1-2013

Phenytoin reduces 5-ala mediated fluorescence in glioblastoma cells

Christopher Steele

Johnathan Lawrence
Northern Michigan University, jolawren@nmu.edu

Richard A. Rovin
Marquette General Hospital

Robert J. Winn
Northern Michigan University

January 2013

Phenytoin reduces 5-ala mediated fluorescence in glioblastoma cells

Neuro-Oncology 15:iii217–iii225, 2013.
doi:10.1093/neuonc/not191

NEURO-ONCOLOGY

2013 WFNO-SNO Abstracts

SURGICAL THERAPIES

ST-001. PHASE 1 TRIAL OF A RETROVIRAL REPLICATING VECTOR (TOCA 511) IN RECURRENT HIGH GRADE GLIOMA PATIENTS DEMONSTRATES THE IMPORTANCE OF REAL-TIME MRI-GUIDED DELIVERY FOR DOSE-RELATED EVALUATION OF SAFETY AND EFFICACY

Manish Aghi[1], Michael A. Vogelbaum[2], Douglas J. Jolly[3], Joan M. Robbins[3], Derek Ostertag[3], Carlos E. Ibañez[3], Harrry E. Gruber[3], Noriyuki Kasahara[4], Krystof Bankiewicz[5], Timothy F. Cloughesy[6], Susan M. Chang[5], Nicholas Butowski[5], Santosh Kesari[7], Clark Chen[7], Tom Mikkelsen[8], Joseph Landolfi[9], E. Antonio Chiocca[10,12], J. Bradley Elder[10], Greg Foltz[11], and Dan Pertschuk[3]; [1]Dept. of Neurological Surgery UCSF, San Francisco CA, USA; [2]Cleveland Clinic, Cleveland, OH, USA; [3]Tocagen Inc., San Diego CA, USA; [4]Dept. of Medecine UCLA, Los Angeles CA, USA; [5]Dept. of Neurological Surgery UCSF, San Francisco CA, USA; [6]Dept. of Neurology UCLA, Los Angeles CA, USA; [7]Moores Cancer Center UCSD, San Diego CA, USA; [8]Dept. of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA; [9]John F. Kennedy Medical Center, Edison NJ, USA; [10]Dept. of Neurological Surgery OSU Med Center, Columbus, OH, USA; [11]Swedish Neuroscience Institute, Seattle WA, USA; [12]Dept. of Surgery Brigham and Womens Hospital, Boston MA, USA

We are conducting investigational dose escalation trials in patients with High Grade Glioma (HGG, NCT01156584 and NCT01470794), using a retroviral replicating vector (Toca 511). Toca 511 (vocimagene amiretrorepvec) encodes an optimized yeast cytosine deaminase that converts 5-fluorocytosine (5-FC) to the anti-cancer drug 5-FU in infected tumors. We report here results of a Phase 1/2 trial of direct intratumoral Toca 511 administration to recurrent HGG patients, followed by repeat courses of oral 5-FC. Six Toca 511 dose levels, escalated by half logs, the mode of administration and the use of extended release 5-FC (Toca FC) were investigated in 25 HGG patients to date. Treatment at all dose levels has been well tolerated. Post-treatment resection in two patients showed viral protein and DNA and RNA sequences including the CD gene, suggesting viral spread and persistence. MRI and clinical improvements were also occasionally observed. Virus was initially delivered via a brain biopsy needle and placement in the tumor was predicted using conventional neuro-navigation. Immediate MRI after injection of Toca 511 spiked with gadolinium showed inconsistent delivery of Toca 511 to tumors. As a result, real-time MRI-guided delivery was introduced using Toca 511 infusion with a stepped-tip cannula. Using this approach, delivery into as many as 4 locations of up to 3 mL of Toca 511 at flow rates of up to 30 μL/min has been achieved without reflux. In a tumor biopsy from a patient who received 1 mL of Toca 511 and subsequent Toca FC, we observed tumor selective vector transduction and expression by PCR and RT-PCR with concomitant tumor necrosis. At higher Toca 511 doses, significant MRI changes consistent with tumor regression were observed post-Toca FC dosing. Completion of this study is planned, including dose escalation of Toca 511 and increasing the dose and duration of Toca FC.

ST-002. ENDOSCOPIC PITUITARY TUMOR SURGERY: THE LEARNING CURVE

Amjad Anaizi, Christopher Taylor, Jennifer Kosty, Lee Zimmer, and Philip Theodosopoulos; University of Cincinnati, Cincinnati, OH, USA

INTRODUCTION: Endoscopic endonasal pituitary surgery is increasing utilized and is being passed on to the next generation of neurosurgeons. This approach can be technically challenging due to lack of 3 dimensional visualization, increased operative working distance and novel/different instrumentation. We present our experience with the exclusive endoscopic endonasal approach over the last 10 years. METHODS: We performed a retrospective review of patients who underwent an endoscopic endonasal pituitary tumor resection between 2003-2012 by a single neurosurgeon/ ENT surgeon team (PT, LZ). We assessed the extent of resection based on comparison of pre and post-operative imaging for each case. We reviewed complications including post-operative hypopituitarism, diabetes insipidus and CSF leaks. We then compared these outcome parameters in the first half of patients operated on (group A) with the second half of patients (group B). RESULTS: A total of 240 patients with adequate follow up were included in the study. Average patient age in both groups was 51 years. F:M ratio in both groups was 1.15:1. In Group A 55.8% had a GTR and 44.2% had a STR. In Group B, 59.2% had a GTR and 40.8% had a STR. The rate of new post-operative pituitary dysfunction was 18.3% in Group A and 15% in group B. The rate of diabetes insipidus was 12.5% in group A and 3.3% in group B ($P < 0.01$). The rate of post-operative CSF leaks was 3.3% in Group A and 2.5% in group B. CONCLUSION: The 2 dimensional view, increased working distance and novel instrumentation can result in a steep learning curve for endoscopic pituitary surgery. Increased experience should result in improved patient outcomes, particularly a decreased rate of diabetes insipidus.

ST-003. FACIAL NERVE PRESERVATION SURGERY FOR LARGE VESTIBULAR SCHWANNOMAS: FUNCTIONAL AND TUMOR CONTROL OUTCOMES

Amjad Anaizi, Eric Gantwerker, Myles Pensak, and Philip Theodosopoulos; University of Cincinnati, Cincinnati, OH, USA

OBJECT: Large vestibular schwannomas pose a unique challenge of achieving surgical cure while maintaining normal facial nerve function. Facial nerve preservation surgery, defined as attempted maintenance of normal facial nerve function at the cost of residual tumor when adherent to the facial nerve or root entry zone, is a novel idea. We present our experience and evaluate functional outcomes and extent of resection. METHOD: We performed a retrospective review of patients treated surgically by a single surgeon team (PVT, MP) for large (Koos 3 & 4) vestibular schwannomas between 2003-2012. We review the extent of resection, post-operative hearing and facial nerve function. We separated the patients into groups based on extent of resection (gross total, near-total and subtotal) and evaluated the tumor control rate and functional outcome. RESULTS: A total of 56 patients were included in the study. Four patients had received radiation treatment to their tumors prior to surgery. 18 patients underwent a retrosigmoid and 38 underwent a translabyrinthine approach. Hearing was preserved in 1 of 5 (20%) GTR patients, 0 of 2 NTR patients and 1 of 3 (33%) STR patients. Good facial nerve function (HBI & II) was achieved long term in 17 of 20 (85%) GTR patients, 11 of the 12 (92%) NTR patients and 22 of the 24 (92%) STR patients. Only the GTR group had HB IV or worse facial nerve function (3 patients). Long term tumor-control was 100% for GTR, 92% for NTR and 83% for STR. 9 STR patients and 1 NTR patient received postoperative radiation therapy. Average follow-up was 33 months. CONCLUSION: Facial nerve preservation surgery is associated with increased chance of long term good facial nerve outcome. The rate of tumor progression following STR is 17%.

ST-004. NASAL CAVITY MALIGNANCIES INVOLVING THE SKULL BASE: IS THERE A ROLE FOR ENDOSCOPY?

Amjad Anaizi, Sanjeet Grewal, Philip Theodosopoulos, and Lee Zimmer; University of Cincinnati, Cincinnati, OH, USA

OBJECT: The role of endoscopy in the resection of malignant lesions remains controversial. Such malignancies are traditionally resected through transfacial approaches and any skull base involvement is addressed through transcranial or combined approaches. We present a series of patients with nasal cavity malignancies involving the skull base treated with purely endoscopic or endoscopic-assisted resections and offer an algorithm to assist in the appropriate selection of these patients. METHOD: We retrospectively reviewed the charts of patients with malignant nasal cavity lesions involving the skull base resected utilizing nasal endoscopy. RESULTS: A total of 9 patients were included in the series. M:F ratio was 3.5:1. Average age at time of surgery was 52 years. Pathology included Esthesioneuroblastoma, sarcoma, SNUC, melanoma, adenocarcinoma and myofibroblastic tumor. 2 patients (22%) had intra-orbital extension and 1 patient (11%) had pterygopalatine or infratemporal fossa extension. All patients had skull base involvement, 5 (56%) of which had intradural extension. 6 patients (67%) underwent a purely endoscopic resection and 3 patients (36%) had a combined approach. 6 (67%) patients had a GTR and 3 (33%) patients had subtotal resection. Average EBL was 780 ml. 67% of patients retained olfaction post-op. Average follow-up was 25 months. 6 (67%) underwent post-operative adjuvant treatment. Complications included 2 post-op CSF leaks. CONCLUSION: Nasal cavity malignancies involving the skull base can often be difficult to resect. Open transfacial approaches are effective, but can be associated with significant morbidity. We believe that endoscopic and endoscopic-assisted techniques offer a minimally disruptive alternative for the management of many of these lesions in appropriately selected patients.

ST-005. SURGICAL RESECTION FOLLOWING PRIMARY RADIATION TREATMENT FOR VESTIBULAR SCHWANNOMAS: DOES RADIATION IMPACT SURGICAL OUTCOMES AND EXTENT OF RESECTION?

Amjad Anaizi, Myles Pensak, and Philip Theodosopoulos; University of Cincinnati, Cincinnati, OH, USA

OBJECTIVE: With the advent of highly focused delivery of radiation, an increasing number of vestibular schwannomas are being treated this way. A minority of these patients will fail this management strategy and require subsequent treatment. Early studies have shown poor post-operative facial function pressumably due to radiation-induced fibrosis and adhesions to surrounding neurovascular structures. We present our experience with salvage surgical procedures following failed primary radiation treatment for vestibular schwannomas. METHODS: We performed a retrospective review of patients with unilateral vestibular schwannomas who underwent resection following failed primary radiation treatment. No patient had prior surgery for the same lesion and NF2 patients were excluded. We present patient demographic information, preoperative radiation treatment modality and preoperative facial nerve function. We review operative approach, pathology, extent of resection, facial nerve function, tumor control and complications. RESULTS: 5 patients with vestibular schwannomas previously treated with radiation underwent surgical resection. 3 patients received prior SRS and 2 patients received prior fractionated radiotherapy. Average time between radiation and surgery was 42 months. No patients had serviceable hearing prior to surgery. All patients underwent a translabyrinthine approach. A gross total resection was achieved in 4 patients (80%), and a subtotal resection in 1 patient (20%). 3 patients (60%) had a good (HBI & II) post-operative facial nerve outcome. 2 patients had a HB IV facial nerve palsy. Pathology revealed WHO I vestibular schwannoma in all patients. No patient had post-operative tumor progression with an average of 27 months follow up. CONCLUSION: Vestibular schwannomas that have failed primary radiation can present a difficult treatment dilemma to the surgeon. Although radiation effects can increase the potential for post-operative cranial nerve dysfunction and decrease the likelihood of achieving gross total resection, surgical resection with modern surgical technique is a safer and more effective than what earlier data would suggest.

ST-006. ENDOSCOPIC SURGERY FOR INTRAVENTRICULAR AND PARAVENTRICULAR TUMORS

Yoshiki Arakawa[1], Yoo Kang[2], Daiki Murata[1], Ko-ichi Fujimoto[1], and Susumu Miyamoto[1]; [1]Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Department of Neurosurgery, Ohno Memorial Hospital, Osaka, Japan

BACKGROUND: Endoscopic management for the ventricular lesions has been widely applicable according to instrument's development. In ventricular and paraventricular tumors, endoscopic biopsy has been less invasive and safer standard surgery. Here, we report our technique to resect intraventricular tumors with endoscopy. PATIENTS AND METHODS: Between 2007 and 2012, 40 patients with intraventricular tumors have been received endoscopic treatment. Our endoscopic system constitutes MINOP Modular Neuroendoscopy System (Aesculap), VISERA Pro video system with HD camera (OLYMPUS) and Navigation system (BrainLAB). Approach to lateral ventricle is performed through frontal craniotomy, in 3 cm diameter. The field exchange technique is composed of the dry field with evacuated CSF and the wet field with artificial CSF filled in. RESULTS: Tumor resection was accomplished in 12 patients. 2 patients received twice endoscopic operations. There were 2 total resection, 4 subtotal resections and 8 partial resections. There was no severe complications associated endoscopic resection of the tumors. CONCLUSION: In the dry field, it is possible to surgical procedures, which are difficult in the wet field. The field exchange technique is necessary in the situation during endoscopic management. Compared to tumor removal with microscope, however, there are difficult handlings in endoscopic tumor resection, which may be resolved by instruments.

ST-007. ORBITAL METASTASES AS PRIMARY CLINICAL MANIFESTATION OF LUNG CANCER: CASE REPORT AND LITERATURE REVIEW

Maria Blagia, Maurizio Paulis, Giuseppe Orunesu, and Salvatore Serra; Department of Neurosurgery, San Francisco Hospital, Nuoro, Sardinia, Italy

INTRODUCTION: Orbital metastases are an infrequent etiology of adult proptosis; approximately 3–7% of orbital biopsies have demonstrated a metastatic tumour, and this diagnosis is often unexpected. Between 2% and 5% of cancer patients will develop an ocular or orbital metastasis. In 25% of these, it is the presenting sign of malignancy. Frequently, this presents a diagnostic challenge and represents a poor prognosis. METHODS: A 50-year-old man presented with swelling of the eyelid margin, local pain and ptosis of his right eye. Past medical history was unremarkable and the patient took no medications. A CT scan revealed extensive bony destruction of the orbital roof and anterior skull base. A right fronto- orbital approach was used for total removal of the osteolytic tumor. RESULTS: A simple thorax x-ray reveals atelectasia on the lower left lobe and via a bronchoscopy we found an endobronchial mass. We obtained a biopsy and the resulting diagnosis was a spinocellular carcinoma, confirming that this is the originating tumor for the orbital metastasis. Histopathological and cytological study confirmed the diagnosis of an orbital metastases associated with abscess. Postoperative MRI demostrate a total removal of the tumour. Three months after surgery the patient's condition is deteriorating and currently is receiving palliative care. CONCLUSIONS: Any patient with proptosis and/or ptosis with a history of cancer should be evaluated for orbital metastasis. Prognosis can be poor, and thus treatment is sometimes palliative in nature, intending to slow the progression of the disease instead of providing a cure.

ST-009. miR-21 IN THE EXTRACELLULAR VESICLES (EVS) OF CEREBROSPINAL FLUID (CSF): A PLATFORM FOR GLIOBLASTOMA BIOMARKER DEVELOPMENT

Johnny Akers[1], Valya Ramakrishnan[1], Ryan Kim[1], Johan Skog[5], Ichiro Nakano[2], Sandeep Pingle[1], Juliya Kalinina[4], Santosh Kesari[1], Xandra Breakfield[3], Fred Hochberg[3], Erwin Van Meir[4], Bob Carter[1], and Clark Chen[1]; [1]University of California San Diego, La Jolla, CA, USA; [2]Ohio State University, Columbus, OH, USA; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Emory University, Atlanta, GA, USA; [5]Exosome Diagnostics, New York, *NY, USA*

Glioblastoma cells secrete extra-cellular vesicles (EVs) containing microRNAs (miRNAs). Analysis of these EV miRNAs in the bio-fluids of afflicted patients represents a potential platform for biomarker development. However, the analytic algorithm for quantitative assessment of EV miRNA remains under-developed. Here, we demonstrate that the reference transcripts commonly used for quantitative PCR (including GAPDH, 18S rRNA, and hsa-miR-103) were unreliable for assessing EV miRNA. In this context, we quantitated EV miRNA in absolute terms and normalized this value to the input EV number. Using this method, we examined the abundance of miR-21, a highly over-expressed miRNA in glioblastomas, in EVs. In a panel of glioblastoma cell lines, the cellular levels of miR-21 correlated with EV miR-21 levels ($p < 0.05$), suggesting that glioblastoma cells actively secrete EVs containing miR-21. Consistent with this hypothesis, the CSF EV miR-21 levels of glioblastoma patients ($n = 13$) were, on average, ten-fold higher than levels in EVs isolated from the CSF of non-oncologic patients ($n = 13$, $p < 0.001$). Notably, none of the glioblastoma CSF harbored EV miR-21 level below 0.25 copies per EV in this cohort. Using this cut-off value, we were able to prospectively distinguish CSF derived from glioblastoma and non-oncologic patients in an independent cohort of twenty-nine patients (Sensitivity = 87%; Specificity = 93%; AUC = 0.91, $p < 0.01$). Our results suggest that CSF EV miRNA analysis of miR-21 may serve as a platform for glioblastoma biomarker development.

ST-010. ROLE OF SURGERY IN PATIENTS WITH INTRACRANIAL NON GERMINOMATOUS GERM CELL TUMORS (NGGCT) TREATED ACCORDING TO SIOP CNS GCT 96 PROTOCOL WITH RESPECT TO THE SITE AND TIME OF RESECTION

Thomas Czech[1], James Nicholson[2], Didier Frappaz[3], Rolf-Dieter Kortmann[4], Claire Alapetite[5], Maria-Luisa Garré[6], Umberto Ricardi[7], Frank Saran[8], and Gabriele Calaminus[9]; [1]Medical University Vienna, Vienna, Austria; [2]Addenbrookes Hospital, Cambridge, UK; [3]Centre Léon Bérard, Lyon, France; [4]Medical University, Leipzig, Germany; [5]Institut Curie, Paris, France; [6]Gaslini Children's Hospital, Genova, Italy; [7]Medical University, Torino, Italy; [8]Royal Marsden Hospital, London, UK; [9]Medical University, Münster, Germany

BACKGROUND: Data from SIOP CNS GCT 96 and other trials suggest improved outcome with delayed resection of residual tumour in patients with intracranial NGGCTs. The relevance of tumor site on this management algorithm has not been evaluated. METHODS: Until 31.05.2012, 200 patients with NGGCT were treated according to SIOP CNS GCT 96. Median

age was 12 years (range 0-30yrs), 150 were boys. Primary tumour site was pineal in 107 and suprasellar in 51 patients. A bifocal tumour was present in 20 patients, and in 22 patients there was another primary tumour site. We analyzed the impact of resective surgery in relationship to the tumour site, pineal vs sellar-suprasellar. RESULTS: In pineal tumours 54/107 had histology at diagnosis with either upfront resection (36/54) or biopsy (18/54). 53/107 had diagnosis by markers only. Of 20 patients with an upfront gross-total resection 7 had an event. Second-look surgery was performed in 29 patients, 4 of these 29 patients had an event. An event occurred in 28/46 patients with residual tumour after chemotherapy who did not undergo second-look surgery prior to radiotherapy. In suprasellar tumours 26/51 had histology at diagnosis with 21/26 resective and 5/26 biopsy procedures. Marker-only diagnosis was done in 25/51 patients. Of 4 patients with primary gross-total resection 1 had an event. Second-look surgery was done in 7 patients, 2/7 had an event. An event occurred in 6/31 patients with residual tumour who did not undergo second-look surgery. CONCLUSION: While second-look surgery seems to improve outcome in NGGCT primarily located in the pineal region, the impact of this strategy is less clear in hypophyseo-hypothalamic tumours and an attempt at second -look gross total resection needs to be weighted against potentially harmful side-effects.

ST-011. RESECTION PROBABILISTIC MAPS FOR QUALITY ASSESSMENT OF GLIOMA SURGERY: A COMPARISON OF TWO SURGICAL CENTERS USING INTRAOPERATIVE STIMULATION MAPPING

Philip De Witt Hamer[1], Eef Hendriks[1], Emmanuel Mandonnet[2], Frederik Barkhof[3], Koos Zwinderman[4], and Hugues Duffau[5]; [1]Neurosurgical Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of neurosurgery, Hôpital de Lariboisière, Paris, The Netherlands; [3]Department of Radiology and Image Analysis Center, VU University Medical Center, Amsterdam, The Netherlands; [4]Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [5]Department of Neurosurgery, Hôpital Gui de Chauliac, CHU Montpellier, Montpellier, The Netherlands

BACKGROUND: Intraoperative brain stimulation mapping reduces permanent postoperative deficits and extends tumor removal in resective surgery for glioma patients. Successful functional mapping is assumed to depend on the expertise of the surgical team. In this study, the extent of glioma resection (EOR) is quantified using a novel approach, so-called resection probability maps (RPM), exemplified by a surgical team comparison, here with long and short experience in mapping. METHODS: Adult patients with glioma were consecutively included by two centers with two and fifteen years of mapping experience. Resective surgery was targeted at non-enhanced MRI extension and was limited by functional boundaries. Neurological outcome was compared. To compare EOR, we applied RPMs to quantify and compare the likelihood of resection throughout the brain. Considerations for spatial dependence of voxels and multiple comparisons were taken into account. RESULTS: The senior surgical team contributed 56, and the junior team 52 consecutive patients. The patient cohorts were comparable in age, preoperative tumor volume, lateralization, and lobe localization. Neurological outcome was similar between teams. The probability of resection on the RPMs was very similar, with none (0%) of 703,967 voxels in left-sided tumors being differentially resected, and 124 (0.02%) of 644,153 voxels in right-sided tumors. CONCLUSION: RPMs provide a quantitative volumetric method to compare EOR, which we present as standard for quality assessment of resective glioma surgery. Stimulation mapping is a robust surgical technique, because both the EOR and the neurological outcome are independent of surgical experience, supporting wider implementation.

ST-012. MANAGEMENT AND OUTCOMES IN PATIENTS WITH GLIOMA-ASSOCIATED EPILEPSY

Yoshua Esquenazi, Jessica Johnson, and Nitin Tandon; Vivian L. Smith Department of Neurosurgery, University of Texas, Houston Medical School, Houston, TX, USA

INTRODUCTION: Seizures are the most frequent presenting symptom in patients with low-grade tumors and are more prevalent when the lesion is located in or around the temporal lobe. Resection strategies in these patients vary between lesionectomy and epilepsy operations with no clear consensus on optimal approaches. METHODS: A prospectively compiled database of epilepsy and tumor patients was used to identify patients who underwent surgical resection of a glial neoplasm but then developed epilepsy, or who presented with epilepsy and were found to harbor a low grade neoplasm. Seizure frequency, histology, type of surgical resection and outcomes were compiled. RESULTS: Of 235 patients that underwent cranial procedures for epilepsy and 79 patients with low/intermediate grade gliomas, 14 (6%) and 20 (25%) respectively had tumoral epilepsy. Etiology was WHO grade 1 gliomas (DNET, Gangliogliomas, JPA) in 33%, grade 2 gliomas in 36% and grade 3 in 30%. One epilepsy patient had a PNET. Median age was 37 years (22 male). Most common locations were temporal - 44% (7 lateral, 5 mesial and 3 extending to insular cortex) and peri-rolandic - 27% (SMA in 5; lateral in 4). In the epilepsy group, following lesionectomy in 3 and tailored resections in the majority, seizure outcomes were Engel class one in all (1A-10, 1B-2) except for one (class 3). In the tumor group 7 additional resections were performed due to seizure recurrence – all related to residual or recurrent tumor after initial surgery. Outcomes were 1A in 18, 1B, 1C and 2A in 1 each. CONCLUSION: We used an aggressive surgical intervention targeting the lesion except where medial temporal structures were involved, where a typical temporal lobectomy was performed. The excellent outcomes (Engel 1 in 94%) relate to aggressive initial tumor resection and re-resection in the context of recurrence

ST-013. SUPRA-MAXIMAL RESECTIONS FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

Yoshua Esquenazi[1], Elliiot Friedman[2], Yi Lin[1], Jay-Jiguang Zhu[1], and Nitin Tandon[1]; [1]Vivian L. Smith Department of Neurosurgery, University of Texas Health Science Center at Houston, Medical School., Houston, TX, USA; [2]Department of Radiology University of Texas Health Science Center at Houston, Medical School., Houston, TX, USA

INTRODUCTION: Despite recent advances, the median overall survival for patients with GBM remains < 2 years. A substantial body of evidence suggests that cyto-reductive surgery is essential for prolonging survival in these patients. A "supra-maximal" resection, using sub-pial techniques for low-grade gliomas may allow for the eradication of proximate nonfunctional, tissue with high degree of infiltration by glioma cells beyond the zone of contrast enhancement and may result in improved outcomes. The purpose of this study is to evaluate the safety, feasibility and any addition survival benefit of this technique in patients with GBM. METHODS: We retrospectively evaluated 79 consecutive patients (2005-2011) operated on for primary GBM with (45) or without (34) carmustine wafer implantation and adjuvant Stupp protocol therapy. Presenting clinical, radiological and outcome data were collected. RESULTS: Median age was 56 years, median KPS was 80 and median preoperative tumor volume was 33 cm^3. Median follow-up was 15 months. GTR, NTR, and STR were achieved in 21, 11 and 47 patients respectively, and in 21, 9 and 27 patients within the intent-to-treat population. Median survival for the whole group was 15 months, and 34.2, 16.5 and 12 months for GTR, NTR and STR respectively. Two transient and two permanent neurological complications related to surgery occurred. Multivariate regression revealed that intraoperative mapping and % residual tumor were the only predictors of survival. CONCLUSION: The sub-pial technique is safe, effective and associated with an overall survival benefit not previously seen in other similar GBM series in which a GTR is achieved. The benefits of the addition of intra-cavitary carmustine wafer placement may be potentiated with the supra-maximal resections. Neurological deficits and complications were favorable compared to other series and did not prevent adjuvant therapy.

ST-014. STEREOTACTIC BIOPSY FOR DEEP SEATED BRAIN TUMORS USING THE LEKSELL STEREOTACTIC FRAME SYSTEM

Takamitsu Fujimaki[1,2], Masahito Kobayashi[1], Kenji Wakiya[1], Miki Ohta[1], Junichi Adachi[2], Kohei Fukuoka[2], Tomonari Suzuki[2], Takaaki Yanagisawa[2], Masao Matsutani[2], Kazuhiko Mishima[2], Jun Sasaki[1], and Ryo Nishikawa[2]; [1]Saitama Medical University Hospital, Moroyama, Japan; [2]Saitama Medical Univresity, Internationa Medical Center, Hidaka, Japan

PURPOSE: To evaluate the results of stereotactic biopsy for deep seated intraaxial lesions. PATIENTS AND METHODS: Sixteen patients with intraaxial lesions suspected of brain tumor. The locations of lesions were, deep white matter of cerebrum 4, basal ganglia 1, thalamus 6, midbrain 2, pons 3. Patients age range was 9 -81 years (median 61 years), and 9 were men and 7 were women. Under local anesthesia the Leksell stereotactic frame was fixed and the MRI were taken. To determine the targets, neuroimages such as enhanced CT scan or PET study were also used as references. After image acquisition patients were transferred to OR and under general anesthesia, several samples were taken with 2.1mm diameter needle by aspiration. Most

of the cases the biopsy was done through frontal lobe, but in some cases through temporal lobe or through cerebellum. The samples were taken deeper and nearer regions of the designed targets with same trajectory, also. If there were cysts, aspiration of the cyst was performed as much as possible. The trajectory should avoid sulci, cortical veins or ventricular system. After biopsy inside the needle were irrigated repeatedly with 0.1 - 0.2 ml saline using thin plastic tube to ensure hemostasis. RESULTS: In all patients appropriate samples for pathological diagnosis were obtained. The diagnoses were 11 gliomas (pilocytic 1, grade II 3, grade III 3, grade VI (GBM) 2, high grade 1, glial tumor 1) 3 lymphomas, 1 germinoma and 1 multiple sclerosis. There were no symptomatic bleeding nor neurological complications. CONCLUSION: With detailed planning, stereotactic biopsy was safely performed even from brainstem. Trajectories other than from frontal can be also considered for lesions. Repeated irrigation with saline might effective to prevent symptomatic bleeding.

ST-015. SPECIFIC TREATMENT CONSIDERATIONS AND OUTCOME DATA IN ELDERLY GLIOMA PATIENTS - A SINGLE CENTER EXPERIENCE

Markus Hoffermann, Lukas Bruckmann, Kariem Mahdy Ali, Martin Asslaber, Franz Payer, and Gord von Campe; Medical University of Graz, Graz, Austria

BACKGROUND: Although High Grade Gliomas (HGG) are significantly more frequent in patients older than 65 years of age, most clinical studies so far have excluded the elderly population. It is well known that age itself is an independent risk factor in glioma patients and individualized treatment is mandatory, given the prevalence of comorbidities in the elderly. Recent multicenter clinical trials have tried to define the role of different adjuvant therapies, but the role of surgery, especially regarding extent of resection, remains a matter of lively discussion. MATERIALS AND METHODS: A retrospective clinical data analysis of 150 patients (90M, 60F) over 65 years with supratentorial gliomas (WHO-IV:137, WHO-III:11, WHO-II:2) was performed, with emphasis on survival data, adjuvant therapies and neurosurgical intervention. RESULTS: Mean progression free survival was 6.8 months and mean overall survival (OS) was 8.6 months. In 156 surgical procedures (GTR:43, STR:32, PR:37, biopsies:30, reoperations:14) we experienced a mortality rate of 3.3% and morbidity of 18.3%, highest in STR. In the High Grade Glioma subgroup, GTR and STR led to significantly improved median OS compared to PR, biopsy or no surgical procedure (15 and 12 months vs. 4, 4 and 2 months; $p = 0{,}000$). Reoperations were performed in selected cases of HGG ($n = 10$) and these patients showed significantly higher OS (21 vs. 7 months median OS, $p = 0{,}035$). Regarding mean OS, adjuvant therapy according to the STUPP-protocol proved to be more efficient (21.4 months, $p = 0{,}000$) than radio- or chemotherapy alone (5.3 and 8.6), concomitant chemoradiotherapy (6.5) or best supportive care (3.4) but not significantly different from radiotherapy followed by chemotherapy (18.6 months, $p = 0{,}94$). CONCLUSION: Our single center experience provides helpful information on the value of neurosurgical treatment and its impact on outcome in elderly glioma patients, despite limitations regarding treatment heterogeneity. It supports the need for further prospective studies in this age group.

ST-016. COMPLETE, BUT NOT PARTIAL RESECTION OF RECURRENT GLIOBLASTOMA PROLONGS SURVIVAL AFTER RELAPSE WITHOUT IMPAIRMENT OF FUNCTIONAL OUTCOME

Christine Jungk, Bernhard Beigel, Vitali Abb, Christel Herold-Mende, and Andreas Unterberg; Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany

OBJECTIVE: Standard of care in newly diagnosed glioblastoma (GBM) is maximal safe tumor resection followed by radio (RT)- and chemotherapy (CHT). At tumor relapse, however, standard of care, particularly the value of re-resection, is still under debate. We addressed the significance of recurrent GBM surgery with regards to functional outcome and survival and special attention paid to the extent of resection (EOR). METHODS: 30 patients were identified from our tumor database, diagnosed with GBM between 2005 and 2010, having been re-resected at least once for tumor relapse and deceased at the time of analysis. Patient demographics, functional status, adjuvant therapies and survival times were extracted from medical charts. EOR was determined on postoperative MRI scans where available. Survival after re-resection (SRR) was calculated by log-rank test. RESULTS: At initial diagnosis, patients were treated by complete (CR) or partial resection (PR) followed by radio-/chemotherapy. 93% of patients received one, 7% two re-resections. Only 10% were treated with second-line RT or CHT prior to re-resection. At 1st re-resection, CR was achieved in 53%, PR in 40%, EOR could not be determined in 7%. Incidence of permanent neurologic deterioration did not increase from initial surgery to re-resection (10% vs. 13,3%). Analyzing patients with CR ($n = 16$) and PR ($n = 12$) at re-resection only, both groups were comparable with respect to demographic data, tumor eloquence, KPS, number of re-resections and adjuvant therapies for tumor relapse. Importantly, SRR was significantly prolonged in completely resected patients (11 vs. 5 months; $p = 0{,}0348$) while the rate of permanent deficits was comparable. CONCLUSION: In this analysis, complete resection of recurrent GBM, compared to PR, was associated with a significantly prolonged SRR without additional neurologic impairment. These findings stress the significance of maximal tumor resection even at the time of relapse. Certainly, larger studies are warranted to confirm these findings.

ST-017. COMPARATIVE STUDY OF LONG-TERM RESULTS FOR INTRACRANIAL MENINGEAL HEMANGIOPERICYTOMA AND MALIGNANT MENINGIOMA IN SINGLE INSTITUTION: FOCUSED IN SURVIVAL AND LOCAL CONTROL

Jeong Hoon Kim, Young Hyun Cho, and Chang Jin Kim; Asan Medical Center, Seoul, Republic of Korea

INTRODUCTION: Both hemangiopericytoma (HPC) and malignant meningioma (MM) are a rare tumor of meningeal origin that behaves aggressively with a high rate of local recurrence and distant metastases. Two diseases are clinically very similar but there are no comparative study for long term outcome between HPC and MM. Therefore, we present our experiences. MATERIAL AND METHODS: We retrospectively reviewed pathologically proven 30 patients of HPC and 39 patients of MM treated from 1991 to 2006 with at least 5 years follow-up period. Data including clinical characteristics, treatment modalities, recurrence and survival were reviewed. Statistical analysis was done with regards to overall survival (OS) and recurrence free survival (RFS) using Kaplan-Meier survival analysis. RESULTS: The median age at presentation of HPC and MM was 43.0 and 52.0 years. Twenty seven of 30 (90%) in HPC and 28 of 39 (72%) in MM underwent complete resection (Simpson Grade 1 and 2). The 3-, 5-, and 10-year overall survival rates of HPC were 100%, 100%, and 43%, and those of MM were 87%, 64%, and 32%, respectively. The 3-, 5-, and 10-year recurrent rates of HPC were 23%, 40%, and 56% and those of MM were 47%, 49% and 75%. Adjuvant radiotherapy (RT) after surgical resection was an important significant prognostic factor for OS and RFS ($p = 0.026$, $p = 0.024$), but complete resection was not in HPC ($p = 0.565$, $p = 0.228$). In contrast, complete resection was important prognostic factor for OS and RFS ($p = 0.004$, 0.047) although adjuvant RT was not significant factor in MM ($p = 0.432$, $p = 0.742$). CONCLUSION: We conclude that both HPC and MM are very aggressive tumor with high recurrent and low survival rate. While complete resection is best treatment modality in MM, surgical resection with adjuvant RT is best treatment modality in HPC. Long-term and meticulous follow-up is mandatory for local recurrences and distant metastases.

ST-018. MRI-BASED HIGH RESOLUTION MAPS FOR PLANNING/GUIDING HIGH PRECISION PROCEDURES IN BRAIN TUMOR PATIENTS

Yael Mardor[1,2], Ouzi Nissim[1], Yuval Grober[1], David Guez[1], David Last[1], Dianne Daniels[1,2], Chen Hoffmann[1,2], Dvora Nass[1], Alisa Talianski[1], Roberto Spiegelmann[1,2], Zvi Cohen[1,2], and Leor Zach[1,2]; [1]Sheba Medical Center, Ramat Gan, Israel; [2]Tel Aviv University, Tel Aviv, Israel

BACKGROUND: Conventional MRI is currently unable to differentiate tumor from non-tumoral tissues (such as radionecrosis). We have applied delayed contrast extravasation MRI for calculating high resolution maps clearly differentiating tumor from non-tumoral tissues. Here we demonstrate the application for improved targeting of high precision procedures. METHODS: 33 patients with primary/metastatic brain tumors post chemoradiation/radiosurgery were scanned by delayed contrast extravasation MRI prior to surgery. High resolution maps were calculated from T1-MRI acquired 2 and 75 min post contrast injection. 44 stereotactic biopsies planned using the maps were acquired from 17 patients, En-block samples were acquired from 3 and gross total samples were acquired from 13. Histological assessment was then compared with the pre-surgical maps for all patients. RESULTS: The maps showed two primary populations: the delayed contrast accumulation population (red in the maps) and the delayed contrast clearance population (blue). In all cases, samples obtained from blue regions in the maps consisted of morphologically active tumor while samples obtained from red regions

consisted of non-tumoral tissues. According to our maps, in this cohort of patients 52.4 ± 1.9% (on average) of the enhancing volume on T1-MRI did not represent morphologically active tumor. CONCLUSIONS: The fact that ~50% of the enhancing volume on T1-MRI represents non-tumoral tissues emphasizes the need for improved targeting of high precision procedures. The excellent correlation between our pre-surgical maps and histology suggests that the maps may be applied for planning of diagnostic stereotactic biopsies, high precision surgeries and focused-radiation treatments (SRS, iMRT) thus significantly improving targeting to regions of morphologically active tumor. Our recent technological development provides 3D maps of 1 mm^3 resolution, providing increased sensitivity to small regions of active tumor. In addition, the 3D maps are naturally registered to the standard FSPGR navigation sequence, thus may be easily loaded onto the NeuroNavigation system for straight-forward application.

ST-019. LONG-TERM OUTCOMES OF PATIENTS UNDERGOING AGGRESSIVE SURGICAL MANAGEMENT OF INSULAR TUMORS

Neena Marupudi and Sandeep Mittal; Wayne State University - Detroit Medical Center, Detroit, MI, USA

INTRODUCTION: Aggressive surgical resection of insular tumors is neurosurgically challenging due to anatomically and functionally complex cortical structure of the insula. The effects of insular neoplasms on surrounding architecture further complicate resection. Some advocate stereotactic biopsy followed by radiotherapy. However, we demonstrate that aggressive surgical management of insular tumors can be achieved with minimal morbidity using specialized microsurgical techniques. METHODS: We performed a retrospective review of all patients undergoing surgical resection for insular tumors at our institution since 2006 (n = 12). Follow-up ranged from 3-months to 6-years (median = 3-years). Each patient underwent circumferential microsurgical dissection and en bloc insular tumor removal. All procedures were performed by a single neurosurgeon. The surgical procedure included skeletinization of insular branches of the middle cerebral artery and preservation of perforators (lenticulostriate arteries). Patients presenting with intractable seizures underwent Wada test and PET imaging prior to surgery. Postoperatively, surgical outcomes were characterized by the following: 1) histological diagnosis, 2) control of seizures, 3) extent of tumor removal 4) development of new neurological deficits, and 5) long-term outcomes. RESULTS: Nine patients had insular tumors histologically classified as gliomas; remaining lesions included metastases and primary CNS lymphoma. All patients underwent gross total resection. No patient had persistent motor or speech deficit on long-term postoperative follow-up. All patients with refractory seizures (n = 5) had good seizure control from the comprehensive resection. Low-grade gliomas involving the insular lobe remain confined. Due to the expansile growth of insular gliomas, the lenticulostriate vessels are extensively shifted and displaced medially. Insular gliomas demonstrate a stereotypic sharp border medially, which initially aids in creating the plane of resection. CONCLUSION: Our neurosurgical technique optimizes volumetric resection of insular tumors with preservation of surrounding neurovascular structures, preventing long-term neurologic morbidity. With new technical refinements in imaging and neuronavigation, radical removal of insular tumors is feasible with minimal morbidity.

ST-020. FRAME-BASED OR FRAMELESS STEREOTACTIC BIOPSY: THE DEBATE CONTINUES

Karine Michaud, Léo Cantin, Sylvine Cottin, and Charlotte Dandurand; CHU de Québec, Quebec City, QC, Canada

Two different systems are available for stereotactic biopsy of cerebral lesions; frame-based and frameless. Multiple studies have shown that the safety and diagnostic accuracy of both systems are equivalent. Yet, most neurosurgeons, depending on their personal experience or preference, use one system preferentially. We reviewed the cases done at our institution between 2000 and 2013 and seeked any differences or biases toward one system or the other. 469 biopsies were done; 289 frame-based and 180 frameless. The 2 groups were matched for age (mean 56.3), sex (59% male), comorbidities, symptoms at presentation, radiographic appearance and localisation of the lesion (deep 21%) and maximal diameter of the lesion (4.4mm). The patients undergoing frame-based bipsoy did so under local anesthesia (83.7%) as opposed to patients undergoing frameless biopsy (92.2% general anesthesia). There were no more morbidities associated with general anesthesia. The surgical time was longer, although not significantly, for the frameless biopsies (p = 0.08). Hemorrhagic complications occuring during the surgery were more frequent for the frame-based system (21.1% vs 12.8%, p = 0.02). Post-biopsy hemorrhage as seen on the post-op CT scan was more frequent in the frameless group (36.7% vs 25.6%, p = 0.001), although this could be accounted for by the fact that the frame-based patients underwent their CT scan sooner after the surgery compared to the frameless group (13.1% vs 9.3%). The diagnostic accuracy of both techniques were similar, with only 1% of blank biopsies in each group. This study, which is one of the largest in the litterature, confirms the equivalent safety and diagnostic accuracy of both techniques. Although there were more hemorrhages during the frame-based procedures, the rate of neurologic complications were similar as were the lengths of stay at the hospital. The study also confirms that both techniques are suitable for deep-seated lesions.

ST-021. LASER INTERSTITIAL THERMAL THERAPY (LITT) AS A TREATMENT MODALITY FOR DIFFICULT-TO-ACCESS HIGH GRADE GLIOMAS: A MULTI-CENTER STUDY

Alireza Mohammadi[1], Ammar Hawasli[2], Analiz Rodriguez[3], Jason Schroeder[1], Adrian Laxton[3], Paul Elson[1], Stephen Tatter[3], Gene Barnett[1], and Eric Leuthardt[2]; [1]Cleveland Clinic, Cleveland, OH, USA; [2]Washington University, St. Louis, MO, USA; [3]Wake Forest University, Winston-Salem, NC, USA

INTRODUCTION: Surgical extent-of-resection has been shown to have an impact in high grade glioma (HGG) outcomes, but it is rarely achievable in difficult-to-access (DTA) tumors. Controlled thermal damage to the tumor may have the same impact in DTA-HGGs. We report our multi-center results of Laser Interstitial Thermal Therapy (LITT) in DTA-HGGs. METHODS: We retrospectively reviewed 35 consecutive DTA-HGG patients (24 GBM, 11 anaplastic gliomas) who underwent LITT in the Cleveland Clinic, Washington University, and Wake Forest University during 5/11-12/12. LITT was performed under MR-thermography guidance using NeuroBlate device (Monteris, Winnipeg). Extent of thermal damage was determined as thermal-damage-threshold (TDT) lines including: yellow TDT-line = 43°C for 2 minutes and blue TDT-line = 43°C for 10 minutes. Pre- and post-operative MRI scans as well as TDT-lines were imported into the iPlan software (BrainLAB, Germany) for volumetric analysis. Extent of coverage (EOC) by TDT-lines and residual tumor volume (RTV) uncovered by TDT-lines were measured. Patient outcomes were evaluated statistically. RESULTS: Median age was 56 years and 40% were female. Treatment was upfront in 19 and salvage in 16 patients. Median tumor volume was 10.1cc (0.7-49cc). One patient died because of meningitis and 7 patients had neurological worsening after procedure (temporary in 5 patients). After a median of 7.2 months follow-up, 80% of patients have progressed and 34% died. Median overall-survival was not reached (1-year overall survival is estimated to be 68% + 9%). Median progression-free-survival (PFS) was 5.1 months. Thirteen patients who had both >99% EOC by yellow TDT-line and <1.5cc RTV uncovered by blue TDT-line had better PFS than others (9.7 versus 4.6 months; p = 0.02) which was still prognostic in the subgroup of 24 GBM patients (p = 0.04). CONCLUSIONS: LITT can be used safely and effectively for treatment of DTA-HGGs. More complete coverage of tumor by TDT-lines improves PFS which can be translated as the extent of resection concept for surgery.

ST-022. USE OF 5-AMINOLEVULINIC ACID FOR DETECTION OF RESIDUAL MENINGIOMA FOR TOTAL REMOVAL AND AVOIDANCE OF NEUROLOGICAL DEFICITS

Shusuke Moriuchi[1], Makoto Dehara[1], Takanori Fukunaga[1], Yasushi Hagiwara[1], Hakao Soda[2], and Masami Imakita[3]; [1]Department of Neurosurgery, Rinku General Medical Center, Izumisano, Osaka, Japan; [2]Department of Neurology, Rinku General Medical Center, Izumisano, Osaka, Japan; [3]Department of Pathology, Rinku General Medical Center, Izumisano, Osaka, Japan

5-Aminolevulinic acid (5-ALA) has been used successfully to resect meningioma without residual mass. The authors report their experience in the resections of 15 patients with meningioma using 5-ALA. Except one case, all meningiomas fluoresced intraoperatively under microscope. Invasions to the dura mater, the brain parenchyma or skull fluoresced, allowing for confirmation of residual tumor and total removal of the meningioma could perform more easily and prevent unexpected neurological deficit by precise removal of the tumor under microscope. In a case with invasions to dura mater or skull, the extent of dural removal was decided by 5-ALA fluorescence with 1-2 cm safty margins. In another case with parenchymal invasions, close removal of the tumor without residual tumor could be performed with 5-ALA fluorescence. With the above methods, no serious side effects or

complications occurred in this study. Not all of meningiomas fluoresced with 5-ALA, and 5-ALA is available for about 90% of meningiomas. 5-ALA would be easy to use and be useful to find residual tumor and also useful to prevent recurrences by total removal in meningiomas.

ST-023. UPDATED THERAPEUTIC STRATEGY FOR ADULT LOW-GRADE GLIOMA STRATIFIED BY RESECTION, HISTOLOGY, AND MOLECULAR MARKERS

Masayuki Nitta[1,2], Takashi Maruyama[1,2], Hiroshi Iseki[1,2], Soko Ikuta[2], Manabu Tamura[2], Mikhail Chernov[2], Saori Okamoto[1], Yoshikazu Okada[1], and Yoshihiro Muragaki[1,2]; [1]Department of Neurosurgery, Neurological Institute, Tokyo Women's Medical University, Tokyo, Japan; [2]Institute of Advanced Biomedical Engineering & Science, Tokyo Women's Medical University, Tokyo, Japan

BACKGROUND: There is no established standard therapy for adult low-grade glioma (LGG), and there is a large difference in therapeutic strategy between institutes. Based on the outcome of ten years in our institute, we have recently established our updated therapeutic strategies for LGG. METHODS: We retrospectively analyzed of 153 patients (mean age; 39 yo, 56 male, 44 female) with LGG who underwent surgical treatment between 2000 and 2010. Pathological subtypes were as follows: 49 diffuse astrocytoma (DA), 45 oligoastrocytoma (OA), 59 oligodendroglioma (O). Patients with ≥95% EOR were observed and others were treated with radiation and/or chemotherapy. RESULTS: Median preoperative tumor volume was 29.0cm^3 and median EOR was 95%. 10-year OS and 5-year PFS for all the patients were 95.1% and 60.2%, respectively. Eight-year OS for DA, OA and O were 70.9%, 91.2%, and 98.3%, respectively. Both OS and PFS were significantly longer in patients with ≥90% EOR than those with <90% EOR ($P < 0.01$). Increased EOR resulted in better PFS for diffuse astrocytoma ($P < 0.01$) but not for oligodendroglioma. Multivariate analysis identified age (HR = 4.08; 95% CI, 1.08-16.96; $P = 0.038$) and EOR (HR = 4.75; 95% CI, 0.7-26.48; $P = 0.039$) as parameters significantly associated with OS. The only parameter associated with PFS was EOR (HR = 2.69, 95% CI, 1.43-5.04; $P = 0.002$). Chemotherapy prolonged PFS in patients with oligodendroglilal subtypes ($P = 0.006$). However, there was no survival benefit of radiation and chemotherapy in diffuse astrocytoma. CONCLUSIONS: Our updated therapeutic strategy for LGG is followings; 1. Patients with ≥90% EOR are carefully observed without any adjuvant therapy regardless of tumor subtype. 2. DA patients with <90% EOR are considered second look resection and if impossible, radiotherapy and nimustine hydrochloride (ACNU) based chemotherapy are conducted. 3. OA and O patients with <90% EOR and co-deletion of 1p19q loci are treated with ACNU and the others are treated with both radiotherapy and ACNU.

ST-024. SURGERY USING A TRACTOGRAPHY-INTEGRATED NAVIGATION SYSTEM AND MOTOR EVOKED POTENTIALS FOR PRESERVATION OF MOTOR FUNCTION IN PATIENTS WITH MALIGNANT GLIOMA

Shiro Ohue, Shohei Kohno, Akihiro Inoue, Daisuke Yamashita, Yoshiaki Kumon, and Takanori Ohnishi; Department of Neurosurgery, Ehime University Graduate School of Medicine, Toon, Ehime, Japan

INTRODUCTION: The optimal surgery for malignant gliomas, at present, is maximal tumor resection without deterioration of neurological function. We evaluated the contribution of using tractography-integrated navigation system and motor evoked potentials (MEPs) to surgical and functional outcomes. METHODS: Subjects comprised 50 patients who underwent resection for malignant glioma near the pyramidal tract (PT) in our hospital. Diffusion tensor imaging (DTI) was performed using a 3-T magnetic resonance scanner, and DTI-based tractography of the PT was loaded into the navigation system for intraoperative guidance. If possible, silicone catheters as fence posts were inserted along the tumor boundaries, avoiding the course of the PT before removal. Cortical MEPs were monitored intermittently during resection. When the line of resection closely approached the PT, subcortical MEPs were used to identify proximity to the PT by observing motor responses. When a response was elicited, removal was abandoned to ensure preservation of the motor function. RESULTS: DTI-based tractography of the PTs was performed successfully in all patients. Fence post techniques using a tractography-integrated navigation system were applied in 46 patients. This fence post technique was useful to clarify the resection plane before resection, and to resect the tumors safely and easily. Amplitudes of cortical MEPs after tumor resection were 30-140% of those obtained before resection. Although no subcortical MEPs were observed at 20-mA stimulus intensity in eight patients throughout tumor resection, the other 42 patients showed obvious responses of subcortical MEPs at ≤20 mA. The degree of resection was total in 22 patients, subtotal in 15, and partial in 13. At one month postoperatively, only one patient showed worsened motor function because of tumor progression. CONCLUSION: A tractography-integrated navigation system and MEPs are useful for preserving motor function during tumor resection in patients with malignant gliomas near the PT.

ST-025. 5-ALA GUIDED RESECTION OF MALIGNANT GLIOMA: A SINGLE INSTITUTION EXPERIENCE

Pierandrea Oppido, Veronica Villani, Antonello Vidiri, Andrea Pace, Alfredo Pompili, and Carmine Carapella; Regina Elena National Cancer Institute, Roma, Italy

INTRODUCTION: Malignant glioma represent a relevant therapeutic issue and the value of extensive surgical resection remains debated; recent evidence suggests that radical removal is associated with better survival. An interesting tool for identifying tumor tissue and increasing the extent of surgery is represented by fluorescence-guided resection, taking advantage of metabolic and structural changes induced by 5-amino-levulinic acid (ALA), a natural precursor of heme biosynthetic pathway. METHODS: The present experience is related to 48 patients affected by malignant glioma (28 newly diagnosed and 20 recurrent tumors): 42 glioblastoma (GBM), 4 anaplastic oligodendroglioma, 1 oligodendroglioma I WHO and 1 pleomorphic xanthoastocytoma. All patients underwent preoperative and early postoperative MRI, showing contrast enhancing lesions. All patients were selected for fluorescence-guided resection. An oral dose of 20 mg 5-ALA /kg bw was administered to each patient. Microsurgical resection was performed by an operating microscope enabled to visualize the fluorescence. All the patients, as first line treatment, have been submitted to radiotherapy and chemotherapy; second and in some cases third line treatments were utilized in recurrent cases. RESULTS: In more than 90% of patients tumor tissue showed intraoperative red fluorescence; mainly in recurrent GBM, when MRI documented heterogeneous lesions with enhancing areas mixed with gliotic scars, fluorescence-guided surgery allowed a better definition of active tissue, with net margins from perilesional "healthy" brain. Early postoperative MRI confirmed gross total resection in 80% of the patients. In the present experience the procedure did not determine any relevant additional neurological deficit. Considering overall survival of recurrent patients we obtained a median extension of at least 9.0 months (4 – 16+ months). CONCLUSIONS: Fluorescence-guided surgery improves tumor detection and allows extended resection of malignant glioma, without any relevant impact on neurological status, resulting helpful mainly in the recurrent setting with a consistent effect on overall survival.

ST-026. THE PROGNOSTIC SIGNIFICANCE OF EXTENT OF RESECTION AND RESIDUAL VOLUME IN GLIOBLASTOMA PATIENTS

Daniel Orringer, Darryl Lau, and Yashar Niknafs; University of Michigan, Ann Arbor, MI, USA

INTRODUCTION: Conflicting evidence exists on the importance of maximal resection in glioblastoma patients. Furthermore, the mechanism by which resection prolongs survival remains unclear. We hypothesize that maximal resection is most beneficial in patients where gross total resection is feasible and that surgical resection confers benefits to glioblastoma patients through both brain decompression (assessed by extent of resection) and a reduction in the volume of viable tumor (assessed by residual tumor volume). METHODS: A consecutive population of patients who underwent craniotomy for GBM resection from 2005-2011 were identified. FIJI image analysis software was used to perform volumetric analysis of pre- and post-operative MRIs to determine tumor volume, EOR and RV. Resectability was determined with a published grading scheme that is based on tumor location relative to brain function. Statistical comparison of survival by EOR, and RV was performed via log-rank test and Kaplan Meir curves. RESULTS: Sixty-five patients had sufficient images for analysis. Overall 1-year survival was 61.5%. Greater EOR ($p < 0.001$) was associated with higher 1-year survival rates: in patients where EOR was greater than 90%, 1-year survival was 85.3%. Higher RV was significantly associated with poorer survival ($p = 0.012$): when RV was greater than 8,000 mm^3, the 1-year survival rate was 35.0%. When RV was less than 8,000 mm^3, 1-year survival rates were in excess of 80%. EOR and RV were found to be significant predictors of survival in patients with resectable tumors ($p < 0.001$ and $p = 0.044$, respectively). However, EOR and RV were not predictive of survival in patients

with non-resectable tumors ($p = 0.399$ and $p = 0.356$, respectively). CONCLUSION: Maximal safe resection likely provides a greater benefit to glioblastoma patients with resectable tumors than to those with non-resectable tumors. Surgical resection may confer a survival benefit by decreasing the degree of compression on the brain and by reducing the volume of viable tumor.

ST-027. FLUORESCENCE GUIDE SURGERY IN HIGH GRADE GLIOMAS USING A HIGH-DEFINITION EXOSCOPE SYSTEM: AN ALTERNATIVE TO MICROSCOPE

Jose Piquer, Jose Luis Llacer, Vicente Rovira, Pedro Riesgo, and Antonio Cremades; Hospital Univesitario de la Ribera, Alzira. Valencia, Spain

INTRODUCTION: Fluorescence-guided microsurgical resections of high-grade gliomas using 5-aminolevulinic acid (5-ALA) have proved to be superior to conventional microsurgery. An optical device, usually a modified microscope, is needed for these procedures. However, an exoscope may be implemented for fluorescence techniques. OBJECTIVE: We present the use of an exoscope to perform tumor resection guided by 5-ALA fluorescence in 21 consecutive patients with high-grade glioma and 2 neuronavigation guided biopsy. METHODS: Twenty-five three were operated using ALA-fluorescence implemented in an exoscope system. Tumor volume and localization were quantified with pre- and postoperative volumetric magnetic resonance imaging in non biopsy cases. RESULTS: In non biopsy cases the age range in our series was 20 to 79 years, with a median of 56 (interquartile range = 45-66). Histological analysis indicated that 14 had glioblastoma multiforme, 2 grade-III oligodendroglioma and 1 anaplastic astrocytoma, 3 metastases and 1 low grade astrocytoma. Total resection was achieved in 15 cases, subtotal resection was performed in 5 patients, and in one case, the result was a partial resection. There was no perioperative mortality. The median fluorescence intensity, on a scale of 1-5, was 4.5 in the GBM group (IQR = 4-5), 3 (IQR = 2.5-3.5) in the cases of anaplastic glioma and 2.5 (IQR = 2.25-2.75) for the oligodendrogliomas. Of the three metastases, one showed a level 4 degree of fluorescence. In the two biopsy cases, 1 was an anaplastic astrocytoma and 1 a glioblastoma multiforme. In both cases the samples obtained from tumor were fluorescence. CONCLUSIONS: An exoscope can be also used to for fluorescence-guided surgery and with 5-aminolevulinic acid (5-ALA) and neuronavigation guided biopsy. With an important advantage of low cost allows the surgeon to perform collaborative surgeries and adds agility to the procedure.

ST-028. PREOPERATIVE nTMS GENERATED MOTOR AND LANGUAGE MAPS: FEASIBILITY AND OUTCOME

Roger Rotta, Nicholas Levine, Sujit Prabhu, Raymond Sawaya, Jeffrey Weinberg, Ganesh Rao, Sudhakar Tummala, and Catherine Tilley; University of Texas MD Anderson Cancer Center, Houston, TX, USA

INTRODUCTION: The management of brain tumors adjacent to speech and motor areas presents a surgical challenge. The goals are maximal safe resection and preservation of neurological function. Pre-surgical functional information about the cortical and subcortical areas at risk is crucial for the avoidance of neurological deficits during tumor surgery. Intraoperatively direct electrical stimulation (DES) is the "gold standard" to identify and preserve essential function. Recently nTMS has been shown to be useful in generating both motor and speech maps prior to surgery. METHODS: We describe our 23 consecutive patients with brain tumors located adjacent to eloquent areas (motor and language). All cases were performed with nTMS, intraoperative DES and awake craniotomy during language mapping. RESULTS: Of the 23 patients 84% were HGG (grade III and IV), 4% LGG (grade II), 4% Grade I and 20% Metastasis. Parietal lobe was the most frequent location of tumors seen in 13 (56%) cases. In 95% of patients a positive response in upper extremity (UE) nTMS, correlated well with those generated by DES (94%). In 4(23%) cases nTMS was superior to DES in isolating the lower extremity (LE) response. Of the 6 (25%) cases performed for speech mapping, 1(17%) case had a true positive response and 1(17%) a false positive while true negative was seen in 4(66%). A gross total resection (GTR) was achieved in 14 (61%) patients, and at 1 month follow-up, 18(78%) had no deficit, 4 (18%) stable and 1(4%) worsening. There were no adverse events during the stimulation. CONCLUSION: Navigated transcranial magnetic stimulation can be safely used in pre-surgical mapping of the motor cortex involving both the UE and LE and the results correlate well with DES. Despite a 66% rate of true negative response in speech mapping, nTMS helped understand the functional cortical organization preoperatively and facilitated successful resection.

ST-029. MINIMALLY INVASIVE SURGICAL RESECTION OF SUBCORTICAL TUMORS USING THE SIX PILLARS SYSTEM

Richard Rovin[1] and Amin Kassam[2]; [1]Marquette General Hospital, Marquette, MI, USA; [2]The Ottawa Hospital, Ottawa, ON, Canada

The neurological cost of access to subcortical tumors often precludes surgical removal, thus denying these patients a biologically meaningful intervention available to their counterparts with more superficially located lesions. By integrating the latest technologies from mapping, image guidance, access, optics, resection and therapeutic platforms, the Six Pillars System optimizes the minimally invasive approach to deep tumors. At the heart of the system is the FDA approved BrainPath device—a 13.5 mm tubular retractor that is directed to the tumor via a trans-sulcal trajectory designed to minimize shear force to the intervening white matter fiber tracts. The first surgeries in the United States using the Six Pillars System were performed at Marquette General Hospital. To date, 17 patients with tumor have been treated. There were six men and eleven women. Five patients harbored primary tumors (two glioblastoma and three grade III astrocytoma). Twelve patients had metastatic tumors. Following surgery, five patients improved neurologically, nine were unchanged, and one patient had a persisting deficit. Two patients had postoperative seizure. No patient developed a postoperative infection. One patient expired, one month after surgery. The average length of stay for patients treated with the Six Pillars System was 2.25 days, compared to 4.82 days for patients undergoing open craniotomy. The authors conclude that the minimally invasive approach to subcortical tumors using the Six Pillars System is safe and effective for appropriately selected patients.

ST-030. LOW-DOSE RATE IODINE-125 BRACHYTHERAPY IN RECURRENT MALIGNANT GLIOMAS

Christoph Schwartz[1], Alexander Romagna[1], Niklas Thon[1], Jörg-Christian Tonn[1], Silke Birgit Schwarz[2], and Friedrich-Wilhelm Kreth[1]; [1]Department of Neurosurgery, Munich, Bavaria, Germany; [2]Department of Radio-Oncology, Munich, Bavaria, Germany

OBJECTIVE: Prognosis of recurrent malignant gliomas (WHO III and IV) is dismal and despite numerous efforts postrecurrent survival (PRS) remains short. This pivotal study evaluates the effectiveness and treatment-associated risks of low-dose rate Iodine-125 stereotactic brachytherapy (SBT) in highly selected patients with circumscribed tumor recurrence. METHODS: Data of patients with treatment between 2003 and 2011 were prospectively collected and retrospectively analyzed. Indications for SBT were histologically verified recurrent gliomas WHO III or IV with a diameter of $<$4cm based on MRI and ^{18}FET-PET, and a KPS of $\geq$70%. Biomarker status included MGMT-methylation, IDH1/2 mutations, LOH 1p/19q. SBT was performed via temporary iodine-125 seed implantation. Reference dose was 50 Gy, dose rates were low ($<$ 15 cGy/h). Date of last follow-up (FU) was 02/2012. Survival analysis was performed with the Kaplan-Meier method. RESULTS: 71 patients (35 males, 36 females) were included. Median age at seed implantation was 52 years, the median KPS was 90%. All patients had received prior treatment. Histological diagnoses included 41 glioblastomas WHO IV, 20 astrocytomas WHO III, 9 oligoastrocytomas WHO III, and 1 oligodendroglioma WHO III. The median tumor volume was 2.5 cm^3 and the median treatment time was 450 hours. The median FU was 34 months. Median PRS after SBT was 9.5 months (CI95% 7.6-18.4) and 25.7 months (CI95% 11.5-42.3) for WHO IV and III tumors. Favorable prognostic factors for PRS after SBT were patient age at SBT ($p = 0.002$) and LOH 1p/19q ($p = 0.04$). Neither tumor grade, nor MGMT-methylation, nor IDH1/2 mutations had any significant impact. Transient morbidity was seen in 17% of patients, no permanent morbidity was found. CONCLUSIONS: Low-dose rate Iodine-125 SBT is an attractive additive local treatment option for highly-selected patients with recurrent malignant gliomas who had previously undergone multimodal therapy. SBT efficacy is seemingly independent from MGMT-methylation and IDH 1/2 mutation status.

ST-031. THE ROLE OF SURGERY FOR ANAPLASTIC GLIOMAS WITH IDH GENE MUTATION

Yukihiko Sonoda[1], Ichiyo Shibahara[1], Ryuta Saito[1], Masayuki Kanamori[1], Toshihiro Kumabe[2], and Teiji Tominaga[1]; [1]Tohoku University, Sendai, Japan; [2]Kitasato University, Sagamihara, Japan

INTRODUCTION: IDH gene mutation was frequently found in anaplastic gliomas. Although IDH gene mutation has been reported to be a favorable prognostic factor, anaplastic gliomas with IDH gene mutations sometimes recurred as secondary glioblastoma. In this study, we investigated the role of

surgery for anaplastic gliomas with IDH gene mutation. METHODS: We analyzed clinical (extent of resection), genetic (1p19q codeletion, TP53 gene mutation) factors for correlation with progression free survival (PFS) and overall survival (OS). RESULTS: Eighty-one patients with IDH mutant anaplastic gliomas were investigated. Thirty patients received total resection on MRI. Median PFS was 187 months and median OS was not reached. Eighteen of 50 patients received less than subtotal resection recurred during follow-up period (median PFS 74 months). 12 of 18 tumors had TP53 gene mutations and other 6 tumors had 1p19q co-deletion. On the other hand, tumor recurrence was observed in only four patients which underwent total resection. Three of those also had TP53 gene mutation. Overall survival of total resection group and non-total resection group were not reached and 136 months respectively ($p = 0.0036$). 10 years survival rate of total resection group and non-total resection group were 93.4% and 50.4% respectively. CONCLUSION: Patients of anaplastic gliomas with IDH mutation had favorable prognosis. Particularly, total resection was significantly associated with survival. Even in patients with IDH mutant gliomas, TP53 gene mutation still had risk for recurrence.

ST-032. PHENYTOIN REDUCES 5-ALA MEDIATED FLUORESCENCE IN GLIOBLASTOMA CELLS

Christopher Steele[1,3], Johnathan Lawrence[1,3], Richard Rovin[2,3], and Robert Winn[1,3]; [1]Northern Michigan Univeristy, Marquette, MI, USA; [2]Marquette General Hosptial, Marquette, MI, USA; [3]Upper Michigan Brain Tumor Center, Marquette, MI, USA

Glioblastoma multiforme (GBM) is a devastating form of cancer, and essentially all GBM tumors recur causing fatality. A new surgical technique, fluorescence-guided resection of GBM using 5-aminolevulinic acid (5-ala), improves the extent of resection and positively impacts the length and quality of patient survival. The fluorescence achieved in neoplastic tissue depends directly on the accumulation of porphyrins derived from the metabolism of the 5-ala prodrug within the cancer cell. However, 5-ala induced fluorescence has been reported to be inconsistent. In an effort to determine the cause of the inconsistent fluorescence, the authors investigated the effect of medications commonly prescribed to brain tumor patients on 5-ala induced fluorescence. A model was developed to quantify intracellular porphyrin accumulation using a U87MG GBM cell line constitutively expressing yellow fluorescent protein (YFP-U87). 5-ala mediated fluorescence within the cells was standardized to cell number via the fluorescence emission spectra ratio of porphyrin (405 nm) to YFP (525 nm). 5-ala induced accumulation of porphyrins was measured after treating YFP-U87 cells with phenytoin, dexamethasone, or desipramine for 3 days. After a 6 hour incubation with 5-ala, no significant difference in porphyrin accumulation was observed in cells treated with dexamethasone or desipramine. Phenytoin, however, significantly reduced the accumulation of fluorescent porphyrins within the YFP-U87 cell line by nearly 30% compared to the control. To optimize fluorescence during surgery and improve patient survival these results suggest that further investigations are warranted to determine the effects of commonly administered medications on 5-ala fluorescence-guided resection of GBM.

ST-033. MALE GENDER IS A RISK FACTOR FOR THE CLINICAL COURSE OF SKULL-BASE CHORDOMAS

Walter Rachinger[1], Matthias Simon[2], Stephan Dützmann[3], Günther Feigl[4], Natalia Kremenevskaya[5], Niklas Thon[1], and Jörg-Christian Tonn[1]; [1]Department of Neurosurgery, Munich, Germany; [2]Department of Neurosurgery, Bonn, Germany; [3]Department of Neurosurgery, Frankfurt, Germany; [4]Department of Neurosurgery, Tübingen, Germany; [5]Department of Neurosurgery, Erlangen, Germany

OBJECTIVE: Chordomas of the skull base are rare, locally invasive and have a poor prognosis. Recently, the expression ratio of the transmembrane cell adhesion proteins N-cadherin and E-cadherin has been suggested to provide additional prognostic information. Aim of this retrospective multicentric confirmatory study was to evaluate prognostic factors including expression of N- and E-cadherins in patients initially treated with microsurgical tumor resection. METHODS: 47 patients (21 women, 26 men, mean age 49 years) treated in five academic centers were included. Histology was centrally reviewed, as well as N- and E-cadherin-expression by immuno-histochemistry. Prognostic factors were obtained from multivariate regression models. For survival analysis the Kaplan-Meier method was used. RESULTS: The median follow-up period was 5.2 years. Gross total resection, subtotal resection and extended biopsy were done in 14.9%, 80.9%, and 4.2%, respectively. Adjuvant radiotherapy (including proton beam irradiation) was applied in 63.8% of the patients. Median progression free survival was 7.3 years. Multivariate analysis identified male gender as an independent risk factor for tumor progression ($p = 0.04$) and death ($p = 0.03$), despite the fact that radical resection was achieved more often in males ($p = 0.036$). Neither expression rates of E-cadherin and N-cadherin nor their ratio did gain prognostic influence. None of the other patient-, tumor- or treatment related prognostic factors (age, duration of symptoms, Karnofsky score, extent of resection, adjuvant radiotherapy) proved to be of prognostic relevance in the multivariate model. CONCLUSION: In skull base chordomas, male patients bear a significantly higher risk of recurrency and death. Expression of E- and N-cadherin has no prognostic significance. These data might help to identify high risk patients in whom more aggressive adjuvant therapy or at least a closer follow-up schedule is warranted. Moreover, further studies are needed to elucidate the potential mechanism of gender disparity with regard to tumor progression and prognosis.

ST-034. PHOTODYNAMIC THERAPY OF BRAIN TUMORS

Harry Whelan, Mike Kelly, Sachin Jogel, Bruce Kaufmann, Andy Foy, Sean Lew, and Brendan Quirk; Medical College of Wisconsin, Milwaukee, WI, USA

We conducted a human brain tumor PDT study that evaluated the toxicity of PDT based on both light-emitting diode (LED) and laser technology in selected patients with recurrent/progressive brain tumors. Two patients displayed neurotoxicity, one after laser treatment using an interstitial fiber directly inserted into the tumor, one with the laser-balloon adapter combination. Escalating doses of Photofrin® were tolerated to the maximum dose of 2.0 mg kg-1. Light dose was 100 J/cm + 2. PDT in the posterior fossa or near eloquent brain was tolerated using the LED or laser-balloon adapter. All patients had tumor responses as documented by MRI scan and the mean time to tumor progression after PDT was 67 weeks. Eight were pediatric patients, all of whom received Photofrin®, who exhibited relapse-free survival times ranging from 8 weeks to 13 years. None showed neurotoxicity. Of the 20 patients, four had tumors in the posterior fossa area, with one developing a significant neurological deficit. This patient was one of the two using interstitial fiber illumination. 111In-Photofrin® was determined using external imaging and quantitation with a gamma camera. 99mTC-DTPA was used as a control for nonspecific uptake. Specific tumor uptake of the 111In-Photofrin® occurred well beyond that resulting from blood-brain-barrier breakdown. A phase 1 study is being performed on pediatric patients with supra or infratentorial primary brain tumors who undergo neurosurgery at the Children's Hospital of Wisconsin in Milwaukee. A minimum of 12 study subjects will be used with four different photofrin dose levels: 0.5 mg/kg, 1.3 mg/kg, 2.0kg/mg, and 3.0 mg/kg. Photoactivation of Photofrin® is controlled by the total light dose delivered over the treatment time. PDT lasers are equipped with a calibration unit to calibrate the fibers and yield the required power density output (mW) necessary to deliver a light dose of 240 J/cm + 2.

ST-035. RE-OPERATION FOR RECURRENT GLIOBLASTOMA MULTIFORME

Raymund L. Yong[1,3], Tianxia Wu[1], Nino Mihatov[1], Michael J. Shen[1], M. Anthony Brown[1], Kareem A. Zaghloul[1], Grace E. Park[2], and John K. Park[1]; [1]National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA; [2]National Human Genome Research Institute, Bethesda, MD, USA; [3]Mount Sinai School of Medicine, New York, NY, USA

BACKGROUND: The standard of care for patients with newly diagnosed gliblastoma multiforme (GBM) is surgical resection followed by radiation and temozolomide chemotherapy. Treatment regimens at the time of tumor recurrence, which occurs in virtually all patients, have not been standardized and repeat surgical resection (re-operation) is considered in only one in four patients. METHODS: This retrospective study comprised 97 consecutive patients who were deemed favorable candidates for re-operation on the basis of previously validated prognostic criteria. Multivariate analyses were carried out to identify pre- and post-operative clinical and radiographic variables independently associated with overall survival after re-operation. Volumetric area under the curve (AUC) analysis of 619 serial post-operative magnetic resonance imaging (MRI) studies (median 4 per patient) was performed to determine the regrowth rate of tumors following re-operation. RESULTS: The median post-operative survival of all patients following re-operation was 12.4 months (95% CI, 9.0–15.6). In a multivariate analysis, progressively larger post-operative residual tumor volume was

independently associated with decreased survival ($p < 0.001$), along with greater age ($p = 0.003$) and lower pre-operative Karnofsky performance status (KPS) ($p < 0.001$). Larger volume residual tumors had higher rates of subsequent regrowth ($p = 0.003$), and a higher regrowth rate in turn independently associated with decreased survival ($p < 0.001$).

CONCLUSIONS: The median survival of patients re-operated for recurrent GBM compares favorably to historical controls. Re-operation should be considered in all patients who meet favorable pre-operative clinical and radiographic criteria. For patients undergoing re-operation, the surgical goal should be to leave a minimal amount of residual tumor tissue in order to slow tumor regrowth and maximize survival benefit.