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Editorial

Proceedings of the WFNS Neuro-Oncology Committee Workshop Rome 2015

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INTRODUCTION

At the 15th Interim Meeting of the World Federation of Neurosurgical Societies, held in Rome in September 2015, the Neuro-Oncology Committee was privileged to hold its first dedicated scientific workshop. This unique gathering of international experts presented current research and discussed key issues in neuro-oncology, and also shared on the state of neuro-oncology around the world. The Committee was joined by authorities from neuropathology, neuro-oncology, and radiation oncology, who provided critical insights and emphasized the need for an integrated, multidisciplinary approach to the management of brain tumor patients. The Committee is pleased to present the proceedings of that meeting in the following set of abstracts. We hope that these

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summaries of the workshop presentations will be a useful resource for neurosurgeons and other physicians with an interest in neuro-oncology. Karolyn Au, Zvi Ram, and Gelareh Zadeh on behalf of the WFNS Neuro-Oncology Committee.

NONMALIGNANT TUMORS

Author: Morten Lund-Johansen, MD, PhD (Bergen, Norway)

Title: Vestibular schwannoma: Radiosurgery, surgery or wait and scan? Quality of life, symptoms and results

The optimal treatment of small vestibular schwannomas (VS) remains a matter of controversy, and a significant volume of literature has been published on the outcome of various management approaches. Before the factors that predict outcome can be determined, however, the question of what outcome is sought must first be answered. Many endpoints have been measured for VS, and modern techniques achieve high levels of facial nerve function and tumor control, however, recent studies indicate that symptoms such as vertigo and tinnitus may be extremely troublesome to patients and are relatively underemphasized. Health-related quality of life (HRQOL) considerations emphasize overall level of function and the pursuit of valued life goals, and data on the impact of VS management on QOL is now emerging.

A prospective, observational study of 193 patients evaluating the effect of conservative management on tumor growth, symptoms, and QOL found that 41% required treatment within 5 years, and that vertigo significantly reduced QOL. In a comparison of 113 patients given Gamma Knife radiosurgery (RS), with 124 patients allotted to conservative management, tumor size and growth rate were significantly reduced and the rate of new treatment was lower in the RS group, whereas hearing loss, symptoms, and QOL were not different. These studies used the Short Form-36 (SF-36) QOL instrument, which may be limited by lack of specificity for fluctuations attributable to symptoms. Comparison of 82 patients receiving microsurgery or RS found more facial nerve and hearing preservation in the RS group, as well as better scores on the Health Status Questionnaire (HSQ) and Dizziness Handicap Inventory (DHI). Another prospective series of 91 patients comparing microsurgery and RS found no difference in SF-36 scores and significantly better Glasgow Benefit Inventory (GBI) scores for the RS group.

The Rochester and Bergen groups studied management and QOL in acoustic neuroma, sending 11 questionnaires to 539 patients treated with RS, observation, or microsurgery. The surveys addressed generic and treatment-specific and disease and symptom-specific QOL indicators; the latter using the recently validated Penn Acoustic Neuroma Quality-of-Life (PANQOL) scale. Importantly, this study also included 103 nontumor controls, and found that the differences between VS patients and controls were greater than the differences among the treatment groups, showing that the diagnosis of VS itself has the largest adverse effect on QOL. Furthermore, the minimal clinically important differences (MCID) identified among treatment modalities generally exceeded differences reported in previous studies, in which conclusions were based on statistical significance alone.

Vertigo was identified as the most important symptom in patients' perception of QOL, demonstrating on SF-36 and GBI questionnaires a greater adverse effect on QOL than the more frequent symptoms of hearing loss and tinnitus, suggesting that this symptom should be a focus of treatment discussion. Furthermore, vertigo and vestibular symptoms were found to be significant predictors of dependence as marked by pension compensation. While some predictive factors for persistent dizziness were identified, treatment modality did not influence Dizziness Handicap Inventory (DHI) score. A remarkable finding emerged from these studies, which was that patients often reported hearing loss and facial nerve dysfunction as the most significant impairments, yet symptom-QOL score association analysis demonstrated that dizziness and headache predicted the greatest loss in HRQOL whereas hearing loss and facial nerve function had little or no bearing on QOL scores. One contributor to this phenomenon may be that patients are biased to focus on certain symptoms by health providers, who provide extensive pretreatment counseling and follow-up evaluation of hearing and facial nerve function, however, rarely inquire about or investigate dizziness and headache.

The literature clearly demonstrates that the field has focused disproportionately on a narrow range of easily-evaluable technical outcomes while paying relatively little attention to less tangible factors that are shown to significantly influence HRQOL. Future efforts to improve VS patient care require refinement of disease-specific QOL instruments and more resources dedicated to the management of dizziness and headache.

Author: Karolyn Au, MD, MSc (Toronto, Canada)

Title: Expanded endoscopic endonasal approach for anterior skull base meningioma

Meningiomas of the anterior cranial fossa (ACF) include olfactory groove meningiomas (OGM), which arise from the cribriform plate and may present with anosmia, seizure, behavioral changes or visual disturbance, and tuberculum sella meningiomas (TSM), which arise from the tuberculum sella and chiasmatic sulcus and most often present with visual deficits. Numerous craniotomy

approaches have been described, including bilateral and unilateral exposures with various degrees of bony removal, suggesting that none is clearly superior; a debate is ongoing as to which of the technique may be more prone to injuring the optic apparatus or its blood supply. The expanded endoscopic approach (EEA) offers advantages such as the ability to decompress the optic nerves at the optic canal, early tumor devascularization, complete avoidance of brain exposure and retraction, and increased illumination within the operative field. In addition, encountering the tumor before the neurovascular structures allows for easier preservation of the vascular supply to the optic apparatus. However, this approach is unable to access significant lateral tumor extension, and may limit the resection of the entire dural attachment. Furthermore, the technique lacks three-dimensional visualization, and requires a learning curve for the surgical team. Therefore, definitive indications for the endoscopic approach remain unclear.

Several meta-analyses have compared the outcomes for open and EEA resection of ACF meningiomas. Komotar *et al*. reviewed series published during 2000–2010. For OGM, open approaches resulted in a significantly greater proportion of gross total resection (GTR) (92.8% *vs* 63.2%, $P < 0.001$), and lower rates of cerebrospinal fluid (CSF) leak (6.0% *vs* 31.6%, $P < 0.001$). A similar pattern was found for TSM, with more GTR (84.1% *vs* 74.7%, $P = 0.041$) and less CSF leak (4.3% *vs* 21.3%, $P < 0.001$) for craniotomy compared to EEA. The rate of vision improvement did not differ significantly between approaches for either tumor location. Recognizing the significant learning curve required for EEA, Clark *et al*. reviewed the series only during 2006–2011 for TSM. This found no difference in GTR, however, EEA cases continued to have higher rates of CSF leak (21% *vs* 5%, $P < 0.05$). However, the rate of vision improvement was also significantly higher for EEA cases (87% *vs* 59%, $P < 0.5$).

As these series indicate that the EEA technique and its indications continue to evolve, a review of the current literature was carried out, including only publications with disaggregated data for patients clearly identifiable for pure EEA procedures. During 2008–2014, three series of OGM were included, finding overall rates of 73.5% GTR, 28.3% CSF leak, and 86.7% vision improvement. Fourteen series of TSM were included during 2007–2014, showing rates of 68.5% GTR, 15.1% CSF leak, and 80.1% vision improvement. This review exposed some challenges in interpreting the available literature, including a lack of consistency in reporting clinical, radiographic, and technical factors as well as short-term outcomes. Clearer outcome reporting is required to understand the potential benefits and limitations of the EEA.

At the Toronto Western Hospital, as the surgical team has become more experienced with EEA, its application has increased. To determine the outcomes, a review was carried out of ACF meningioma cases during 2006–2015 resected by pure EEA. Nine OGM cases were identified, of which 2 had presented with visual dysfunction, and 5 demonstrated optic apparatus involvement on magnetic resonance imaging (MRI). Of the 20 TSM, 13 had visual dysfunction on presentation and 2 had endocrinologic abnormalities, and 17 demonstrated optic apparatus involvement on imaging. All cases were performed using an expanded endoscopic endonasal transphenoidal approach to the ACF by a combined neurosurgery and rhinology team, assisted by neuronavigation. Surgical technique included multilayer reconstruction of the skull base with intra and extradural fascia lata or synthetic collagen supported by cellulose polymer and fibrin glue, as well as routine use of a vascularized nasoseptal flap. A GTR was achieved in 78% of OGM and 70% of TSM, while a post-operative CSF was identified in 33% of OGM and 10% of TSM. Both OGM patients with pre-operative visual deficits experienced improvement, while 62% of the TSM cases had visual improvement and none had permanent endocrinologic dysfunction.

At this time, our experience and the literature as a whole led to the conclusion that the EEA for ACF meningioma is a feasible option in appropriately-selected patients. In our experience, unfavorable features for this approach include tumor extension >3 cm above the ACF or lateral to the optic canal, extensive intratumoral calcification, or hydrocephalus or extreme frontal lobe mass effect. While CSF leak remains the most significant complication, its management is improving and its occurrence is decreasing. Further reporting of outcomes is necessary by surgeons performing the technique, with consistency and details in short-term outcomes description, as well as long-term follow-up for recurrence, and neurocognitive outcomes in order to understand predictors of subtotal resection, CSF leak, and vision improvement.

Author: Atul Goel, MD (Mumbai, India)

Title: Is it possible to design a treatment strategy for meningiomas?

No two meningiomas, like two fingerprints, have ever been alike. All meningiomas have a unique clinical presentation, radiological features, nature of extension, histological behavior, and pattern of mitosis. Moreover, the outcome is unique. The cause, course, or cure of any meningioma is not only not known, i.e., is unknowable or is unlikely to be known.

You can only "debulk" – for the dream of total removal is one of a mirage. A meningioma tells a tale a normal meninx is waiting to tell. Even if it were totally removed, the next normal meninx can throw a meningiomatous tantrum. Recurrence of a meningioma is independent of the extent of tumor resection.

You remove the tumor, the whole tumor and nothing but the tumor – without removing the tumor diathesis or the ability to form a tumor. Its not the treatment but the cellular behavior that decides the outcome.

"Once a meningioma -- always a meningioma." All meningiomas can be classified into good or bad – only by hindsight.

Each meningioma is unique and not amenable to any genetic analysis, prevention, chemotherapy, or radiation. It is best lived with, ablated when diseasing, and re-ablated when it recurs to disease again. Every neurosurgeon should have a plaque in front of his clinic stating: There are some patients whom we cannot help; there are none whom we cannot harm.

Key points

- Resect meningiomas "radically"
- Patients should improve in their symptoms
- If "symptomatic recurrence" then reoperate
- If recurrence is beyond the scope of safe knife, then consider radiation as palliation.

Author: Gelareh Zadeh, MD, PhD (Toronto, Canada)

Title: Clinical and molecular predictors of meningioma recurrence

Predicting the patients who are likely to experience recurrence following meningioma resection, and who would therefore benefit from adjuvant radiation or close clinical follow-up, remains a challenge. Atypical or World Health Organization (WHO) II meningiomas are marked by increased mitotic activity, higher recurrence rates, and decreased survival. WHO III tumors are anaplastic and exhibit frank features of malignancy, inevitably recurring, and substantially diminishing survival. In 1956, Simpson described a classification system to describe the extent of surgical resection, however, it is limited by dependence on the operating surgeon's report. Simpson grades 1–3 are considered gross total removal (GTR), whereas grades 4–5 are subtotal resections (STR). While WHO grading of histology and the extent of resection (EOR) are strong predictors of tumor recurrence, they do not account for all recurrence patterns.

The proliferative index measured by MiB-1 or Ki-67 is often considered in decision-making regarding adjuvant radiotherapy, but it is not specific and does not contribute to WHO grading. Mitotic counts form an important component of meningioma grading, however, detection may be challenging, and comparison based on high-power fields can be confounded by variations in tumor cellularity. Therefore, can additional information on tumor biology and mitotic index predict meningioma recurrence and support the predictive significance of EOR?

Histone H3 is specifically phosphorylated at serine 10 during mitosis. Immunohistochemistry (IHC) for phosphohistone H3 (pHH3) allows highly sensitive and specific detection of mitotic cells. Meningioma specimens from 363 patients were examined, with an additional 300 cases in a validation cohort. Mitotic index based on pHH3 IHC was determined, and WHO grade, Simpson grade, MiB-1, and recurrence data were also collected. Mitotic index as determined by pHH3 staining correlated with MiB-1 proliferative index. As expected, WHO grade was significantly associated with recurrence-free survival (RFS). Classification and regression tree (CART) analysis defined three cutoffs based on mitotic index: 0–2, 3–4. and ≥5. In multivariate analysis, pHH3-defined mitotic index groups significantly predicted RFS independent of Simpson grade, WHO grade, and MiB-1 index. Mitotic index also predicted RFS within subgroups stratified by WHO grade, extent of resection, and location (skull base and nonskull base). Thus, pHH3-defined mitotic index was found to be an accurate and useful adjunct for diagnostic work-up that added prognostic information beyond WHO grade, MiB-1 proliferative index, and EOR.

Many recent studies have shown that methylation profiling of solid tumors has revealed biologic subtypes that often carry clinical implications. A group of 140 meningioma samples were profiled on the Illumina 450K methylation chip, along with two validation sets of 48 samples each. Unsupervised clustering and analyses for RFS were performed using log rank and Cox proportional hazards methods, and correlated with EOR and WHO grade. On this analysis, a specific set of CpG sites showed hypermethylation of approximately 900 markers, identified two methylation subgroups analogous to the CpG island methylator phenotype (CIMP). These findings were reproducible in two validation sets. The hypermethylated (M-CIMP+) subgroup was enriched for WHO grade III tumors, contained tumors with median MiB-1 proliferative index and pHH3-defined mitotic index significantly higher than the nonhypermethylated (M-CIMP-) subgroup, and was associated with a poorer RFS. On multivariate analysis, the M-CIMP+ group was independently predictive of RFS after adjusting for WHO grade, pHH3 mitotic index, and EOR.

These findings indicate that molecular markers such as pHH3-defined mitotic index and methylation profile can provide data that can predict recurrence for meningioma. This information may assist in clinical decision-making such as determining the need for adjuvant radiotherapy.

GLIOMAS

Author: Kenneth Aldape, MD (Toronto, Canada)

Title: Molecular classification of lower grade glioma

The observations of Cushing and Bailey regarding the histological appearance of glial tumors and their

resemblance to normal glial cells have formed the basis of primary brain tumor classification since the 1920s. The 2007 WHO classification of diffuse gliomas differentiates among astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas, designating them at minimum grade II, and if bearing anaplastic features, grade III. Astrocytomas demonstrate a tendency to progress to glioblastoma (WHO grade IV), with median survival for grade II lesions approximately 60 months and for grade III tumors approxmately 36 months. In addition, recent studies have revealed that these lesions are characterized by mutations in *IDH*, *TP53*, and *ATRX*. Oligodendrogliomas bear a better prognosis, being chemosensitive and demonstrating a median survival of 120 months and 60 months for grade II and grade III, respectively. These tumors are characterized by 1p/19q codeletion, as well as mutations of *IDH*, *CIC*, *FUBP1*, and the *TERT* promoter. However, a number of tumors are more complicated to classify, including oligoastocytomas and other lesions of ambiguous morphology; neuropathologists demonstrate only 60–70% concordance in the diagnosis of diffuse glioma.

The Cancer Genome Atlas (TCGA) Research Network profiled 293 lower-grade gliomas (LGG) using multiple platforms, including exome sequencing, DNA copy number, DNA methylation, and mRNA, miRNA, and protein expression. Unsupervised analysis of the data demonstrated three to five tumor subtypes, and integration of data from the DNA methylation, DNA copy number, mRNA expression, and miRNA expression platforms in a cluster of clusters analysis identified three molecular classes. These classes were distinguished first by IDH mutation, and the IDH mutant tumors further by 1p/19q codeletion status. When correlated with clinical outcomes, these classes demonstrated significantly different event-free and overall survival, with the best prognosis associated with IDH mutation as well as 1p/19q codeletion (IDHmut-codel), less favorable with IDH mutation and no 1p/19q co-deletion (IDHmut-non-codel), and the worst with wildtype IDH (IDHwt). In fact, tumors in the IDHwt class frequently presented clinically such as glioblastoma, and demonstrated mutation profiles and frequencies similar to IDH wildtype glioblastoma.

To integrate the molecular findings of the TCGA LGG study with conventional histopathology, a retrospective cohort of 558 WHO grade II and III diffuse gliomas was assessed for IDH mutation status and histology. Survival analysis demonstrated a statistically significant difference in outcome based on WHO grade (II vs III) among the IDHwt tumors, but not the IDHmut tumors. In addition, a mitotic index (MI) cut-off of 4 per 1000 tumor cells was used to distinguish low-proliferative tumors (MI 0–4) from high-proliferative tumors (MI >4); MI (low vs high) was significantly associated with overall survival among the IDHwt tumors, but not the IDHmut tumors. When all 558 tumors were examined by Cox multivariate analysis, IDH status (mutant vs wildtype), 1p/19q status (codeleted vs non-codeleted), mitotic index (low vs high) and patient age at diagnosis were all significant predictors of overall survival. However, when separated by IDH mutation status, MI and age remained significant predictors for the IDHwt cohort, however, only 1p/19q status was significant in the IDHmut cohort. These data indicate that, among IDHmut tumors without features of glioblastoma, traditional features such as patient age and tumor proliferation may not adequately distinguish low-risk from high-risk cases.

Recent evidence demonstrates that the six existing histopathologic diagnoses can be distilled into three robust, clinically-relevant molecular classes, i.e., IDHmut-codel ("oligo"), IDHmut-non-codel ("astro"), and IDHwt ("pre-GBM"). There is no molecular correlate of oligoastrocytoma, and most IDHwt LGG have molecular alterations and clinical behavior similar to glioblastoma, although this requires further refinement. Furthermore, the grading of IDHmut LGG may need re-evaluation.

Author: Manfred Westphal, MD (Hamburg, Germany)

Title: Clinical aspects of the "low grade glioma" changing landscape

The 2007 WHO classification of grade II and III central nervous system (CNS) tumors distinguishes astrocytic, oligodendroglial and oligoastrocytic tumors on the basis of morphology and immunohistochemistry. Histological classification poses some difficulties, including subjectivity in interpretation of histological findings with resultant interobserver variability, as well as variable outcomes among patients with the same histologic diagnosis. Novel diagnostic, prognostic, and predictive biomarkers are needed, and the upcoming update to WHO classification will include molecular markers. However, the encoding of both low-grade and anaplastic tumors as "malignant" reflects the reality of their oncologic behavior, which even new molecular insights cannot predict; we still do not know which patients will progress or when, and we are unable to predict the growth pattern of a given tumor.

Nevertheless, new molecular insights are changing some clinical considerations such as providing better estimates of prognosis, improving the language of discussion and comparability, tailoring risk-adapted therapy with timely indications for chemotherapy, radiation, or targeted therapies, and driving soluble and imaging-based biomarker development. On the basis of *TERT* promoter mutation, *IDH* mutation, and 1p/19q codeletion, grade II/III gliomas can be divided into groups that significantly correlate with age at presentation as well as with survival. Thus, the term "low grade glioma" is

imprecise and for most clinical studies inadequate because it lumps together astrocytomas, oligodendrogliomas, and oligoastrocytomas when they are in reality different diseases. The different genetic background of these tumors forms the basis for clinically-relevant biomarker development, which may guide stratification of patients into prognostic and treatment groups.

Several years ago, mutations in *IDH* were found in a subset of glioblastoma, particularly tumors that had progressed from lower-grade lesions. Immunohistochemical detection of mutant IDH1 protein is now used as a specific marker of tumor cells. The presence of *IDH* mutation is also associated with improved survival in glioblastoma and anaplastic astrocytoma, and in fact has greater prognostic significance than grade. Furthermore, mutant IDH1 has demonstrated potential as an immunological target, with a vaccine targeting the neoantigen protein inducing CD4+ T-cells. Such findings have opened the door to testing multiple peptide-based anticancer vaccines in clinical trial settings.

While biomarker detection currently relies on physical sampling of tumor or blood, the effects of the neomorphic enzyme on cellular redox state and epigenetic modification may in future be exploited to identify *IDH* mutations in a noninvasive manner. For instance, magnetic resonance spectroscopy (MRS) can be used to detect 2-hydroxyglutarate in tumors *in vivo*, the presence of which is correlated with mutation in IDH. In addition, MRS imaging of hyperpolarized [13C] α-ketoglutarate can provide highly sensitive noninvasive, real-time *in vivo* monitoring of mutant IDH1 activity.

However, these technologies remain in development, and at present, "low grade glioma" remains a categorical term. Molecular markers are correlated to clinical findings but have provided very few targets for therapy; their role at this time is to assist with risk assessment to influence therapeutic decisions.

Author: Jörg-Christian Tonn, MD (München, Germany)

Title: Refined glioma imaging using advanced MRI and PET – what neurosurgeons want to know

Many clinical decisions in glioma management depend on the answer to certain key questions, yet existing imaging modalities answer these questions imperfectly. The development of advanced imaging techniques promises to improve the noninvasive characterization of primary brain tumors.

Where is it and how big is it? It is well-recognized that gliomas extend far beyond the areas of MRI contrast enhancement. In 24 astrocytomas not stratified by WHO grade, Bisdas *et al*. found that relative cerebral blood volume (rCBV) on perfusion-weighted MRI was predictive for recurrence and for 1-year progression-free survival (PFS). Roy *et al*. compared the ability of multiple MRI parameters, including T1-/T2-weighted, dynamic contrast-enhanced, diffusion tensor, and spectroscopic imaging to distinguish low-grade from high-grade tumors. The best performance for a single measure was obtained for rCBV, which demonstrated a sensitivity and specificity of 100% and 88%, respectively. Combination of measures increased classification sensitivity and specificity to 100% and 96%, respectively. Focusing on glioblastoma, Jain *et al*. found that increased rCBV in the nonenhancing region (NER) was the most significant predictor of both PFS and overall survival (OS) in multivariate analysis. Other significant factors were NER crossing midline, as well as Karnofsky performance status and age – but not contrast enhancement. The Response Assessment in Neuro-Oncology (RANO) working group emphasized the importance of accounting for both the enhancing and nonenhancing tumor, although the difficulty in assessing residual tumor burden is acknowledged, and the use of volumetric and advanced imaging methodologies is encouraged.

Positron emission tomography (PET) imaging using a variety of tracers provides information regarding the metabolic activity of tumors, and can be integrated with structural imaging from conventional MRI. For instance, the tumor volume identified by ^{18}F-FET PET is larger than the enhancing region on T1+gadolinium sequences, but is itself smaller than the volume marked by T2 change. Arbizu *et al*. found different patterns of MRI (T1-Gd or T2) and ^{11}C-methionine (MET) PET volume integration, with a larger PET volume associated with glioblastoma, a larger MRI volume associated with low-grade glioma, and a pattern of difference in both directions associated with anaplastic astrocytoma. Galldiks *et al*. found that the pretreatment volume of ^{11}C-methionine (MET) uptake was a significant predictor of survival, while pretreatment contrast enhancement on MRI was not. In addition, Idema *et al*. found that the proliferative volume as demonstrated by ^{18}F-FLT PET was associated with overall survival on multivariate analysis, whereas the contrast-enhanced MRI volume was not. Interestingly, when comparing modalities, Filss *et al*. found that ^{18}F-FET PET was better able to demonstrate the extent of gliomas compared to rCBV. Again focusing on glioblastoma, Suchorska *et al*. additionally found that a smaller biological tumor volume (BTV) prior to chemoradiation as identified by ^{18}F-FET PET was the most important prognostic factor for longer PFS and OS.

Is it all the same? The intratumoral heterogeneity of gliomas can pose a challenge for selective diagnostic sampling. Correlation was made between regional histopathology and MRI by Barajas *et al*., who assessed the contrast-enhancing and nonenhancing regions of glioblastomas for features such as proliferation,

microvascular hyperplasia and necrosis. They found that in contrast-enhancing regions, perfusion parameters were most predictive of malignant histopathology, whereas in nonenhancing regions, diffusion parameters were most predictive. Comparing contrast-enhancing and nonenhancing regions for RNA expression, Gill *et al*. found that expression from contrast-enhancing regions resembled that of The Cancer Genome Atlas (TCGA) proneural, classical, or mesenchymal subtypes, whereas nonenhancing regions resembled the neural subtype. Examining tumors with an MRI "grade II appearance," Kunz *et al*. correlated ^{18}F-FET PET to histopathology on serial biopsy samples. They found that ^{18}F-FET uptake kinetics significantly correlated with histopathologic homo/heterogeneity, and that as many as 44% of tumors demonstrated high-grade features, which was predicted by ^{18}F-FET PET hot spots. This group further found that the three ^{18}F-FET PET uptake groups were predictive for PFS.

Where is function? The use of neuronavigation for preoperative planning and intraoperative guidance is currently standard using routine MR imaging. Integrated multiparametric imaging may become commonplace in the future.

What is still in? While a number of technologies are available to increase tumor resection, their impact on outcome remains to be demonstrated. A Cochrane review by Barone *et al*. evaluating randomized trials of intraoperative MRI, 5-ALA, neuronavigation, and DTI-neuronavigation did not find evidence of improved OS with the use of these aids. Emerging techniques such as intraoperative ultrasound integrated with MRI neuronavigation can offer structure updates over the course of a procedure, demonstrating the amount of remaining tumor; however, such techniques require additional study.

Multiple studies have shown that contrast enhanced-MRI is insufficient for clinical decision making, and that measures such as rCBV and consideration of the nonenhancing volume may be equally or more important. Amino acid-based PET tracers can delineate tumor volume and borders and detect heterogeneity within a glioma. Future studies of imaging modalities need to include volumetric analysis, and should be performed prospectively to correlate with clinically significant parameters.

Author: Francesco DiMeco, MD (Milan, Italy; Baltimore, USA)

Title: Contrast-enhanced ultrasound (CEUS) for real-time image guidance in brain tumor surgery

The application of imaging technology in brain tumor surgery has evolved remarkably in the past century. Roentgenography led to the development of CT, which was followed by MRI. MRI technology has widespread use in neuronavigation, which correlates the patient's head fixed in a frame to a virtual image dataset in three dimensions. Neuronavigation uses standard sequences acquired on typical clinical scanners and its routine use is familiar to most neurosurgeons, however, it lacks real-time updating, and the images acquired preoperatively become increasingly less reflective of true anatomy as the operative procedure progresses. Intraoperative acquisition of MRI images provides accurate imaging throughout the procedure in standard sequences that are familiar to clinical users. However, acquiring these images requires a pause in the procedure, prolonging procedure times. Furthermore, these units are costly and require dedicated space and equipment. Other technology to guide surgery, such as 5-ALA fluorescence, gives real-time visual feedback on remaining tumor that increases the EOR, but only works with some specific tumor subtypes (namely, high-grade gliomas).

Intraoperative ultrasound is a relatively inexpensive modality that provides dynamic imaging with excellent spatial and temporal resolution. The images generated, however, are different in appearance from those acquired using CT or MRI technology, and orientation and interpretation require training and practice. Ultrasound can be used for surgical planning and navigation, with fusion to preoperative MRI images and intraoperative tracking of the ultrasound probe. The application of these techniques was demonstrated in a series of 58 patients, in which initial registration error was <2 mm but brain shift >4 mm occurred in 48. The intraoperative ultrasound was able to correct for the brain shift and maintain accurate navigation throughout the cases. Ultrasound was even integrated with diffusion tractography to demonstrated adjacent white matter tracts.

The utility of intraoperative ultrasound is increased with the use of contrast enhancement, a dynamic and continuous modality that offers real-time visualization of vascularity and tissue resistance. Contrast-enhanced ultrasound (CEUS) allows for highlighting of neoplastic lesions compared to baseline ultrasound, and though a well-established live-imaging technique in many contexts, has not previously been used for brain imaging. The contrast agent consists of gas-filled microbubbles that resonate at frequencies specific to their diameter when pulsed by low-acoustic-power ultrasound waves. These harmonics are detected and elaborated through the transducer using contrast-specific algorithms, resulting in continuous, nondestructive ultrasound scanning. This permits real-time assessment of tumor contrast enhancement, measurement of lesion vascularity during different dynamic phases, and analysis of tissue perfusion, as well as online evaluation of treatment efficacy, making CEUS an ideal method for intraoperative visualization of

brain lesions. An observation study was, therefore, carried out to compare intraoperative CEUS with baseline ultrasound and preoperative MRI for brain tumors in 71 patients. A qualitative assessment was initially made of tumor and normal parenchyma echogenic characteristics, tumor boundaries and specific anatomic landmarks, and online correlation performed between B-mode imaging and MRI to fuse the images in a neuronavigation system. Offline assessment included timing of arterial and venous phases, degree of contrast enhancement with comparison to brain parenchyma, and pattern of contrast distribution. In all cases, the brain lesion was successfully visualized intraoperatively using iCEUS, along with afferent and efferent blood vessels.

As part of a European Union funded project named "Theraglio," development is ongoing for microbubble-driven multimodal imaging and therapeutic techniques, by incorporating into the polymeric multilayer bubble wall a fluorescent dye for fluorescence microscopy, superparamagnetic ion oxide nanoparticles for MRI detection, ^{19}F PFC gas for high-contrast MRI and ultrasound, RGD motif or VEGFR2 antibodies that target the microbubble to gliomas, and anti-neoplastic drugs to be delivered.

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Author: Marcos Maldaun, MD (Sao Paulo, Brazil)

Title: Extent of resection and applications of intraoperative MRI in brain tumor surgery

Among all the prognostic factors for glioblastoma (GBM) patients' survival, including age, Karnofsky performance status (KPS), *MGMT* promoter methylation, and *IDH1* mutation status, EOR has been proven to play a major role, and yet it is the only one that the neurosurgeon can really alter. One excellent tool that helps the surgeon achieve a maximal resection is the intraoperative MRI (iMRI), which provides real-time imaging during surgery. We can divide iMRI into three subtypes: it can be performed in a brain suite (MRI scanner inside the operating room), next-door MRI (MRI scanner located in a separate but adjacent room), and transoperative MRI (the patient is removed to the imaging department of the hospital and returned to the OR after scanning). There are several publications proving the safety and importance of iMRI in the EOR for many high-grade and most low-grade tumors. We present some other important situations in which iMRI could play a role:

- Correct brain shift
- Perform tumor board immediately after scanning the patient to discuss the possibilities of treatment for residual disease, or in cases with frozen section demonstrating treatment effect determining the need for reoperation with oncologist and radiotherapist
- Excellent option in brain metastasis radionecrosis, where the extent of resection is difficult to define under the microscope
- An option to define EOR in infiltrative skull base tumors that are otherwise analyzed only by serial margin pathology
- We also present a new technique in 15 cases of gliomas that underwent awake craniotomy to achieve a safe resection combined with next-door iMRI to maximize resection. A gross total resection was achieved in 9 of 15 cases; only 3 temporary deficits occurred, with no infections. The median length of surgery was 5.2 hours. From our point of view, this is an ideal means of carrying out maximal (using iMRI) safe (performing awake craniotomy) resection.

We conclude that iMRI is another helpful, safe, and complementary tool, and that performing awake craniotomy in the iMRI is an excellent option to achieve maximal safe resection.

Author: Zvi Ram, MD (Tel-Aviv, Israel)

Title: Awake craniotomy – surgical pearls and pitfalls

A greater EOR of intrinsic brain tumors has been shown to be significantly predictive of OS. Accomplishing a maximal resection, however, is limited by the presence of functionality in the involved brain. Furthermore, anatomy varies widely among individuals, and functionality is relative to the adjacent areas of brain, networks of connectivity, and even to the function being performed. Functionality also encompasses a range of complexity, and preservation of function requires consideration of a variety of sensory and cognitive modalities. Intraoperative stimulation mapping (ISM) and monitoring of various neurological functions is a technology used to achieve maximal tumor resection when lesions are located within or adjacent to functional brain regions. In resections of supratentorial infiltrative gliomas involving eloquent locations, procedures performed with ISM were less than half as likely to be associated with late severe neurologic deficit than cases performed without ISM, but they also achieved a greater EOR.

The technique of awake craniotomy for intraoperative mapping requires careful patient selection; limited cooperation due to personality or cognition, severe dysphasia rending language mapping impossible, and underlying respiratory problems preclude the use of awake craniotomy. The baseline evaluation, which is carried out 1–2 days prior to surgery, includes formal speech evaluation, a comprehensive neuropsychological evaluation, and assessment of the patient's emotional state and ability to cooperate during awake surgery. Patients also meet with a social worker and a member of the monitoring team for detailed review of the operative procedure and in-hospital course.

A therapeutic serum concentration of anticonvulsant medication is confirmed the day before surgery, and dosing adjusted as necessary.

On the day of surgery, minimal doses of sedatives and anxiolytic medications are administered. Scalp nerve blocks using local anesthetic injection are performed according to the location of the planned pin placement and incision site. Skin electrodes for motor and visual evoked potential recording are placed. All sedatives and analgesics are discontinued following skull pinning in order to carry out a neurocognitive evaluation, prior to skin incision. Throughout awake surgery, patients receive supplemental oxygen through a nasal cannula, and spontaneous ventilation is monitored by capnography. If light sedation is required, remifentanil may be infused.

Cortical mapping of speech and motor function is performed by direct cortical 50 Hz bipolar stimulation using an Ojemann Cortical Stimulator. Stimulation is increased in 2 mA increments, beginning at a baseline of 4 mA to a maximum of 10 mA, or until a functional response is elicited. Effects of stimulation on behavior and performance, such as speech arrest, anomia, hesitation, error in finger tapping or any motor response, and the anatomic and radiologic locations corresponding with these effects are noted, along with the stimulation intensity that elicited them. Motor function is a complex process involving primary motor cortex, supplementary motor area (SMA), pre-motor area, and corticospinal tracts (CST). Function of the SMA is monitored with finger tapping, which requires comprehension, movement initiation, motor activity, and rhythm. Along with assessing function, the stimulation threshold within white matter provides an estimate of the distance from the CST. Significant inter-individual variability exists in language site organization. This may be due to anatomic variations, mass effect from tumor, or brain reorganization resulting from neural plasticity. Speech arrest during language mapping may, therefore, be produced far beyond the classical Broca's region. Differentiation between dysarthria and speech arrest is crucial; speech arrest is recognized by a cessation in fluent function (i.e., number counting) without simultaneous involuntary motor responses in the muscles affecting speech.

Intraoperative seizures occur in 15–20% of cases. EEG recordings from a cortical strip electrode can identify seizure activity before it manifests clinically. In most cases, seizures can be aborted with application of iced irrigation fluid over the brain surface, although in very rare cases, conversion to general anesthesia may be necessary. Of 424 awake craniotomies initiated during 2003–2010, 28 (6.6%) failed to be completed. In 25 (5.9%) patients, intraoperative monitoring was unsuccessful. In 9 (2%) cases, induction of general anesthesia was required, in 5 cases due to seizure, in 3 due to severe restlessness, and in 1 due to acute brain edema. Failure of awake craniotomy was significantly associated with a higher rate of major complication, such as hematoma requiring emergency repeat craniotomy, as well as with a lower rate of gross total resection. Identified causes of failure included poor patient selection, patient oversedation resulting in an inability to cooperate with mapping, and seizures caused by overstimulation. Because of these occurrences, the institution's protocols were changed in 2012. The simplicity and ease of performing awake craniotomy with intraoperative stimulation mapping lends itself to widespread and immediate adoption.

LANDSCAPE OF WORLD NEURO-ONCOLOGY

Author: Kathleen Khu, MD (Manila, Philippines)

Title: Neuro-oncology in the Philippines

- Approximately 67% of healthcare in the Philippines is privately funded
- Patients who cannot afford private medical care can receive treatment in government hospitals, however, the waiting time is long and some services are not available
- Neuro-oncology in the Philippines subscribes to the multidisciplinary approach but limitations include lack of centralized neuro-oncology care and suboptimal management of multidisciplinary clinics and brain tumor boards
- The number of neuro-oncology practitioners in the country is very few in relation to the population they serve; there are approximately 120 neurosurgeons (with 2 neurosurgical oncologists), 50 radiation oncologists, 2 neuro-oncologists, 160 medical oncologists, 3 neuropathologists, and 400 general pathologists serving a population of 100 million
- The medical care of a brain tumor patient usually starts with the neurosurgeon; after the operation, depending on the histopathology results, appropriate referrals are made to a radiation oncologist and neuro-oncologist for adjuvant treatment
- Challenges in the practice of neuro-oncology in the Philippines include lack of financial resources, lack of neuro-oncology practitioners, resistance from hospital administration and other medical specialists, and lack of research opportunities
- Steps to improve the state of neuro-oncology in the Philippines include increasing awareness of

brain tumor treatment options and outcomes, establishing multidisciplinary clinics and brain tumor boards in larger hospitals, facilitating slide reviews by neuropathologists, using telemedicine to reach patients and practitioners in far-flung areas, and lobbying for the creation of a neuro-oncology database in national specialty societies.

Author: James Balogun, MD (Owo, Nigeria)

Title: Neuro-oncology in Nigeria

Nigeria is located on the West African coast with an estimated population of 170 million people, making it the most populous black nation. The country's health allocation is 2–4% of the national budget in recent years. The national health insurance scheme remains unchanged since it was signed into law 15 years ago, covering <20% of the population, mainly employees of the government. Thus, payment for healthcare is generally out-of-pocket, posing a tremendous challenge to the populace, 70% of which live below the $1/day income level.

The spectrum of brain and spinal tumors does not differ significantly from what is observed in other climes, though patients tend to present late with larger tumors, major neurological deficits, and hormonal/metabolic dysfunction. Delayed presentation is usually due to ignorance, religious beliefs, poverty, poor understanding and detection of neurological diseases by primary care physicians, and unavailability of specialists, all of which have contributed to the morbidity and mortality associated with brain tumors in our local environment.

The workforce available to provide basic care for neuro-oncology patients is abysmal; there are approximately 50 neurosurgeons (1 per 3.4 million population), three of whom have subspecialty neuro-oncology training. The country has no medical neuro-oncologists or dedicated pediatric neuro-oncologists, with hematologists/oncologists filling the gaps. Radiation oncologists are not specialized, and are concentrated in a few hospitals in larger cities. Available specialists are disproportionately distributed, with a higher concentration in the southern part of the country that is less prone to ethnoreligious crises and has a more educated population.

Imaging modalities available are mainly CT and low-field MRI. Recently, higher-field MRI with capacity for physiologic studies have been acquired mainly by private outfits with higher attendant costs borne by patients. Functional MRI, PET, and advanced modalities are not available.

The state of operating rooms poses one of the most important challenges, with dependence on functional but obsolete instruments such as Hudson brace, Gigli saw, and operating loupes rather than microscopes. Stereotactic navigation, intraoperative electrophysiology for monitoring and brain mapping, and ultrasonic aspirators are lacking. Endoscopy is available in few centers.

Pathological evaluation of tumors consists largely of hematoxylin and eosin with very few centers capable of performing immunohistochemistry. Molecular and genetic profiling is absent. Practically speaking, all glioblastomas are the same!

Adjuvant therapy is limited by few cobalt radiotherapy machines and fewer linear accelerators; there are seven teletherapy radiotherapy machines, compared to an estimated need for 145. Chemotherapeutic agents such as temozolomide are not readily available in the country, and are unaffordable for most patients. Opportunistic infections may be a life-threatening complication for patients who can afford the medications.

Training in the art and science of neuro-oncology is paramount to expanding the frontiers of neuro-oncology in Nigeria and must be vigorously pursued. Subspecialty training is necessary to not only improve clinical care but also to increase the ability to carry out quality research. The formation of a critical mass of specialists can then be a seed for regional centers within the country, which can also receive world-class faculty on short visits.

Medical missions can be tailored to the particular needs of the host country, especially to teach unique skills such as awake craniotomy. Not only can telepathology help mitigate the dearth of neuropathologists but it can also provide a viable platform for teaching and collaboration. Finally, the biomedical industry can increase its presence to make access to equipment and consumables easier and reduce the often outrageous markups by middle-men. Neuro-oncology in Nigeria has a long way to go but the country has an important role to play in the treatment of neuro-oncological conditions within the West African subregion, Africa and the world at large due to its strategic location, population, and economy.

Author: Marcos Maldaun, MD (Sao Paulo, Brazil)

Title: Difficulties of neuro-oncology in Latin America and the creation of SNOLA

The standard-of-care treatment for GBM is described as good preoperative MRI for surgical planning (potentially including DTI, perfusion, and functional scans), maximal safe resection, pathology identification of GBM including IDH1 and MGMT status analysis, 48-hour-postoperative MRI, concurrent external beam RT and temozolamide, and subsequent monthly temozolamide for at least 6 cycles, and MRI control every 3 months. In theory, this is well-established and easy to plan. Unfortunately, the reality for most Latin American centers is that this standard of care is an impossible mission. We performed

a survey including public and private hospitals in Brazil, which showed that <30% have the ability to perform maximal safe resection, <20% follow RANO imaging criteria, <10% have molecular information including MGMT status, <10% have multidisciplinary tumor board meetings, and only 30% follow the Stupp treatment protocol. Based on government numbers, we expect 5500 GBM cases per year, however, in 2012, only 1900 patients received temozolamide. We wonder what happened to the other patients.

In this challenging context, we created the Society for Neuro-Oncology Latin America (SNOLA), a multidisciplinary organization dedicated to promoting advances in Neuro-Oncology through research and education in Latin America. We received support from SNO and EANO, and in the first year we accrued >100 members, promoted satellite meetings in Florida, Peru, and Brazil in 2015, and plan others in Uruguay, Mexico, and the Dominican Republic in 2016. We are also planning the largest neuro-oncology conference in Latin American history in Rio de Janeiro in March 2016, the SNOLA 2016 Update on Neuro-oncology. More than 22 international speakers over three days will discuss almost all CNS tumors, new technologies such as immunotherapy and SNOLA guidelines in a political forum. Over 800 delegates are expected at this conference. We also provide all news and treatment advances, video lectures, and access to Neuro-Oncology Journal on our trilingual website. We offer observerships and fellowships in North American and Latin American brain tumor referral centers for young physicians aiming to become leaders in neuro-oncology. The SNOLA mission has just started and faces many challenges, but strives to create a multidisciplinary concept to improve knowledge and care in Latin American neuro-oncology.

ADVANCES IN BRAIN THERAPEUTICS

Author: Frederick F. Lang, MD (Houston, USA)

Title: Delta-24-RGD for glioblastoma--evolution of oncolytic virotherapy to viro-immunotherapy

Beginning with the pioneering work of Robert Martuzza, MD, who engineered the herpes simplex virus as the first oncolytic virus to be used to treat brain tumors, there have now been a large number of viruses that have been developed for the purpose of treating cancer, including polio virus, measles virus, reovirus, and adenovirus. In this context, Delta-24-RGD is a new oncolytic adenovirus that has recently undergone preclinical and clinical testing. This lecture describes this virus, the preclinical studies supporting the translation of the virus, and a recently completed clinical trial. Through these discussions, the novel concept of viro-immunotherapy is introduced and explored.

Delta-24-RGD is a tumor selective, replication-competent, oncolytic adenovirus with enhanced infectivity, developed by Juan Fueyo, MD (Department of Neuro-Oncology, University of Texas MD Anderson Cancer Center). Because it is replication competent, it maintains its ability to produce viral progeny and to lyse cells. Local injection of the virus results in infection of nearby cells, replication and packaging of new virus, lysis of the cells, and release of increased numbers of viral particles that can then infect another round of cells. With each round of infection, replication and lysis, not only are tumor cells killed but more virus is produced, resulting in spread through the entire tumor. Delta-24-RGD is also tumor selective. The basis of Delta-24-RGD's tumor selectivity is a 24-base pair deletion in the *E1a* gene, which renders the viral E1a protein incapable of inactivating the cellular Retinoblastoma (Rb) protein, which guards the cell cycle by holding cells in G0 and sequestering cellular E2F. Because of the 24 base deletion, viral *E1a* cannot bind Rb and so Delta-24-RGD cannot replicate in normal cells with functional Rb. However, Delta-24-RGD replicates freely in tumor cells because Rb is inactivated in most tumors, either due to mutation of the *Rb* gene or through loss of the upstream regulator p16. Finally, Delta-24-RGD has enhanced infectivity. Specifically, to increase infectivity Delta-24-RGD was engineered to express an integrin-binding RGD-motif in its fiber knob, permitting the virus to enter tumor cells independent of the normal entry pathway, the Cocksackie-Adenovirus Receptor (CAR), and entering entirely through integrins.

Preclinical *in vitro* and *in vivo* studies proved that Delta-24-RGD was capable of curing animals harboring "professional" glioma tumors, such as U87 and D54, and that it was also effective against patient derived cancer stem cells, also known as Glioma Stem Cells, which drive glioma formation. Equally important analyses of post-treatment specimens proved that the virus could replicate and spread through tumors.

Based on these preclinical results Delta-24-RGD was evaluated in a recently completed Phase I clinical trial, which showed that direct intratumoral injection of Delta-24-RGD was safe in patients. Analyses of post-treatment specimens taken 14 days after intratumoral injection proved that Delta-24-RGD could replicate in and kill human glioma cells. Although not appropriately powered for analyzing response, there was a remarkably good outcome as three patients (15%) achieved complete radiographic responses that were durable for over 3 years. Lastly, several observations suggested that, in addition to the oncolytic effects of the virus, there is an immune component to these responses. First, in all complete responders, 1–4 months after injection of Delta-24-RGD, the contrast enhancement on MRI worsened before it resolved, a pattern consistent with an inflammatory

reaction; and second, analyses of tumors surgically resected from several patients during this period of increased enhancement revealed almost no tumor cells, but large numbers of macrophages and CD8 cytotoxic T cells, consistent with a TH1 immune response. These observations are consistent with a model in which viral oncolysis results not only in cell kill, but also in release of tumor associated antigens; because the virus is highly immunogenic, it overcomes the immunosuppressive tumor environment resulting in increased antigen presentation and activation of a cytotoxic CD 8 T cell response against the tumor antigens.

This hypothesis has been tested in immune-competent mouse models. In recently published reports, we have shown that Delta-24-RGD increases inflammatory cell infiltration that is tumor specific and that Delta-24-RGD promotes increase in presentation of tumor-associated antigens, activating CD8 cells. In conclusion, Delta-24-RGD is a novel biological agent whose intrinsic properties have been exploited to provide hard-to-replicate solutions to many of the problems of cancer therapy.

Author: Ghazaleh Tabatabai, MD, PhD (Tübingen, Germany)

Title: Update on molecular-guided therapeutic strategies

To begin the discussion, why does the treatment of primary brain tumors require molecular guidance? An abundance of evidence demonstrates that patients with the same histological diagnosis have different responses to the same therapeutic strategies with different clinical outcomes. Furthermore, the tumor tissue of patients with the same histological diagnosis is highly heterogeneous, and even the tumor tissue of an individual patient may exhibit a high degree of heterogeneity. The molecular features that characterize various glioma subtypes now lead to the identification of molecular biomarkers with potential diagnostic, prognostic, and predictive roles, as well as surrogate markers of disease and most importantly therapeutic targets.

The general approach to a new glioma diagnosis is to first determine whether an *IDH1/2* mutation is present. Tumors containing mutant *IDH* (mIDH), are then stratified by 1p/19q codeletion status. Among tumors with wild-type *IDH* (wtIDH), WHO histologic grade II and III lesions are stratified by 1p/19q codeletion status. Patients with WHO grade IV tumors are stratified by age, and older patients further by *MGMT* promoter methylation status. A number of clinical trials undertake to determine the additional clinical applicability of molecular biomarkers in treatment algorithms.

The CATNON phase III trial, which completed recruitment in July 2015, is a collaborative effort among the EORTC, MRC, NOA, NCI-C, and RTOG to compare concomitant temozolomide (TMZ) and radiotherapy followed by adjuvant TMZ vs radiotherapy alone in WHO grade III tumors with intact 1p/19q. The primary outcome is overall survival, and secondary outcomes include PFS, neurologic deterioration-free survival, and toxicity and QOL measures.

The NOA-16 trial is the first-in-man trial of the IDH1 peptide vaccine targeting the *IDHR132H* mutation. It compares WHO grade III and IV tumors containing mIDH and *ATRX* loss in three arms, i.e., radiotherapy with immune monitoring by IDHR132H antibody ELISA, concomitant radiotherapy and TMZ followed by adjuvant TMZ, and adjuvant TMZ with *IDHR132H* vaccine with imiquimod starting after the first two cycles. The primary outcomes are vaccine safety and tolerability and immunogenicity. Imaging analyses will include standard MRI as well as MRS for 2-hydroxyglutarate.

While *MGMT* promoter methylation is used in treatment decision-making for older patients (>65–70 years), its applicability in patients <65 years of age with newly-diagnosed gliblastoma is being studied. Among methylated tumors, comparison is made between Stupp protocol *vs* Stupp + cilengitide or lomustine, and among unmethylated tumors, comparison is made between Stupp protocol *vs* radiotherapy + enzastaurin, bevacizumab/irinotecan or temsirolimus.

The frequent occurrence of *EGFR* amplification as well as deletion resulting in expression of the EGFRvIII mutant in glioblastoma makes it an appealing target for therapy. A number of strategies have been developed, including tyrosine kinase inhibitors, monoclonal antibodies, toxin conjugates, anti-EGFR vaccines, and chimeric antigen receptor T-cell, and investigations continue in hopes that one of these may prove effective. The occurrence of EGFRvIII in primary *vs* secondary glioblastoma also provides insight into the biology of tumorigenesis, and its difficulty as a target has deepened understanding of escape mechanisms from targeted therapy and challenges for patient stratification.

Emerging targets in newly-diagnosed and recurrent tumors undergoing clinical study include APG101, PD1-L, CTLA-4, FGFR, cMET, and PI3K, and will hopefully add to the molecular guidance of therapeutic decisions already used in clinical practice. Molecular diagnostic testing must be performed in experienced labs with validated assays. Challenges moving forward will be administrative (managing logistics, costs, coordination of studies) as well as biological (rational combination of treatments, strategies to overcome escape mechanisms). Synergistic and collaborative research efforts are needed to ultimately translate knowledge into improved clinical outcomes.

Author: Igor J. Barani, MD (San Francisco, USA)

Title: Advances in Radiation Therapy: Highlights with focus on brain metastases

Radiation therapy has long been the mainstay of brain metastasis management, however, the wide availability of radiosurgery, as well as improved survival from systemic treatments with associated concerns for long-term adverse neurocognitive effects, have raised questions about the appropriate use of whole-brain radiotherapy (WBRT). The evidence yielded by several recent clinical trials is reviewed to address these issues.

Adjuvant WBRT following surgery or stereotactic radiosurgery (SRS) has been shown to reduce both local and distant intracranial recurrence, but it causes neurocognitive deficits likely through multiple mechanisms. To spare the adverse effects of WBRT, SRS alone is often given to patients with ≤4 tumors, whereas WBRT is still administered in the setting of more lesions. However, the concept of reserving local treatment for "oligometastatic" disease has its basis in technical and not biological reasons. JLGK 0901 was a prospective observational study in patients with 1–10 newly-diagnosed brain metastases. Inclusion criteria restricted the largest tumor to <10 cc and cumulative tumor volume to ≤15 cc in patients with good functional status and no leptomeningeal disease. Median OS was 12 months, and only 8% of the patients died of neurologic causes. Patients with one brain metastasis survived significantly longer than those with more, however, no difference in survival was seen between patients with 2–4 and 5–10 tumors. Furthermore, no differences were seen between the latter groups for occurrence of new lesions or for salvage procedures. These results suggest that sparing WBRT for ≥5 tumors is as appropriate as doing so for ≤4 lesions. Technique optimization to minimize exposure of large brain volumes to low-dose radiation is necessary when treating multiple metastases by SRS, but it can be performed safely.

Other studies have examined alternative strategies for preventing radiation-induced cognitive decline. RTOG 0614 was a placebo-controlled, double-blind randomized trial of the NMDA receptor antagonist memantine to prevent neurocognitive decline in patients receiving WBRT. Assessments included cognition and quality of life instruments as well as evaluation of tumor control. Only 32% of patients completed the protocol, and hence the study was underpowered to achieve its primary endpoint. Although memantine was found to reduce the relative risk of cognitive decline, time to cognitive decline, and rate of decline in some domains, the significance of these results in unclear. RTOG 0933 was a phase II study of intensity-modulated RT to avoid the hippocampus during whole-brain radiotherapy (HA-WBRT). The primary endpoint was Hopkins Verbal Learning Test-delayed recall (HVLT-DR) at 4 months, with comparison made to patients who received WBRT in a prior phase III trial. This study found a significantly lower rate of HVLT-total recall deterioration in the group that received HA-WBRT.

NCCTG N0574 was a phase III randomized trial of SRS ± WBRT in patients with 1–3 brain metastases, each measuring <3 cm. Cognitive testing using 6 instruments was performed before and following treatment. This study was unique in using a primary endpoint of cognitive progression (CP), defined as decline of >1 standard deviation from baseline in any test at 3 months. Cognitive deterioration was significantly greater at 3 months in the SRS + WBRT group, involving immediate recall, delayed recall and verbal fluency, whereas intracranial disease control was better in this group at 6 and 12 months. There was no difference in overall survival.

These studies support the existing body of evidence indicating that WBRT causes worse cognitive decline than SRS alone in patients with brain metastases. However, level I evidence still does not support the use of SRS for >4 brain metastases, and hence the questions remain regarding when WBRT is appropriate – whether it should be used upfront in select patients, or as salvage therapy, and in which patients. Furthermore, despite the vast effort and millions of dollars spent on conducting clinical trials, the NCI is primarily interested in studies that improve survival outcomes, and there is a lack of consensus on measuring "soft" outcomes such as cognitive function or quality of life. Perhaps the question that must be asked is whether it is truly reasonable to expect that we can answer every clinical question with clinical trial evidence?