of the Section to attend this meeting, and to extend invitations to their neuro-oncology colleagues. I suspect that this will be one of the best satellite symposiums in the history of the Section.

I also would like to encourage Section members to submit abstracts and to attend the first-ever international meeting on neuro-oncology organized between the European Association of Neurological Societies (EANS) and the AANS/CNS Section on Tumors. As described in this newsletter, this meeting will be held in Tel Aviv, Israel, Nov. 11-14, 2013, and will bring together neurosurgical oncologists in all subspecialties (glioma, metastases, spine, skull base, radiosurgery, pediatrics, peripheral nerve) from the United States and all parts of Europe. Meeting Co-Chairs Zvi Ram, MD, (EANS); Shlomi Constantini, MD, MSc, (EANS); and Jeffrey Weinberg, MD, FAANS, FACS, (AANS/CNS Tumor Section) have organized an outstanding Scientific Program Committee, and have invited speakers from across the globe. I hope that all members of the Section on Tumors will be able to attend this historic meeting, which I envision to be the first of many international collaborative meetings co-sponsored by the Section and the EANS.

In addition to organizing outstanding educational activities such as the free-standing meetings described above and the symposia within the annual meetings of the AANS and CNS, I would be remiss if I did not point out that through hard work and dedication over the past two years, the current Executive Committee has made progress in many initiatives, including: 1) strengthening the financial basis of the Section; 2) securing for the first time a contract with our section-sponsored journal, the *Journal of Neuro-Oncology*, that defines our relationship and established a fair price; 3) working with the Society of Neurological Surgeons and the Accreditation Council for Graduate Medical Education (ACGME) to develop the tumor components for the Matrix Curriculum and the Milestone Project; 4) developing the cranial module for The National Neurosurgery Quality Outcomes Database, organized

through NeuroPoint Alliance; 5) continuing support of research through donations to the Neurosurgical Research Educational Fund (NREF) and through the Brainlab International Research Fellowship; 6) advancing the Section’s role in clinical research by securing Section representation in the Alliance for Clinical Trials in Oncology, thereby giving organized neurosurgery “an official seat” in a critical clinical trial organization for the first time; 7) advocating for members’ interests through donations to the Washington Committee; 8) securing a contract to develop an agile and effective website as the new face of the Section on Tumors; 9) establishing a new award, the Ab Guha Award, which recognizes an accomplished neuro-oncology investigator who achieves significant results both in the laboratory and the clinic and who embodies the collaborative and volunteer spirit; 10) reaching out to other sections, such as the Spine Section, and to other like-minded organizations, such as SNO and EANS, to broaden our influence and enhance our membership offerings; 11) supporting the interests of our younger members through receptions at annual meetings; and 12) continuing communication through this outstanding newsletter.

Clearly, all of these successes would not have been possible without the dedication and hard work of the membership of the Section. So as I finish my term, I express my gratitude to all the members of the AANS/CNS Section on Tumors for your support throughout the past two years. I hope that I have helped to further the mission of the Section. As I pass the torch to our next chair, Dr. Barker, I am confident that the Section on Tumors will continue to lead the way in our continued quest to cure central nervous system tumors.

Sincerely,



Frederick F. Lang, MD, FAANS
Chair
AANS/CNS Section on Tumors

The 10th Biennial Satellite Tumor Symposium

The 10th Biennial Satellite Tumor Symposium of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors will be held April 26-27, 2013, at the Hilton New Orleans Riverside Hotel. This meeting is scheduled conveniently on the Friday and Saturday just before the start of the 2013 AANS Annual Scientific Meeting, which takes place April 27-May 1, 2013, at the Ernest N. Morial Convention Center. All neurosurgeons, physicians and scientists interested in central nervous system tumors are encouraged to attend.

The Scientific Program Committee has organized an outstanding program in which the most recent advances in clinical, translational and basic neuro-oncology will be presented. Exciting keynote lectures are planned, including those by Eric Holland, MD, PhD (“Mouse models of Glioma Subtypes”); and by Linda Liau, MD, PhD (“Imaging Paradigms to Characterize Tumor Genetics”). Evening seminars on the “Latest Advances in Immunotherapy” and “Surgical Adjunct to Optimize Tumor Resection” have been arranged.

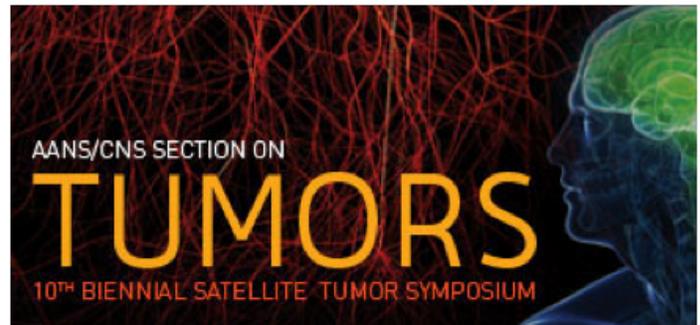
The Scientific Program Committee also has organized the first comprehensive seminar of its kind on the “Multi-disciplinary Management of Meningiomas.” Co-sponsored by the Society of Neuro-Oncology (SNO), this special session will take place on the second day of the Satellite Symposium and explore all aspects of meningiomas from a multi-disciplinary perspective. Expert neurosurgeons, pathologists, translational scientists, radiologists, radiation oncologists and medical oncologists will discuss:

- Molecular categorization of meningiomas
- Current mouse models of meningiomas
- Recent advances in meningioma imaging
- Multi-modal therapeutic approaches to meningiomas
- The newest molecular therapeutic targets
- Evolving clinical trial opportunities for patients with meningiomas

Submit your abstracts now, including meningioma abstracts for the special session.

The Satellite Symposium will feature peer-reviewed oral and poster presentations, including select talks with accompanying expert discussants. In addition, the Multi-Disciplinary Management of Meningiomas seminar will feature meningioma-focused abstracts. We encourage you to submit your most exciting work related to the therapy and science of tumors of the central and peripheral nervous system, and/or abstracts specifically related to meningiomas.

The abstract center is open currently. To submit an abstract, visit <https://myaans.aans.org/MyAANS.aspx> and login. Select “Abstract Corner” from the left sidebar and then select “AANS/CNS 10th Biennial Satellite Tumor Symposium” to complete the form. You will need your MyAANS login (e-mail on file with AANS) and password to access/edit your abstract during the submission period.



Note: You do not need to be a member of the AANS to create an account. If you have any questions on how to submit your abstract, or if you have forgotten your login information, please contact Rhonda Foss at rdf@aans.org.

Please note that this submission site works best by using the Firefox browser. A free download is available at <http://www.mozilla.org/en-US/>.

The abstract submission deadline is Monday, Feb. 4, 2013.

For information on the AANS/CNS 10th Biennial Satellite Tumor Symposium, visit <http://www.aans.org/TUMOR/default.html>.

Skull Base Surgery Update Nicholas Levine, MD, FAANS

The 23rd Annual North American Skull Base Society (NASBS) Meeting was held at the Doral Golf Resort and Spa in Miami from Feb. 15-17, 2013. The meeting — which had its highest attendance of all-time with more than 400 participants — was preceded by open and endoscopic dissection courses that were held on Feb. 13 and 14. Plans for the 24th Annual Meeting in San Diego are underway. Abstract submission for the meeting will open May 2013.

The combined course for senior neurosurgery, head and neck surgery residents and fellows will be held once again at Louisiana State University in New Orleans, and promises to be a defining experience for trainees interested in multidisciplinary skull base approaches and techniques.

AANS 2013 Annual Meeting Preview

Christopher McPherson, MD, FAANS

This year's American Association of Neurological Surgeons (AANS) 81st Annual Scientific Meeting program offers exciting and innovative presentations highlighting the excellent work done by neurosurgeons. On Monday, April 29, 2013, Antonio Chiocca, MD, PhD, FAANS, will present the Ronald L. Bittner Lecture titled "Viruses: Cause or Treatment of Malignant Glioma?" Several of the top-ranked abstracts focusing on innovations in the diagnosis, management and treatment of tumors will be presented. Finally, a new and exciting addition to the scientific session is the first Neurosurgical Face-Off: "Acoustic Neuromas, Radiosurgery versus Surgical Resection." Jason Sheehan, MD, PhD, FAANS, will present the case for radiosurgery, and John Golfinos, MD, FAANS, will present the case for surgical resection. This promises to be a lively debate.

On Tuesday, April 30, 2013, the Tumor I Section will focus on the "Management of Challenging Brain Tumors," featuring case-based, clinical presentations by the experts sharing pearls and challenges to managing some of the most difficult brain tumors. Frederick Lang Jr., MD, FAANS, will present on insular tumors

and Jeff Bruce, MD, FAANS, FACS, will share his expertise on pineal region tumors. Alessandro Olivi, MD, FAANS, will discuss lateral ventricular and thalamic tumors and, in addition, James Rutka, MD, PhD, FAANS, will talk about the management of fourth ventricular and brainstem tumors.

On Wednesday, May 1, 2013, the Tumor II Section symposium will be the "Future of Skull Base Surgery." This session will focus on the changing landscape of skull base surgery, discussing the issues of minimally invasive and endoscopic surgery versus open surgery and the role of molecular therapeutics. Harry van Loveren, MD, FAANS, will open the session to discuss the past, present, and future of skull base surgery. Theodore Schwartz, MD, FAANS; Franco De Monte, MD, FAANS, FACS; and Randy Jensen, MD, PhD, FAANS, will also be speaking during the session.

The 2013 AANS Annual Scientific Meeting promises to be one of the most interesting and educational events highlighting the innovations and advances neurosurgeons are making in the diagnosis, treatment, and management of brain and spine tumors.

CNS 2012 Annual Meeting

Viviane Tabar, MD, FAANS

The American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors presented its program at the CNS annual meeting in Chicago. The main symposium, titled "Primary Spinal Neoplasms: Treatment and Science Updates," was held on Oct. 9, 2012. The symposium presented an updated perspective on current management of primary spinal tumors, along with an overview of the latest findings in tumor biology and ongoing clinical trials. Frederick Lang Jr., MD, FAANS, introduced the symposium. George Jallo, MD, FAANS, presented his talk on intramedullary spinal cord tumors. This was followed by an excellent discussion by Paul McCormick, MD, MPH, FAANS, on the surgical management of schwannomas. Schwannomas account for more than 90 percent of intradural extramedullary tumors. Neurofibromatosis type 2 (NF2) and schwannomatosis represent a particularly challenging problem that requires a careful balance of observation and surgical intervention. Ongoing research is focused on the NF2 gene product merlin or neurofibromin, whose functional loss is responsible for the development of schwannomas. Merlin acts a tumor suppressor protein as it inhibits mitogenic signaling by integrins and tyrosine receptor kinases as well as nuclear ubiquitin

ligase. These proteins could represent attractive targets for molecular therapy.

Lawrence Rhines, MD, FAANS, provided an in-depth discussion of the management of chordomas. Along with the refinement of surgical techniques that aim at the complete resection of these unusual tumors, there remains concern about the high rates of recurrence despite surgery and radiation. In recent years, much progress has been made in dissecting the molecular biology of chordomas, leading to clinical trials with receptor tyrosine kinase inhibitors, such as Imatinib. The speakers subsequently held a panel discussion and responded to questions from the audience.

Dr. Lang then introduced the special lecturer, Jay Loeffler, MD. The Section on Tumors had extended a special invitation to Dr. Loeffler, who shared his expertise in proton beam therapy, and emphasized the distinct biology and applications of this modality. The symposium was well-attended, and the audience provided much positive feedback.

The Section on Tumors was equally well-represented at the digital poster sessions and at the scientific sessions, which featured diverse and mostly award-winning presentations.

Academic Community Alliance (ACA) Committee

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

The goal of the Academic Community Alliance (ACA) committee is to create avenues of communication between academicians and community neurosurgeons for dissemination of up-to-date clinical information, and to provide a venue for open dialogue regarding difficult brain tumor cases. To meet this goal, video content for the online brain tumor library (The Neurosurgical Atlas, shown in Figure 1) and for the mobile “AANS Operative Grand Rounds” application continues to be developed and uploaded.

The American Association of Neurological Surgeons (AANS) Operative Grand Rounds is an ever-expanding archive of videos related to tumor resection techniques ranging from “Brain Mapping for Resection of Insular Gliomas: Lessons Learned” by Bob Carter, MD, PhD, FAANS, to “Principles of Radiosurgery: Methods and Outcomes” (Figure 2) by Jason Sheehan, MD, PhD, FAANS. These archived videos are accessible via the Neurosurgical Atlas website, and are free to download via mobile applications.

The free AANS Operative Grand Rounds mobile application is available for both Apple and Android devices (Figure 2). These mobile applications allow for easy access to all videos contained within The Neurosurgical Atlas, and provide instant access to topics relevant to practicing physicians.

Future Neurosurgical Atlas plans include continued expansion of the educational video content and hosting of regional webinars that will focus on pairing academic and community neurosurgeons together for bi-directional education activities.

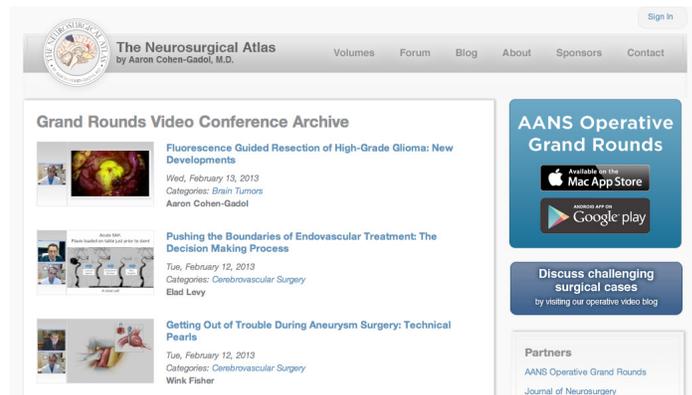


Figure 1. A screen capture of the “Grand Rounds Video Conference Archive” Web page showing archived operative videos. Users can submit challenging cases for review by experts in the field and the greater neurosurgical committee at-large at this link: <http://www.neurosurgicalatlas.com/index.php/aans>.



Figure 2. A screen capture of the mobile application “AANS Operative Grand Rounds,” available in the Apple and Android application stores for video-content viewing.

Education and Awards

Andrew T. Parsa, MD, PhD, FAANS

Education: Practical Courses

The practical courses and seminars 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 AANS course is co-directed by Mike Weaver, MD, FAANS, and Andrew Parsa, MD, PhD, FAANS. The Congress of Neurological Surgeons (CNS) features an update course that runs all day with focus on benign tumors in the morning and malignant tumors in the afternoon. The CNS course is co-directed by Jason Sheehan, MD, PhD, FAANS, and Dr. Parsa. The attendance for both practical courses and all seminars continues to be excellent, due to the outstanding faculty from the AANS/CNS Section on Tumors.

Awards

The Awards Committee continues to be active with ten awards and one research grant award administered through the Section on Tumors Awards Committee. Most of the awards are limited to Section members, providing an additional incentive for membership. Support for the awards program encourages submission of high-quality neuro-oncology work to our meetings. The awards given at the 2012 CNS Annual Meeting in Chicago were as follows:

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 meetings to a highly-ranked abstract in either clinical or basic science as related to neuro-oncology. The 2012 CNS recipient was Pascal O. Zinn, MD, PhD, for his paper titled “Radiogenomic Mapping of MRI-FLAIR phenotypes.” A \$500 award and a framed certificate were presented to the winner.

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 CNS winner was Raymund L.M. Yong, MD, for his abstract titled “Establishing a link between genomic patterns in GBM.” A \$2,000 honorarium accompanied this award.

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 non-academic setting with the best abstract related to central nervous system tumors. Charles Teo, MD, won the award at the CNS in 2012 for his paper titled “Surgical Management of Adult Intrinsic Brainstem Tumors.” A \$1,000 honorarium accompanied this award.

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 CNS winner was Shih-Shan Lang, MD, for the paper titled “Development of Pediatric Glioma Models for BRAF-targeted Therapy.” This award includes a \$1,000 honorarium.

National Brain Tumor Society (NBTS) 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 CNS meeting, the award was given to Ian F. Pollack, MD, FAANS, for his talk titled “Peptide Vaccine Therapy for Childhood Gliomas.” In addition, Dr. Pollack was awarded a \$1,000 honorarium.

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 on the paper must be a member of the AANS/CNS Section on Tumors. The 2012 CNS recipient of this award was Gillian Harrison for her paper “Quantitative Volumetric Response after Gamma Knife Radiosurgery for Meningiomas.” A monetary component of \$1,000 was included along with an award certificate.

Synthes Skull Base Award

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. This award is given at the annual meetings of the AANS and CNS. The winner for the 2012 CNS meeting was Isaac Yang, MD, for his presentation “Stereotactic Radiotherapy is Associated with Improved Hearing Preservation and Tumor Control for Vestibular Schwannoma.” The award includes a \$1,000 honorarium.

Case Review in Neuro-Oncology

Christopher McPherson, MD, FAANS

A right-handed 43-year-old white female, previously healthy, presented with a generalized tonic clonic seizure and was admitted to the neurology service. Following her seizures, she recovered completely and was neurologically intact. She complained of headache requiring management with decadron. An MRI was obtained and showed two lesions hyperintense on FLAIR (Fig. 1 a, b, c) — a large right temporal non-enhancing lesion and a second lesion in the cingulate gyrus with patchy enhancement (Fig. 2). The patient underwent extensive work-up by neurology with negative lumbar puncture results. MRI spectroscopy and perfusion then was obtained and showed results of elevated choline: creatinine ratio in both lesions and elevated perfusion consistent with tumor, likely glioma.

1. What would be your initial management recommendation?
 - A) Observation
 - B) Surgery (Either biopsy or resection)
 - C) Empiric Radiation +/- Chemotherapy
2. Assuming surgery is your recommendation, what would be your surgical plan?
 - A) Biopsy of the temporal lesion
 - B) Biopsy of the cingulate lesion
 - C) Surgical resection of the larger temporal lesion
 - D) Surgical resection of the cingulate lesion
 - E) Surgical resection of both lesions

The patient underwent biopsy of the cingulate lesion without complication. Pathology showed WHO II Diffuse Astrocytoma. The tumor stained positive for IDH-1 and p53, with a Ki-67 index of two percent. The specimen tested positive for MGMT methylation and 1p19q was intact.

3. What would be your recommendation at this point?
 - A) Observation
 - B) Surgery for planned maximal resection of the temporal lesion
 - C) Surgery for planned maximal resection of both lesions
 - D) Radiation therapy alone
 - E) Radiation therapy with temozolomide
4. If the pathology had been WHO II Oligodendroglioma 1p19q co-deleted, what would your recommendation be in that situation?
 - A) Observation
 - B) Surgery for planned maximal resection of the temporal lesion
 - C) Surgery for planned maximal resection of both lesions
 - D) Radiation therapy alone
 - E) Radiation therapy plus chemotherapy

To review the results of a survey regarding the management of this case from the Section on Tumors' executive committee, go to the Section website at www.tumorsection.org.

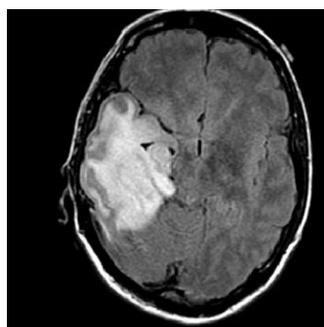


Figure 1a

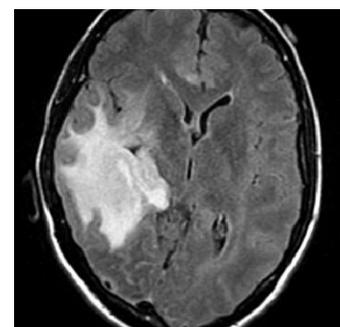


Figure 1b

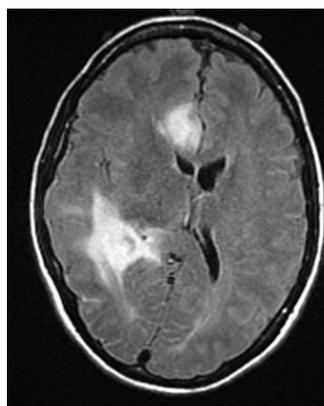


Figure 1c

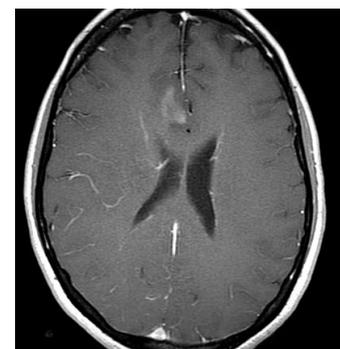


Figure 2

Update From Australia: Australian Neuro-Oncology to Go Global

Charlie Teo, MD

The Cure for Life Foundation (CFLF) was established in 2003, and within three years became the largest funder of brain cancer research in Australia. The Foundation has raised over eight million dollars since, and continues to fund most of the dedicated laboratories in Sydney and several other cities. The Cure for Life Foundation's strategy has changed from a traditional grant-making body to one that also funds collaboration, enablers and gaps to accelerate the cure for brain cancer.

The Foundation is leading this change through the joint development and funding of a national collaborative brain cancer research initiative Brain Cancer Discovery Collaborative (BCDC) pioneered in January 2012 by Associate Professor Terrence Johns (Monash University) and Dr. Kerrie McDonald (The University of New South Wales [UNSW]) bringing together core brain cancer researchers involved in basic, pre-clinical and clinical research to catalyse exponential growth in discovery and a higher volume of clinical trials.

The next step will be to take this national template and go global. To this end, the CFLF will hold "think tanks" on seven continents. The first one, scheduled for March in Australia, will be attended by a variety of leading experts from within the brain cancer community including Webster Cavenee, PhD, distinguished professor and director of the Ludwig Institute of Cancer Research at the University of California, San Diego; Sarah Caddick, Neuroscience Advisor to Lord Sainsbury of Turville and the Gatsby Charitable Foundation; Kees Kleiheus van Tol, system architect for the World Health Organization's PUBCAN database; and outside experts who have the perspective, influence and intellect to offer fresh insights on how to reorganize ways of working to affect and sustain change.

The Foundation continues to support a number of research programs including "The Involvement of the Kynurenine Pathway in Glioma Pathogenesis," led by Professor Gilles Guillemin at Macquarie University and The Brain Cancer Wing of the Lowy Cancer Centre at the UNSW headed by Dr. Kerrie McDonald.

Dr. McDonald's group recently published in the *European Journal of Cancer* evidence for a single nucleotide polymorphism (SNP) within the MGMT promoter. They found that this SNP was strongly prognostic when patients were treated with temozolomide. The test to detect the SNP is simple, quick and accurate, giving hope that this test could replace the much more cumbersome MGMT methylation test. Dr. McDonald and the CFLF inaugural visiting fellow, Prof. Paul Kleihues, published a review on biomarkers and their use in glioblastoma. This can be found in the *Frontiers of Neuro-oncology* journal. Professor Andrew Boyd and Dr. Bryan Day, both members of the Brain Cancer Discovery Collaboration, showed that the receptor tyrosine kinase EphA3 is frequently overexpressed in glioblastoma multiforme (GBM) and, in particular, in the most aggressive mesenchymal subtype. These results identify EphA3 as a functional, targetable receptor in GBM.

Charlie Teo, MD, at the Center for Minimally Invasive Neurosurgery, continues to run a fellowship program that attracts more than 200 applications internationally. Since our last newsletter, Mike Sughrue, MD (University of California, San Francisco), Dave Wilson, MD, (Barrow Neurological Institute), and Samy Elhammady, MD, (University of Miami) have completed the fellowship and have published six peer-reviewed articles in the neuro-oncological literature.

In Queensland, from a clinical perspective, the first case in Australia of Gliolan-assisted resection of a GBM was performed at the Wesley Hospital more than a year ago now, and Prof. Walker and his team continue to use this technology regularly. The role of Vivien Biggs, their neuro-oncology nurse practitioner, continues to expand. Unfortunately, her position continues to be a rare one in Australia.

From a research and trial perspective, they have had their research presented at local, national and international meetings, including the Society of Neuro-Oncology meeting held in Washington, D.C., in November 2012, Cooperative Trials Group for Neuro-Oncology (COGNO) in early 2012, and Neurosurgical Society of Australasia (NSA) in September 2012.

Scientists and clinicians continue to collaborate in the fields of immunotherapy (the role of cytomegalovirus in glioma), and phase I trials (adoptive T cell therapy for recurrent GBM). In addition, they are continuing their research together with neuropsychologists at both University of Queensland and Griffith University into neuropsychological deficits in brain tumour patients, and the psychosocial impacts of brain tumours on patients and their families, respectively.

Following on from a phase I study in recurrent GBM, they soon are starting a phase I study into adoptive T cell therapy in newly diagnosed GBM.

In Western Australia (WA), they have had another active year in brain tumor research. In clinical trials research, the main Perth neuro-oncology site, Sir Charles Gairdner Hospital, currently is participating in the ACT IV study for newly diagnosed glioblastoma and the JBAL study for recurrent glioblastoma. They recruited a number of patients to the now-closed Australian CABARET study for recurrent glioblastoma. In addition, they continue to randomize registered patients to the EORTC low-grade glioma study and to participate in the CATNON trial for newly diagnosed anaplastic astrocytoma. In local research, a quantitative study of the needs of more than 100 patients with high-grade glioma and their caregivers has completed accrual recently, and results currently are being analyzed. The same team has received funding to start a randomized study of an intervention to reduce carer unmet needs and distress, and they hope to receive further funding to expand the intervention to other Australian sites.

The scientists in WA also have recently completed a pilot study of C-MET and FLT-PET imaging in high grade glioma, and continue to collect biospecimens and clinical data for the Australian Genomics and Outcomes of Glioma (AGOG) biobanking project.

Update From Italy

Francesco DiMeco, MD

A number of spending cuts and new restrictions have been implemented by the Italian government as a consequence of the economic downturn. Most likely, this course of action will have a heavy impact on the Health Care Service, too. The bulk of such measures will be aimed mainly at resizing public hospitals, where the majority of Italian neurosurgeons practice. Moreover, the central government's financial support (via the National Health Fund) to the health service will be reduced further by approximately three billion euros in two years, starting this year. Neurosurgeons in Italy clearly are concerned about how these cuts will affect the health-care system as a whole, in addition to their clinical and academic activities.

The Italian Neurosurgical Society has recently created a section on brain tumors, which will be coordinated by Professor Lorenzo Bello from Milan. The aims of the section are as follows:

- 1) To provide society members with updates about research and clinical practice guidelines in the field of brain tumors.
- 2) To coordinate and support society activities related to brain tumors.
- 3) To integrate the section activities with those of other groups at an international level.

- 4) To provide patients with a platform for sharing information and support about brain tumors and related conditions.

The 61st Congress of the Italian Neurosurgical Society (SINCH) will be held Oct. 10-12, 2013, in Palermo, Italy.

The next European Association of Neurological Societies (EANS) Congress will be held Nov. 11-14, 2013, in Tel Aviv, Israel, as a joint meeting with the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors. The meeting will focus on major topics in neuro-oncology, and will bring together neurosurgeons from all over the world who have interest and expertise in neuro-oncology. The stimulating scientific program will highlight the latest scientific achievements, enhance existing knowledge, and aim to improve diagnosis, prevention and treatment of neoplastic central nervous system disorders. The program will include state-of-the-art plenary lectures, selected keynotes and ample opportunity for interactive discussions, as well as meet-the-expert sessions with the world's leading neurosurgeons, neuro-oncologists and scientists. We look forward to seeing our North American colleagues in Tel Aviv.

Update From Japan

Fumio Yamaguchi, MD, PhD

In Japan, Phase III clinical trial of 5-aminolevulinic acid for photodiagnosis of malignant glioma had been conducted as a joint project of SBI Pharma and Novel Pharma. Now we are awaiting the official approval of its use for malignant glioma.

The clinical trial titled "Photodynamic Therapy for Malignant Brain Tumors Using Solid-state Lasers and Talaporfin Sodium" is currently being carried out at Tokyo Women's Medical University and Tokyo Medical University. Vaccine therapies also are under investigation. Another trial in progress is a clinical trial of personalized peptide vaccine for HLA-A24 patients for recurrent or progressive glioblastoma multiforme, conducted at Kurume University. The result of this project will be disclosed around 2015.

Future meetings for neurosurgery and neuro-oncology in Japan include the following:

- The 33rd Annual Meeting of the Japanese Congress of Neurological Surgeons
May 10-12, 2013, Osaka, Japan | <http://www.jcns2013.jp/>
- The 31st Annual Meeting of the Japan Society of Brain Tumor Pathology
May 24-25, 2013, Tokyo, Japan | <http://btp31.umin.jp/index.html>
- 2013 Current Trends in the Management of Malignant Gliomas

July 27, 2013, Tokyo, Japan

- The 4th International MASSIN Congress
Sept. 4-6, 2013, Kobe, Japan | <http://www.massin2013.jp>
- The 18th Annual Meeting of the Japanese Congress for Brain Tumor Surgery
Sept. 19-29, 2013, Otsu, Japan | <http://www.congre.co.jp/bts2013/index.html>
- The 72nd Annual Meeting of the Japan Neurosurgical Society
Oct. 16-18, 2013, Yokohama, Japan | <http://www.jns2013.jp/>
- The 31st Annual Meeting of the Japan Society for Neuro-Oncology
Dec. 8-10, 2013, Miyazaki, Japan

In addition, two other recent meetings were held:

- The 23rd Annual Meeting of the Japan Society for Hypothalamic and Pituitary Tumors
March 15-16, 2013, Kagoshima, Japan | <http://jshpt23.umin.ne.jp/>
- The 22nd Conference on Neurosurgical Techniques and Tools (CNTT 2013)
April 12-13, 2013 Matsumoto, Japan | <http://cntt2013.umin.ne.jp/>

Tumor Section Guidelines

Steven N. Kalkanis, MD, FAANS

In keeping with our goal to generate topical guidelines initiatives addressing critical knowledge and practice gaps in our profession, the Section on Tumors continues to lead the way with three major guidelines efforts this year.

The progressive/recurrent glioblastoma guidelines, led by Jeff Olson, MD, FAANS, along with Tim Ryken, MD, FAANS, and Steve Kalkanis, MD, FAANS, have entered the final stage of the review process and soon will be sent to the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Guidelines Committee for ultimate approval and endorsement. This guideline initiative focuses on the difficult questions asked in tumor boards across the country, such as how best to treat glioblastoma multiforme (GBM) at recurrence. Specific chapters address the following issue 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
- Future innovations

Our newest effort, also spearheaded by Dr. Olson, focuses on the clinical practice guidelines for low grade glioma (LGG). This effort is being co-led by Mark Linskey, MD, FAANS, Dr. Ryken and Dr. Kalkanis, with many of the executive committee members from the AANS/CNS Section on Tumors also playing a leading role in the various chapters: Role of Imaging (Sarah Fouke, MD), 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, led by Chirag Patil, MD, and Zack Litvack, MD, is in its writing stage with final drafts expected this spring.

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

Tumor Section Membership Committee

Allen Waziri, MD

Membership in the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors continues to expand, resulting in a greater than six percent increase in active membership over the past year. This year will offer new highlights for Section members. In collaboration with the Society for Neuro-Oncology, the Tumor Section Satellite Meeting will be held in conjunction with the AANS Annual Scientific Meeting in New Orleans this April. In addition, we will partner with the European Association of Neurological Surgeons to co-host their annual meeting in Tel Aviv, Israel, this November. We will continue our recent tradition of collaboration with the Young Neurosurgeons Committee by hosting receptions at each of the national meetings of the AANS and CNS. We expect each of these events to bring new opportunities for collaboration, education and social interaction with our many colleagues from around the globe who care for patients with neurological tumors.

Medical Neuro-Oncology

Susan Chang, MD

Presentation of results of several international randomized phase III trials evaluating the use of antiangiogenic strategies for newly diagnosed and recurrent glioblastoma is anticipated at the upcoming American Society of Clinical Oncology meeting in June 2013. This year, the Society for Neuro-Oncology (SNO) will host the 4th Quadrennial World Federation of Neuro-Oncology (WFNO) meeting in San Francisco from Nov. 21-24, 2013. Mitchel Berger, MD, FAANS, FACS, is the chairman of the meeting and extends a warm welcome to members of the tumor section to share in this educational event. A town hall meeting is planned at the WFNO and will review the results of all of these studies in one session. The event will provide a forum for open and interactive discussion about how these results may impact clinical care and efforts for further research. Members of the Section on Tumors are invited to submit abstracts for the WFNO meeting via the SNO website, www.soc-neuro-onc.org.

Pediatric Neuro-Oncology

George Jallo, MD, FAANS

The Pediatric Neuro-Oncology committee coordinates the interests of the Section on Tumors with the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Pediatric Section.

Upcoming Meetings

ISPN Meeting: The 41st annual meeting of the International Society for Pediatric Neurosurgery is being held Sept. 29-Oct. 3, 2013, in Mainz, Germany. The main topic of the congress is outcome in adult patients with congenital malformations. The organizing committee has put together an enriching scientific and cultural program that will interest pediatric and general neurosurgeons.

Section for Pediatric Neurosurgery Annual Meeting: The 42nd Annual Meeting of the AANS/CNS Section of Pediatric Neurological Surgery is scheduled from Dec. 3-6, 2013, in Toronto.

Clinical Trials

Highlights of clinical trials which are recruiting patients:

1. **Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas (DIPG)** — This is a multi-institutional study estimating the overall survival of children and young adults with diffuse intrinsic pontine glioma treated (DIPG) with a molecularly-based treatment strategy, compared to historical controls.

Four biopsies of tumor tissue will be obtained by surgical biopsy prior to treatment stratification if tolerated. The exact biopsy location will be determined by the treating neurosurgeon at the designated participating site with the goal of minimizing procedural risk. Following biopsy, all patients will receive local radiotherapy to consist of 59.4Gy delivered using conventional conformal or other standard treatment planning with adjuvant bevacizumab. Radiation planning can begin with the pre-operative images. Based upon molecular parameters after biopsy, patients will potentially receive erlotinib and/or temozolomide at the start of radiotherapy. Bevacizumab will be given concurrently with radiotherapy beginning at least three weeks from the biopsy and at least two weeks after the start of radiation therapy to ensure that primary wound healing has occurred.

2. **Convection Enhanced Delivery of 124I-8H9 for Patients with Non-Progressive Diffuse Pontine Gliomas Previously treated with External Beam Radiation Therapy** — This single-institution study is to test the safety of “convection-enhanced delivery” (CED) to deliver 124I-8H9, for the first time 124I-8H9 in the brainstem. This will be one of the first times that CED has been performed in the brain stem. 8H9 is something called an antibody. Antibodies are made by the body to fight infections and sometimes cancer. The antibody 8H9 is

produced by mice, and can attack many kinds of tumors. A radioactive substance, 124I, is attached to 8H9. 124I-8H9 sticks to parts of tumor cells and can cause the tumor cells to die from radiation. Studies also have been done on humans using 124I-8H9 to treat other kinds of cancer.

3. **Pilot Study of Glioma-associated Antigen Vaccines in Conjunction with Poly-ICLC in Pediatric Gliomas** — This is single-institution pilot study to evaluate the effects of vaccinations with HLA-A2 restricted Glioma Antigen-Peptides in combination with Poly-ICLC for children with newly-diagnosed malignant or intrinsic brainstem gliomas (BSG); or non-brainstem high-grade gliomas (HGG); or recurrent unresectable low-grade gliomas (LGG); or recurrent high-grade gliomas.

Society for Neuro-Oncology

Michael Vogelbaum, MD, PhD, FAANS

The Society for Neuro-Oncology (SNO) has partnered again with the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Section on Tumors (SOT) to collaboratively develop a meeting program. This year's Tumor Satellite meeting will devote one day to the multidisciplinary management of meningiomas. The program, which was developed by Patrick Wen, MD, (SNO); Leland Rogers, MD, (SNO); and Michael Vogelbaum, MD, PhD, (SNO and SOT), will cover all aspects of meningioma, including recent advances in pathology, imaging, biology, treatment options and clinical investigation. In addition, there will be oral presentations of original science selected from abstract submissions. This collaborative effort is intended to deepen the interactions between surgeons and medical specialists who treat patients with meningioma and, hopefully, it will serve as a template for these types of future interdisciplinary educational initiatives.

SOT members also should be aware of the upcoming World Federation of Neuro-Oncology (WFNO) meeting, which will be held during the SNO Annual Meeting Nov. 21- 24, 2013, in San Francisco. The WFNO meeting is held every four years, and was last held in the United States in 2001. In addition to the usual program consisting of an education day, sunrise educational sessions, plenary and concurrent original science oral presentations, poster sessions, and special invited lectures, this year's WFNO meeting also will feature a course on how to develop and run clinical trials, which will be led by Susan Chang. Additional details and registration information will be available on the SNO website.

Topic Review in Neuro-Oncology: The Recent Unraveling of the Genetics Underlying Meningiomas

Jennifer Moliterno Gunel, MD; Victoria E. Clark; Philip H. Gutin, MD, FAANS; and Murat Gunel, MD, FAANS

Surgical intervention and radiation remain the primary therapeutic options for meningioma as there is currently no effective standard chemotherapy. Radiotherapy seems almost counterintuitive as it is an independent risk factor for meningioma formation and possibly malignant transformation. Nonetheless, treatment decisions are dictated by the patient's clinical status as well as tumor characteristics, including size, location and involvement of critical neurovascular structures with the removal of challenging tumors potentially associated with significant morbidity and post-operative residual disease. While extent of surgical resection and histologic grade are important for predicting tumor behavior, they are imperfect measures as even benign meningiomas that are gross totally resected often can recur. Identification of molecular aberrations ultimately could render a superior method for classification and prediction of meningioma behavior and serve as potential targets for the development of rational medical therapies.

Unlike gliomas and medulloblastomas, in which the genetic landscape has been studied extensively, until recently, relatively little was known about the underlying molecular genomics of sporadic meningiomas. With an explosion of published findings on meningioma genetics in the first two months of 2013, this has changed.

Mutations in Five Genes are Responsible for the Majority of Sporadic Meningiomas

Since the discovery of germline merlin/neurofibromin 2 (NF2) mutations underlying the neurofibromatosis type 2 tumor suppressor syndrome in 1993 [1], NF2 inactivation has been shown in ~50 percent of sporadic meningiomas [2]. Indeed, most of these meningiomas show loss of both copies of NF2 due to chromosome 22 deletions, in which the NF2 gene is located. Subsequent studies suggest NF2/chromosome 22 loss meningiomas to be histologically [3] and clinically distinct than NF2 intact ones, but the molecular mechanisms underlying these differences also have remained obscure until now.

In contrast to candidate gene approaches, which are hypothesis-driven and inherently biased toward the gene(s) of interest, genome-wide approaches, such as sequencing all of the coding regions of the genome in a single experiment (whole exome sequencing), are powerful because they provide an unbiased approach to the identification of new genes. These genome-wide approaches are hypothesis-generating, and can be tested in follow-up experiments. The recent application of these technologies to the study of meningiomas has revealed interesting new insight into meningioma formation. In two recent reports published online in January 2013 in *Nature Genetics* and *Science*, we and others have shown that mutations in two known neoplasia genes, v-akt murine thymoma viral oncogene homolog 1 (AKT1) and smoothed, frizzled family receptor (SMO), underlie meningioma

tumorigenesis, through activation of the PI3K and Hedgehog pathways, respectively [4] [5].

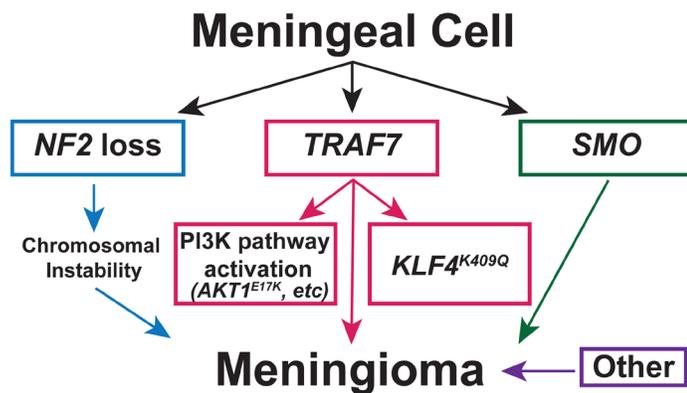
The clinical importance of this finding lies in the fact that both of these pathways, which have been shown to be constitutively activated in several cancers, can be therapeutically targeted with the use of specific agents, suggesting at least the theoretical possibility that individualized chemotherapy can become a reality for patients with these subsets of meningiomas. Identification of a chemotherapeutic agent with low toxicity might provide a less morbid alternative for certain patients and potentially could negate the need for irradiation. Vismodegib, for example, has already gained FDA-approval for use in metastatic basal cell skin carcinoma, in which Hedgehog pathway activating SMO mutations have been reported. Several other drugs that target PI3K signaling (i.e. perifosine) are currently in clinical trial.

Although the finding of SMO and AKT1 mutations affords a new insight into the genetics of sporadic meningiomas, the genomic architecture of meningiomas is undeniably deeper and more complex. For instance, we have also shown that AKT1 mutations typically co-exist with coding somatic mutations in a novel neoplasia gene, TNF receptor-associated factor 7 (TRAF7). Interestingly, TRAF7 mutations are found in nearly half of non-NF2 meningiomas. Although not much is known regarding the biology of TRAF7, it has been shown to be an ubiquitin ligase, playing an important role in the degradation of various proteins and possibly interacting with MAP kinase pathways. Thus targeting the aforementioned PI3K/AKT pathway in patients harboring meningiomas with co-occurring TRAF7 mutations might prove less effective.

Besides AKT1, we and others have demonstrated TRAF7 mutations also can co-exist with an identical mutation, K409Q, in the Kruppel-like factor 4 (KLF4) gene [5] [6]. KLF4 is one of the four so-called "Yamanaka factors," which possess the capability of reprogramming terminally differentiated somatic cells into pluripotent stem cells [7]. The induced pluripotent stem cell (iPSC) technology, which was awarded the Nobel Prize in 2012, now has widespread use in molecular studies. The recurrent K409Q mutation in KLF4 is within its DNA binding domain, suggesting that this variant changes its binding specificity, potentially leading to altered expression of genes important in meningioma formation.

A New Classification System for Meningioma With Clinical Relevance

Based on the discovery of mutual exclusivity and co-occurrence patterns of mutations in these five genes, these findings allow for the molecular classification of meningiomas into three major subtypes: tumors with (1) NF2/chromosome 22 loss; (2) TRAF7 and either KLF4 or AKT1 (E17K) mutations (i.e. TRAF7/AKT1/KLF4); and (3) activating SMO mutations. Important genomic



differences exist between these subtypes and have potential clinical implications. NF2 mutant meningiomas, for instance, show chromosomal instability and are more likely to be higher grade, whereas non-NF2 mutant tumors typically are benign, genomically stable and demonstrate a very small number (typically less than 10) of genome-wide protein altering somatic mutations. The three meningioma subgroups are clearly distinguishable based on their differential gene expression, supporting the notion that they indeed are biologically relevant and distinct subclasses [5]. Taken together, these findings have potential clinical significance as they offer a novel way for predicting distinct biological behavior, as well as malignant potential.

Additionally, the anatomical distribution and histological profiles of meningiomas also were found to correlate with their mutational profiles. Based on grouping cerebral meningiomas into those originating along the skull base or those located along the cerebral hemispheres, we observed a significant difference between these two groups. Specifically, tumors with NF2/chromosome 22 loss were far more likely to localize to the hemispheres than to the skull base. Along non-skull base regions, the frequency of NF2/chr22loss meningiomas followed an anteroposterior gradient such that the vast majority of posterior cerebral (parieto-occipital) or cerebellar meningiomas were NF2/chr22loss tumors. In contrast, along the medial skull base regions, especially near the midline, virtually all meningiomas were either TRAF7/AKT1/KLF4 or SMO mutant; NF2/chr22loss meningiomas were observed only along the lateral skull base. Meningiomas with only the recurrent SMO L412F mutation (n= 5) all localized to the medial anterior skull base. Thus, for the first time, it seems that the simple evaluation of a patient's MRI can offer insight into the molecular profile of the meningioma. Such information could prove especially meaningful once meningioma targeted therapies are developed better.

Not surprisingly, mutational profiles showed a correlation with histological diagnosis as well. The strongest association was found with secretory meningiomas, a subtype known to follow a more aggressive clinical course due to increased brain edema [8]. In our series, all 12 secretory meningiomas carried both TRAF7 and KLF4 mutations; similar findings were found in another recently published study of 16 secretory meningiomas [6]. KLF4 and TRAF7 mutations were mutually exclusive with NF2 mutations. Of the more common histological subtypes, we found ~80

percent of both fibrous and psammomatous meningiomas had NF2/chr22loss, while this was seen in only 23 percent of pure meningotheliomatous tumors. Nearly half of the latter subtype (49.2 percent) harbored non-NF2 mutations.

Inherited Variation Also Increases Risk of Meningioma Formation

Besides the aforementioned somatic mutations, germline variation also confers significant genetic risk to the formation of some meningiomas and thus should be considered in evaluating patients. As mentioned above, inherited germline mutations in NF2 was established two decades ago as a risk factor for meningioma formation [1]. More recently, a genome-wide association study has shown a common MLL10 variant to modestly increase meningioma risk (1.46 fold) [9]. Germline mutations in SMARCB1, a chromatin remodeling gene that also is somatically mutated in a minority of meningiomas, have been found in cases of familial schwannomatosis with multiple meningiomas [10] but rarely contribute to the formation of multiple meningiomas in the absence of schwannomatosis [11]. Finally, germline loss-of-function mutations in chromatin remodeling gene SMARCE1 recently have been shown in cases of familial multiple spinal meningiomas with clear cell histology. These findings suggest that mutations in this gene may delineate a specific familial meningioma subtype [12].

Conclusion

Integrative genomics approaches have recently revealed the molecular basis of the majority of non-NF2 mutant meningiomas, specifically identifying previously unrecognized subtypes characterized by novel TRAF7, KLF4, AKT1, and SMO mutations. Three distinct meningioma subgroups now have been defined based on their underlying mutational profile with corresponding potential for chromosomal instability, malignant transformation, anatomical location and histological subtype. Based on the mutually exclusive distribution, these molecular subtypes represent diverse biological classes with important clinical implications. Furthermore, the mutational profile of a meningioma can now largely be predicted based on information obtained by simply reviewing the patient's MRI. Depending on the molecular make-up of an individual tumor, the potential use of drugs that inhibit a specific pathway could prove to be effective in the management of meningiomas in the near future. Such personalized medicine, particularly for patients with tumors located in challenging locations, those who are poor surgical candidates and/or those with residual disease, could prove invaluable and possibly obviate the need for pre- or post-operative radiotherapy.

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Clinical Trials Sub-Committee Report

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

The clinical trials sub-committee of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Section on Tumors executive committee is dedicated to increasing the involvement of neurosurgeons in brain tumor clinical trials. While the sub-committee is interested in increasing involvement of neurosurgeons in trials of all kinds, including observational trials and those for every type of brain tumor, for this newsletter we want to draw attention to a Phase II clinical trial for newly diagnosed glioblastoma multiforme (GBM).

RTOG 0913 is studying concurrent use of RAD001 (Everolimus), an mTOR inhibitor, with temozolomide and radiation followed by adjuvant RAD001/temozolomide to treat newly diagnosed glioblastoma. Led by principal investigator Prakash Chinnaiyan, MD, the trial comes on the heels of the phase I study that showed that the maximum tolerated dose of RAD001 is 10 mg/day. Tumors for which RAD001 is approved

include advanced kidney cancer and non-resectable pancreatic neuroendocrine tumors, as well as subependymal giant cell astrocytomas in tuberous sclerosis patients. This format of combining an investigative agent with Stupp protocol treatment should provide information about the efficacy of the drug in the newly diagnosed setting, as well as how the drug interacts with treatments already proven effective for newly diagnosed GBM.

The randomized phase II portion of the trial is currently open for accrual and it compares the Stupp protocol (arm 1) to the experimental phase I protocol (arm 2). The phase II results could provide further insight into whether Akt/mTOR axis activation and/or tumor MGMT gene methylation status predict response to the drug. Results are eagerly anticipated.

Topic Review *continued from page 13*

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