ASNO-COGNO Scientific Meeting 2016

Asian Society for Neuro-Oncology (ASNO) &
Cooperative Trials Group for Neuro-Oncology (COGNO)

Sunday 11 September – Wednesday 14 September 2016

Sheraton on the Park, Sydney, Australia

Neuro-Oncology: is the landscape changing?

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Mao Qing, Yang Yuan

CNS Metastases

Paper ID: 120

METACHRONOUS BRAIN METASTATIS FROM OSTEOSARCOMA

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Introduction: Brain metastases from osteosarcoma are uncommon. The prognosis of metastatic osteosarcoma is inapparent. The pattern of dissemination of this neoplasm is usually hematogenous, with lungs and bone being the main targets. We observed the occurrence of brain metastasis in patient with osteosarcoma who got several operations.

Patient and method: A25-year old men presented to neurosurgery department with severe headache at November 2011. He was treated with two neoadjuvant chemotherapies (high-dose MTX) and a limb-salvage operation of right distal femur at August 2007. Postoperatively, he received an additional 4 cycles of chemotherapy with a high-dose MTX , a further 5 cycles of Gembine-Doextaxel and MAID chemotherapy . He got a VATS lobectomies at 2009 and 2011.

On preoperative brain CT, high density hematoma of 5cm-sized ovoid shape was found on left frontal lobe with focal calcifications and midline shift (Figure 1a). The heterogeneous enhanced lesion was also found around a calcification region (Figure 1b). The solitary metastatic lesion was excised by craniotomy.

The pathology confirmed osteoblastic osteosarcoma (Figure 2).

The additional was also done from August 2012 to September.

Discussion and conclusion: The common primary sites are distal femur, proximal tibia, proximal fibula, humerus and pelvis. Metastatic spread is hematogenous, most commonly to the lungs and skeleton.

There are only a few reports of long-term survival among osteosarcomas that has metastasized to the brain. All previously reported cases had pulmonary metastases before the detection of brain lesion. The advances in chemotherapeutic strategy and aggressive lung surgery have significantly improved the prognosis for these patients. However, the present patients had no active pulmonary metastasis after active lung metasectomy.

Although the prognosis of present patients require long-term follow-up, patients survived at 5 years disease-free interval after complete surgical removal of the brain metastasis.

Paper ID: 148

EFFECT OF TEMOZOLOMIDE ON BRAIN METASTASIS OF NEUROENDOCRINE CARCINOMA

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Neuroendocrine neoplasms (NENs) constitute a relatively rare and heterogeneous group of tumors, arising from cells of the diffuse neuroendocrine system most commonly encountered in the gastrointestinal (GI) tract and the lung. We successfully isolate the primary neurosphere cells from the metastatic brain tumor of neuroendocrine carcinoma. The cells within the sphere were positive to neural stem cell markers CD133. TMZ is an oral alkylating agent with proven activity against primary brain tumors. This drug has also been shown to have activity in patients with advanced neuroendocrine tumors, particularly those of pancreatic origin. We investigate the effect of TMZ on neuroendocrine carcinoma in vitro and in vivo using neuroshere cells.

Paper ID: 143

SURGICAL TREATMENT OF ELOQUENT AREA METASTATIC BRAIN LESIONS FROM UNUSUAL PRIMARIES

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Aims: Brain is one of the commonest site for metastases in cancer patients and incidence of brain metastases in increasing by the day due to improved survival of cancer patients. Metastasis in eloquent areas of the brain may present significant treatment challenges. There are very few reports about the treatment of eloquent area metastases arising from unusual sources. We present a short series of patients harboring metastatic lesions in eloquent brain region from unusual primary sources.

Methods: During a 2 year period from 2013 to 2015, 10 consecutive patients harboring a cerebral metastasis within the eloquent area of brain from an unusual primary source underwent stereotaxy assisted microsurgical resection. No cortical mapping was used for any of the patients. Eloquent locations included the primary sensorimotor and speech cortices. Unusual source was defined as primary cancer not commonly known to metastasize to brain(all sources except lung, breast, melanoma). All patients were discussed at a multi-disciplinary tumor board. We present the clinical results after operative treatment of metastases within the eloquent brain area, with functional outcome at 3 months.

Results: There were 5 men and 5 women(mean age 47.6 years) who underwent 10 microsurgical operations after a

stereotactical localization to remove metastatic lesions in eloquent region of brain. There were no perioperative complications. At 3 months follow up, all patients were alive. There was symptomatic improvement or stabilization after neurological improvement in all of the patients. Karnofsky scores improved in all of the patients at 3 months evaluation.

Conclusion: Lot of unusual primary cancers do metastasize to eloquent areas of brain. Complete microsurgical resection of eloquent area metastases from unusual primaries is feasible and beneficial. Patient selection and consequent surgical treatment can lead to significant improvement in the quality of life of such patients.

Paper ID: 69

ANALYSIS OF MRI PERFUSION IMAGING IN HIGH GRADE GLIOMA PATIENTS USING QUANTITATIVE AND QUALITATIVE ASSESSMENTS OF RELATIVE CEREBRAL BLOOD VOLUME (RCBV)

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Aims: Progress MR Perfusion imaging in high grade glioma (HGG) has the potential to differentiate between tumour progression versus treatment effect, with relative cerebral blood volume (rCBV) the standard quantitative measurement. An alternative qualitative assessment is via rCBV colour maps. This study aimed to compare MRI perfusion using rCBV versus visual maps and how both methods correlated with histopathology findings. .

Methods: Serial MRI datasets (n=21) from 12 HGG patients diagnosed between 2013-2015 undergoing re-do resection were collated. Studies demonstrating increased T1 enhancement up to two time-points immediately preceding re-resection were analysed. Histopathology findings were categorized as 'active, quiescent 'treated' tumour or 'treatment effect', with three radiology readers blinded to these results. For each reader, r-CBV surrounding the resection cavity in enhancing areas was calculated, , with colour maps categorized as Increased(I), Equivocal(E) or Decreased(D).

Results: There were twelve patients with n=10 Glioblastoma, n=1 grade 3 and n=1 transformed grade 2 astrocytoma (undergoing two re-do surgeries). On histopathology review of n=13 specimens, n=7 were 'active', 5 'quiescent' and 1 showed 'treatment effect'. The rCBV for the 'active' cases ranged between1.0 to 12.3, whereas rCBV was overall lower (1.1-4.5) for quiescent cases, and only 0.6 for the 'treatment effect' case. The colour map analysis of n=7 'active' cases showed at least 2 readers were concordant in 4 cases, n=2 cases showed no concordance between readers and in n=1 'active' case, there was complete concordance however colour maps were designated 'decreased'. 5 of 7 'active' cases showed consensus amongst at least 2 readers. Of n=5 'quiescent' cases, at least 2 readers agreed on 4 studies. There was no emerging trend in inter-reader concordance using colour maps.

Conclusion: These results show reasonable correlation between histopathology and quantitative assessment of rCBV. Qualitative needs further exploration in a larger patient cohort to substantiate its utility.

Paper ID: 113

RADIOSURGICAL TREATMENT FOR ELDERLY PATIENTS WITH BRAIN METASTASES (O)

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Aims: This study was designed to investigate the treatment results of Gamma Knife radiosurgery (GKRS) for elderly patients (age ≥65) with brain metastases and the relevant factors associated with survival.

Methods: We retrospectively analyzed the data of 106 patients treated with GKRS for 1 to 15 brain metastases. The median age at the time of treatment was 72 years (65~86), and the median Karnofsky performance status score was 90 (50~100). The most common primary tumor site was the lungs (n =86). The mean lesion volume was 2 cc (0.001~41.2). A median prescription dose of 20 Gy was delivered to the median 50 % isodose line.

Results: The median overall survival time was 5.8 ± 1.0 months. During the median follow-up duration of 5.6 ± 1.1 months (0.2~54), 85 patients died of primary cancer progression, and 1 died of uncertain cause. Twenty-two patients underwent repeat GKRS or whole brain radiation therapy for newly developed or progressive brain metastases. Among various factors, primary tumor control ($p = 0.001$, HR: 0.215, 95% CI: 0.116~0.398) and female ($p < 0.001$, HR: 0.521, 95% CI: 0.330~0.822) were significant favorable factors for survival after univariate and multivariate analysis. The median survival time of patients with controlled primary tumor vs. uncontrolled was 33.9 ± 12.0 vs. 4.0 ± 0.5 months, and the median survival time of female patients vs. male patients was 14.6 ± 4.1 vs. 4.2 ± 0.6 months.

Conclusions: GKRS for elderly patients with brain metastases appears to provide outcomes comparable to younger patients. According to our results, we suggest that radiosurgical treatment should be recommended to female patients with brain metastases when their primary cancer is controlled, even when they are aged 65 years or more. Age should not be an impediment to treatment in this selected group.

Paper ID: 121

GAMMA KNIFE RADIOSURGERY FOR PATIENTS WITH METASTASIS FROM THE LUNG CANCER

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Aims: For patients with brain metastasis from lung cancer, radiosurgery is one of the available options to control tumor. We assess early outcomes after Gamma knife radiosurgery for metastatic brain tumor from the lung.

Methods: We retrospectively reviewed data in all patients who had undergone Gamma knife radiosurgery to treat brain metastases from lung. Post-treatment imaging studies were used to assess tumor response every three month. The patient groups differed in age, lesion volume, status of the primary tumor, lesion numbers. Between November 2012 until December 2015, 122 patients with brain metastasis from lung were treated with gamma knife radiosurgery and 77 patients, 383 lesions were followed up at least 3 months with MR image and included in this study.

Results: The mean age of patients was 56 years (range 35 - 88years) and total 402 lesions treated. Main symptoms were headache and motor weakness. The mean follow up period was 8.8 months. The median prescription and maximal dose to the lesion were 20Gy(range 12 - 25Gy) and 40Gy(24 - 50Gy). The local control rate at 3 month was 87%. Eighty-six percent tumor control achieved at 6 months followed-up MRI. Metastasis from the small cell lung cancer lesion showed high control rate(96%/ 3months, 95%/ 6months) than non-small cell lung cancer(84%/3months, 84%/6months)

Conclusions: Gamma knife radiosurgery for metastases from the lung provided safe and effective local tumor control in the majority of patients.

Paper ID: 118

INTRAOPERATIVE HYPERTHERMIA FOR METASTATIC BRAIN TUMORS

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Objective: Metastatic brain tumors occur in 30-40% of patients with cancers and the incidence keeps rising along with the development of cancer therapeutics. Surgery is a beneficial treatment modality in certain patients' groups; however, the reported local recurrence rate in the surgical bed is up to 35%. To reduce the postoperative local recurrence rate, we designed a novel intraoperative hyperthermia treatment device and did prospective clinical trial under the approval of Korean FDA.

Material and methods: After resection of a metastatic brain tumor, we applied hyperthermia device which is compatible with size of resection cavity, and we maintained temperature of 42.5°C with depth of 5mm from resection margin for 60 minutes in order to damage malignant cells. Between February 2010 and September 2015, 63 patients (40 males and 23 females, with a mean age of 56 (35-74) years) underwent intraoperative hyperthermia treatment after the resection of brain metastasis. 42 patients had non-small cell lung cancer (NSCLC), 7 patients were breast cancer. Other patients were small cell lung cancer, hepatocellular carcinoma, germ cell tumor, endometrial cancer, ovarian cancer and melanoma each one, respectively. Mean follow up time after surgery was 11.45 months (1-44.85 months).

Results: Local recurrence occurred in 10 patients (15.8%). Among NSCLC, 8 patients showed local recurrence (8/42, 19%). The mean time to recurrence (TTR) was 4.6 months. 13 patients (TTR 6.9 months) received preoperative whole brain radiation therapy, and 17 patients (TTR 8.48 months) did not receive brain radiation therapy. 17 (40.4%) among 42 NSCLC patients did not receive preoperative or immediate postoperative brain radiation therapy, however, only one patient (4.2%) showed local recurrence.

Conclusion: The results in this study suggest that intraoperative hyperthermia after resection of metastatic brain tumor provide better local tumor control.

Paper ID: 131

HELICAL TOMOTHERAPY USE IN HYPOFRACTIONATED RADIOSURGERY FOR OLIGOMETASTATIC BRAIN DISEASE: A SINGLE INSTITUTIONAL EXPERIENCE

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Aims: To review radiation dosimetric and clinical outcomes associated with Helical Tomotherapy (HT) in hypofractionated stereotactic radiosurgery (SRS) for patients with oligometastatic brain disease.

Methods: Retrospective review of the CNS HT program at Liverpool Hospital from 2014-2016 was conducted. Clinical variables and disease-specific GPA score (ds-GPA) were documented. For each RT plan, dose Conformity Index (CI) and Homogeneity Index (HI) was documented, with CI and HI of 1.0 considered ideal. Acute toxicity was scored as per CTCAE v4.03.

Results: Fourteen patients (5M/9F, median age at HT 69 years), with ECOG 0-1, with 1-2 initial and/or progressive brain metastases were assessed. Their ds-GPA ranged from 1-4. Primary malignancies included lung (7), melanoma (2), breast (1), colorectal (1), renal (1), endometrial (1) and unknown (1). Median dominant lesion size was 22mm. Three patients had prior whole-brain radiotherapy. HT was delivered to intact lesions in n=9 and to surgical cavity in n=5. One patient had 2 lesions treated concurrently. The

commonest fractionation scheme was 15Gy in 1 fraction (n=6). Median PTV ranged from 1.18-83.54cc (median 10.84cc). CI and HI ranged from 0.81-1.06 and 1.11-1.35 respectively. HT utilised a frameless system using megavoltage CT image verification. Acute toxicity rates were low, with no patients experiencing headache, n=1 with Grade I nausea and n=5 with Grade 1-2 fatigue. Progress neuro-imaging (MRI=8, CT=2) at 1-2 months post HT demonstrated 5 partial responses and 5 with stable disease. At median follow-up of 4 months (range 0-9), three patients progressed intracranially, two with concomitant extra-cranial progression. There was 1 local (within HT field) relapse, 1 distant brain relapse, and 1 patient experienced both. Eleven patients remain alive, with median survival not yet reached.

Conclusions: Helical Tomotherapy for oligometastatic brain disease is associated with high-quality radiation dosimetry, low acute toxicity, and good intracranial control rates at early follow-up.

Paper ID: 55

SURGERY AND RADIOSURGERY IMPROVES OUTCOMES IN OLIGOMETASTATIC BRAIN METASTASES FROM BREAST CANCER : IMPLICATIONS FOR A RESOURCE-CONSTRAINED DEVELOPING COUNTRY (O)

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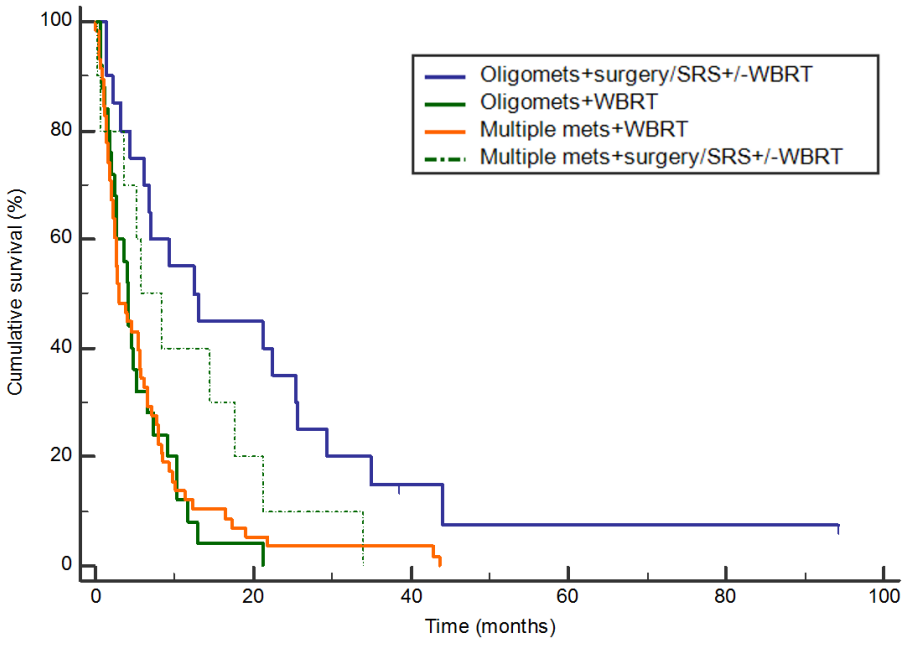
Aims: Breast cancer is the second most common cause of solid-tumour brain metastases and prognosis is universally poor. Whole brain radiotherapy (WBRT) does not improve survival and is associated with significant neurocognitive morbidity. Surgery or stereotactic radiosurgery (SRS) may improve outcomes. This present study explores its role and the influence of other prognostic factors in a resource-constrained developing nation.

Methods: This is a retrospective review of 113 breast cancer patients with brain metastases treated at two tertiary referral centres in Malaysia from January 2006 to July 2012. The primary outcome was overall survival (OS). Univariate and multivariate relationships for patient demographics, tumour characteristics and treatment-related prognostic factors were analyzed using Cox's proportional model.

Results: Death was recorded in 111/113 patients. The median OS for the cohort was 4.70 months. Median OS (see Figure 1) for patients with 1-3 metastases treated with surgery/SRS with or without WBRT was 12.56 months (n=20) while 1-3 metastases and WBRT was 4.08 months (n=25), HR 2.74 (95% CI: 1.56-4.81), p=0.0002. For patients with multiple metastases and WBRT, median OS was 2.99 months (n=58) and multiple metastases and surgery/SRS with or without WBRT was 5.75 months (n=10), HR 0.65 (95% CI: 0.36-1.17), p=0.1991. ECOG performance score, treatment modality, prior systemic treatment, subsequent systemic treatment, RPA and ER status were significant on univariate analysis but age, Her2 status, GPA, presence of seizures was not. Only treatment modality and subsequent systemic treatment was statistically significant on multivariate analysis.

Conclusion: For patients with 1-3 brain metastases, surgery and SRS improved OS compared to WBRT alone. Provision of surgical/SRS services is likely to benefit Malaysian patients with breast cancer. Challenges for widespread adoption include modest GDP-per-capita USD$10.538, low rates of personal insurance coverage and manpower shortage.

Figure 1. Kaplan-Meier curve by treatment modality



Cell Signaling, Biology and Circulating Biomarkers

Paper ID: 213

OPPOSING ONCOGENIC AND TUMOUR SUPPRESSIVE FUNCTIONS OF RICTOR/MTORC2 SIGNALLING IN ADULT GLIOMA AND PAEDIATRIC SHH MEDULLOBLASTOMA

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Glioblastomas are the most common and lethal brain cancers in adults. These aggressive tumours develop rapidly without pre-existing lower-grade gliomas. This rapid clinical course makes it challenging to determine the temporal sequence of oncogenic events during tumour development.

Aims: The current project aims to understand critical molecular alterations leading to glioblastoma initiation and progression, and test whether manipulation of these alterations could reverse the tumour development.

Methods and results: We generated a mouse model of glioblastoma driven by a *p53* mutation. These *p53*-mutant gliomas lose the syntenic region of human chromosome 10q, which is mapped to mouse chr19 and chr7. Loss of mouse chr19, containing *Pten* gene, activates PI3K/Akt signalling. Remarkably, Rictor/mTORC2 deletion inhibits Akt signalling, causing a significant delay and reduction in *p53*-mutant driven glioma formation. Unexpectedly, Rictor/mTORC2 loss promotes *p53*-mutant driven medulloblastomas with unique features of paediatric SHH-medulloblastoma. Mechanistically, Rictor/mTORC2 loss inhibits the generation of glioma precursors from neural stem/progenitor cells in the adult brain, while causing a delay in differentiation of granule cell precursors in the developing cerebellum, a cell-of-origin of SHH-medulloblastoma.

Conclusion: Malignant gliomas in a *p53*-mutant driven mouse model acquire the hallmark chromosomal alteration of human glioblastoma. The inhibitory effects of Rictor/mTORC2 loss demonstrate critical roles of PI3K/Akt signalling in *p53*-mutant driven gliomagenesis. However, Rictor/mTORC2 loss promotes SHH-medulloblastomas, revealing its unexpected function for preventing sustained proliferation of cerebellar progenitors. High and low levels of *RICTOR* expression are associated with poor survival of adult glioblastoma and paediatric SHH-medulloblastoma, respectively. This study reveals tumour-promoting and -suppressing roles of Rictor/mTORC2 in adult and paediatric brain tumours.

Highlights:

- *p53*-mutant driven gliomas acquire chromosomal alterations of adult glioblastoma.
- Rictor/mTORC2 loss delays and reduces glioma formation, and prolongs survival.
- *Rictor* deletion cooperates with *p53* loss to promote SHH-MB formation.
- Low *RICTOR* expression is associated with poor survival in paediatric SHH-MBs.

Paper ID: 147

SIGNIFICANCE OF EGFR OVEREXPRESSION ON ECOG SCORE IN LOW GRADE GLIOMA: A PRELIMINARY REPORT

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Aim: The aim of this study was to report frequency of EGFR overexpression in low-grade glioma groups and relationship with an ECOG score 2 year after operation.

Methods. 17 cases of adult astrocytoma where histology confirmed, performed immunohystochemistry to evaluate EGFR overexpression. All of patients were evaluated for an ECOG score at 2 year after operation.

Results. Nine patients were high-grade glioma, 67% with positive EGFR overexpression and there was one patient still alive with an ECOG score 2. Eight patients are low-grade glioma. All of this group with positive EGFR overexpression have an ECOG score 0.

Conclusion: Low-grade glioma with positive EGFR overexpression showed poor ECOG score at 2 year after operation.

Paper ID: 106

THE EARLY CHANGES IN PROTEIN EXPRESSION IN THE RHESUS OPTIC NERVES INJURED BY A SINGLE DOSE/FRACTIONATION STEREOTACTIC RADIOSURGERY

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Aims: Radiation-induced optic neuropathy (RION) is a severe complication of using stereotactic radiosurgery (SRS) to treat anterior visual disease. This study is designed to obtain and analyze the early changes in protein expression in rhesus optic nerves injured by SRS.

Methods: The unilateral intraorbital optic nerves of 3 rhesus monkeys were injured by gamma knife surgery (GKS) with a single dose/fractionation scheme (marginal dose of 15 Gy, 50% isodose curve), while the contralateral optic nerves served as the control. The bilateral intraorbital optic nerves of 3 rhesus monkeys were dissected and performed a non-marker quantitative proteomic analysis at 72 hours after GKS. The function information of differential expression protein were obtained through BLAST sequence alignment with human protein.

Results: A total of 41 proteins fit the criteria for differential expression (change>2.0-fold, P value<0.05 or exclusive expression). Of the differentially expressed proteins, 7 proteins were significantly down-regulated (change>2.0-fold, P value<0.05) at the injured optic nerves, 18 proteins were exclusively expressed in the contralateral optic nerves, and 16 proteins were exclusively expressed in the injured optic nerves. The major functions of the low-expression proteins in the injured optic nerves were related to cytoskeleton, endocytosis, proteolysis, bicarbonate homeostasis, cell proliferation, growth and differentiation. The major functions of the high-expression proteins were related to inflammation and immunization,

Conclusions: This study indicated that the GKS with a marginal dose of 15 Gy on a 50% isodose curve had a significant impact on protein expression at 72 hours after GKS in the optic nerve. At 72h after GKS, the intrinsic function of the cell were impaired in the injury side optic. The cells endocytosis and pinocytosis were declined and shown a significant inflammation and immunization.

Paper ID: 75

MIR-338-3P: A POTENTIAL BIOMARKER FOR INVASIVENESS OF GH-SECRETING PITUITARY ADENOMAS

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Aims: Aberrant microRNA (miRNA) expression is common in numerous tumors. Role of miRNA in pituitary adenoma is limited. Expression profiles of miRNA were analyzed in the growth hormone (GH)-producing pituitary adenomas according to the tumor invasiveness.

Methods:RNA samples extracted from 2 groups tumor samples (microadenoma and invasive adenomas) were analyzed by miRNA microarray.

Results: In invasive adenoma the expressions of hsa-miR-338-3p, 432-5p were increased, whereas miR-652-3p was decreased significantly. In an in vitro study using GH3 cells with E2 treatment, miR-338-3p levels increased, whereas miR-652-3p levels decreased. Transfection of GH3 cells with miR-338-3p inhibitor showed suppression of GH and prolactin mRNA expressions, and cell proliferation. In wound healing assay and matrigel invasion assay, miR-338-3p mimic-transfected GH3 cells showed significantly increased cell migration and invasion, whereas miR-338-3p inhibitor transfection did not. qRT-PCR analysis showed upregulation of Pttg1 mRNA levels by miR-338-3p mimic, whereas miR-338-3p inhibitor downregulated it. Immunofluorescent staining revealed higher numbers of Pttg1 positive cells in the tumor tissues expressing higher miR-338-3p.

Conclusions:These results provide an evidence of miR-338-3p may play an important role in the invasiveness of GH-producing pituitary tumor and the modulation of Pttg1 expression.

Paper ID: 108

UNDERSTANDING THE TUMOUR SUPPRESSIVE FUNCTION OF EPHRIN A5 SIGNALLING IN ADULT BRAIN CANCER

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Aims: Glioblastoma (GBM) is the most common and aggressive malignant primary brain cancer and is associated with very poor patient outcomes. Standard treatment involves surgical resection, post-operative radiation and temozolomide chemotherapy. This necessitates further research into new therapeutic approaches and, in particular, therapies which target chemo-resistant tumour propagating cells, often referred to as cancer stem cells.

Results: It was recently reported that the EphA3 receptor is frequently elevated in GBM, particularly in the mesenchymal subtype and is most highly expressed in tumour-initiating cells. Our data in GBM tissue shows that tumour cells expressing the high-affinity EphA3 ligand, ephrin A5; are distinct from EphA3 expressing cells. The

ephrin A5 positive cells express the known glial differentiation marker GFAP, are less proliferative and less stem cell-like. EphA3 is expressed in the vimentin positive, highly proliferative, mesenchymal cells in GBM. Though we detected both EphA3 and ephrin A5 at elevated levels in GBM tissue; ephrin A5 and GFAP expression was lost when primary GBM tissue were cultured under conditions known to support mesenchymal cells and enrich for the more de-differentiated stem cell-like cells. Conversely, EphA3 expression was lost when GBM cells were forced to differentiate *in-vitro*. Our data thus indicates that ephrin A5 could be employed as a soluble differentiation agent in GBM. In order to understand the mechanism of action of ephrin A5 in GBM we are employing a SILAC based quantitative phosphoproteomic approach. This will provide a catalogue of phosphoproteins regulated by ephrin A5, and could result in the identification of novel druggable targets.

Conclusions: This work confirms our hypothesis of distinct EphA3 and ephrin A5 expression in GBM and explores the potential of soluble ephrin A5-Fc protein to activate EphA3; induce cell differentiation and reduce GBM aggressiveness.

Paper ID: 17

CEACAM1L MODULATES STAT3 SIGNALING TO CONTROL THE PROLIFERATION OF GLIOBLASTOMA-INITIATING CELLS

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Aims: Glioblastoma-initiating cells (GIC) are a tumorigenic cell subpopulation resistant to radiotherapy and chemotherapy, and are a likely source of recurrence. However, the basis through which GIC are maintained have yet to be elucidated in detail. We herein demonstrated that carcinoembryonic antigen-related cell adhesion molecule Ceacam1L acts as a crucial factor in GIC maintenance and tumorigenesis by activating c-Src/STAT3 signaling.

Results: we showed that monomers of the cytoplasmic domain of Ceacam1 bound to c-Src and STAT3 and induced their phosphorylation, whereas oligomerization of this domain ablated this function. Our results suggest that Ceacam1L-dependent adhesion between GIC and surrounding cells play an essential role in GIC maintenance and proliferation, as mediated by signals transmitted by monomeric forms of the Ceacam1L cytoplasmic domain.

Conclusions: Ceacam1 is known to be involved in various biological functions, including proliferation, angiogenesis, tumorigenesis, and inhibition of both cytokine production by and cytotoxic activity of immune cells, as an intracellular and intercellular factor. We showed that Ceacam1L-overexpressing hGICs formed larger colonies in soft agar and tumors with massive hemorrhaging in the brains of immunodeficient mice, whereas the knockdown of Ceacam1 blocked GIC proliferation. In addition to previous findings in which Ceacam1 acted as a major effector of vascular endothelial growth factor-induced angiogenesis, we revealed that Ceacam1L regulated the expression of Angpt1, interleukin 18, and secretogranin II, all of which play an important role in vascular development and angiogenesis in GICs. Since neovascularization is not only a common characteristic of GBM, but has also been correlated with poor outcomes, these findings indicate that Ceacam1L is an indispensable therapeutic target for GBM.

Paper ID: 49

LIGAND DEPENDENT EPHB4 SIGNALING SUPPRESSES THE INVASION AND MIGRATION OF GLIOMA CELL

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Introduction: Despite the standard treatment of surgical resection of the glioblastoma followed by radiation and chemotherapy, patient survival remains a challenge. Extensive evidence implicates the Eph receptor family of tyrosine kinases and its ligand, ephrin, in glioma malignancy. The role of Eph-ephrin tyrosine kinase is gradually cleared. However in glioma, EphB4 that ligand is ephrinB2 has not been investigated yet. We sought to reveal the correlation of EphB4 with glioma malignancy.

Materials and methods: We examined the difference of invasion and migration ability using Matrigel chamber assay and scratch assay by adding recombinant ephrinB2 (2, 4μg/ml) to activate EphB4 in U87 and SNB19 which expressed EphB4. We also conducted invasion and migration assays on EphB4-knockdown cells. Signaling pathways related to invasion and migration were analyzed by western blotting. In addition, we confirmed the localization of EphB4 and ephrinB2 expressing cells at the tumor core and invasive area.

Results: Phosphorylation of EphB4 by ephrinB2 led to suppress the cell invasion and migration. Reduction of EphB4 by siRNA negated the decreased invasion and migration by addition of ephrinB2. The levels of Akt phosphorylation corroborated with these results. Double immunofluorescence stain with EphB4 and ephrinB2 antibodies showed that EphB4 and ephrinB2 is co-expressed in GM cells at the central portion of the tumor, whereas ephrinB2 was only expressed in tumor cells at invasive area.

Conclusions: Ligand dependent EphB4 forward-signaling plays a role as "stay there" signaling. Extinction of its signaling promotes the release of tumor cell on its location.

Paper ID: 15

GROWTH FACTOR, GRANULIN EXPRESSION IN PATIENTS WITH BRAIN TUMORS: RELEVANCE TO THE PROGNOSIS

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Aims: Granulins are cysteine-rich polypeptides which belong to a family of growth factors to mediate cell cycle progression and cell motility. Granulin expression is found in several human cancers including gliomas and meningiomas. However, its clinical significance has not been verified. We investigated the relationship between granulin expression and prognosis in intracranial brain tumors.

Methods: We studied the expression of granulin in 295 patients who underwent tumor removal for their intracranial tumors. The pathological types of brain tumors was classified according to World Health Organization (WHO) classification, and categorized into non-aggressive (WHO grade I and II) and aggressive (WHO grade III and IV) group. Granulin was investigated by reverse transcriptase polymerase chain reaction (RT-PCR). And also, its expression was analyzed in the respects of clinical characteristics including demographic data and prognostic parameters.

Results: Granulin was detected in 107 (36.0%) of 295 patients, 57 (28%) of 201 patients with non-aggressive group, and 50 (53%) of 94 patients with aggressive group. Its expression was correlated to age or gender. However, progression-free survival (PFS), recurrence, and mortality were relevant to granulin expression of brain tumors ($P < 0.05$ by Log-rank test).

Conclusions: We have confirmed the expression of granulin in diverse brain tumors, and its expression is correlated to prognostic parameters of brain tumors. These results indicate that granulin may be a novel target to manage intracranial tumors.

Paper ID: 140

EXPRESSION CHANGE OF THE VASOHIBIN FAMILY BY BEVACIZUMAB TREATMENT

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Aims: The vasohibin family is the group of genes induced by VEGF stimulation in vascular endothelial cells. Vasohibin 1 (VASH 1) not only inhibits angiogenesis but also enhances the maintenance of endothelial cells by strengthening their resistance against stress. Vasohibin 2 (VASH 2) is homologue of VASH 1 and sprouts front to stimulate angiogenesis. It has not been reported that the expression of VASH 1/2 and changes of them by administration of bevacizumab (BEV) for patients with glioblastoma (GBM). In this study, we analyzed the VASH 1/2 expression before and after BEV treatment, and the association between their expression and clinical features, tumor histology, and vascularization in tumors.

Methods: 5 patients with recurrent GBM (5 males, 40 - 69 years old) treated with BEV (9 - 22 times/ 2weeks) in our hospital from 2010 through 2015 were registered. We assessed the expression of VASH 1/2, VEGF, VEGFR 1/2, and CD 34 by immunostaining with specimens obtained from operation and autopsy. The expression levels of each molecule was assessed by 4 levels (0 - 3+). Microvessel density (MVD) with CD 34 staining was counted.

Results: Expression level of VASH 1 before BEV treatment were weak (1+ or 2+) in all specimens, whereas those of VASH 2 were various. In the autopsy specimens, expression level of VASH 1 increased in 3 cases, and attenuated in 2 cases. Those of VASH 2 decreased in all cases. Although MVD decreased in all cases (reduction ratio : 23.9 - 67.7%), reduction ratio were lower in cases that VASH 1 attenuated (23.9%, 25.5%). Decrease of MVD correlated with VASH 2 and reduction ratio of MVD linked to VASH1. These results were consistent with the function of VASH for angiogenesis.

Conclusion: The changes of MVD by BEV might be dependent on the expression of VASH.

Paper ID: 171

ELEVATED TERT EXPRESSION IN TERT WILD-TYPE ADULT DIFFUSE GLIOMAS: HISTOLOGICAL EVALUATION WITH A NOVEL TERT-SPECIFIC ANTIBODY (O)

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Aims: Recent studies have shown that *telomerase reverse transcriptase* (*TERT*) promoter mutations (*TERT*mt) are correlated with the up-regulation of the TERT mRNA expression. They are also highly characteristic for glioblastoma with *isocitrate dehydrogenase* (*IDH*) wild type (GBM IDHwt) and oligodendrogliomas with *IDH* mutation (*IDH*mt) and 1p/19q codeletion (OLG codeleted) whereas they are absent in diffuse astrocytomas with *IDH*mt. TERT can be a suitable marker for those gliomas and a desired object of a novel TERT-targeting therapy.

Sensitive and specific methods are thus urgently needed to detect TERT expression *in situ* for precise diagnostics of gliomas as well as to validate the applicability of a TERT-targeting therapy.

Methods: A novel human TERT-specific monoclonal antibody against the synthetic peptide of TERT (302-321 amino acids) derived form Human TERT cDNA was developed base on its optimal sensitivity to immunohistochemistry (IHC) for human tissue. Specificity to TERT was further verified by immunoprecipitation. Using IHC the expression of TERT was evaluated in a series of glioma samples including astrocytomas with *IDH* mutation, OLG codeleted, GBM IDHwt and U87 glioblastoma cell line.

Results: An increase in TERT expression was identified across all types of gliomas as well as U87 independent of the presence of the *TERT*mt while reactive astrocytes did not showed its expression. The endothelial cells within tumor tissues were also positive for TERT.

Conclusions: This study for the first time showed that elevated TERT expression in TERT wild-type adult diffuse gliomas, suggesting that an anti-TERT therapy could be effective for all types of gliomas regardless of the mutational status of *TERT* promoter.

Paper ID: 161

CIRCULATING TUMOUR CELLS IN GLIOBLASTOMA

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Background: Solid tumours can shed cells into the bloodstream to produce circulating tumour cells (CTCs), and the presence of CTCs can have prognostic significance. Despite the fact that the blood-brain barrier is considered to impede CTC formation, CTCs have recently been described in glioblastoma (GBM) patients.

Aim: To develop a reliable method to isolate GBM-CTCs by immunomagnetic targeting.

Methods: Ten antibodies against candidate cell surface proteins were tested for their interaction with GBM cells and lack of interaction with blood cells by FACS analysis and immunocytostaining, and 5 antibodies were tested as candidates for GBM-CTC identification amongst residual lymphocytes. Suitability of selected antibodies for immunomagnetic GBM cell isolation and identification was tested using the IsoFlux rare cell isolation kit with defined numbers of cultured GBM cells. The most promising antibody combination was used to isolate and identify individual GBM-CTCs from patient blood. GBM-CTCs were then further isolated using the ALS CellCelector and whole genome amplification (WGA) performed to prepare for down-stream biomarker analysis.

Results: Three antibody targets were identified as suitable for GBM cell isolation, while GFAP was the best biomarker for GBM-CTC identification. GBM-CTCs have so far been isolated from 4 out of 10 patients when different combinations of isolation antibodies were tested. WGA was performed on CTC samples and screening for GBM specific biomarkers EGFRvIII and IDH1 is currently underway.

Conclusions: We have for the first time identified suitable antibodies to positively immunomagnetically isolate and identify GBM-CTCs. Further, this has allowed down-stream analysis for relevant GBM biomarkers.

Paper ID: 166

MALIGNANCY OF PI3K MUTANT NEURAL STEM CELL-DERIVED BRAIN TUMORS CAN BE SUPPRESSED BY TARGETING CREB

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Aims: To decipher the signaling and transcriptional regulatory networks regulating brain tumour growth

Methods: A Pik3ca and PTEN inducible and conditional brain-specific mutant mouse model was generated targeting oncogenic mutations to the neural stem and progenitor cells. Cells derived from these mice were used to measure tumour cell functions.

Results: Upstream signals transmitted via the PI3K and MAPK/ERK pathways cooperate with the cAMP Response Element Binding (CREB) to regulate neural stem/progenitor cell (NSPC) proliferation. These pathways are among the most common pathways constitutively dysregulated in cancer but the precise roles for these in brain cancer development remain elusive. We demonstrate that targeting a Pik3ca oncogenic mutation to NSPCs in mice is sufficient to initiate tumourigenesis but simultaneous loss of tumor suppressor PTEN is necessary for the development of invasive astrocytic tumors. Although these tumors require CREB to maintain their proliferative potential and an aggressive malignant phenotype, CREB is not required for tumor initiation. Human glioblastoma gene expression data points to a MAPK-CREB-dependent transcriptome to drive proliferation.

Conclusions: Our study demonstrates the importance of PI3K pathway in driving tumourigenesis of neural stem cells and adds to the growing evidence that the transcription factor CREB, is of key importance in oncogenesis and a novel potential therapeutic target.

Paper ID: 167

MAPK PATHWAY ACTIVITY DETERMINES GBM TUMOUR CELL SENSITIVITY TO CAMP-TRIGGERED BIM-DEPENDENT APOPTOSIS: A MECHANISM TO EXPLOIT FOR MORE EFFECTIVE CANCER CELL KILLING

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Aims: To decipher the mechanisms by which cAMP agonists kill glioblastoma cells.

Methods: We used a panel of four human glioblastoma (GBM) cell lines to investigate the mechanisms by which cAMP signaling triggers apoptosis. Western blotting and cell viability assays were used to test the effects of single agent and combinations of cAMP agonists and a MAPK small molecule inhibitor.

Results: In some cell types, activation of the second messenger cAMP leads to increased expression of pro-apoptotic Bim and subsequent cell death. We demonstrate that suppression of the cAMP pathway is a common event across various cancers and that pharmacological activation of cAMP in GBM cells leads to enhanced BIM expression and apoptosis. Interestingly, the GBM cell lines we investigated were differentially sensitive to cAMP agonists. We identified the MAPK signalling axis as the determinant of cAMP agonist sensitivity in GBM cells, with high MAPK activity corresponding to cAMP resistance and low activity corresponding to sensitisation to cAMP-induced apoptosis. Sensitive cells were efficiently killed by cAMP agonists alone, while targeting both the cAMP and MAPK pathways in resistant GBM cells resulted in efficient apoptosis. Finally, we identified CD44 as a potentially useful biomarker to distinguish between cAMP agonist sensitive and resistant GBM cells. Thus, CD44 may be useful in identifying tumors which may be sensitive to cAMP agonists alone or cAMP agonists in combination with traditional anti-cancer drugs.

Conclusions: Our data offers a new paradigm for improved GBM treatment using existing chemotherapeutic compounds in combination with existing FDA-approved cAMP agonists.

Paper ID: 70

MTORC2 PROMOTES HISTONE ACETYLATION THROUGH METABOLIC REPROGRAMMING IN GLIOBLASTOMA (O)

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Aims: Metabolic reprogramming including aerobic glycolysis (Warburg effect) is a core hallmark of cancer. We previously reported that one of the mTOR (mechanistic target of rapamycin) complexes, mTORC2 is an essential component to promote the glycolytic metabolism in malignant brain tumor glioblastoma (GBM) (Masui et al. Cell Metab 2013), but there still remains an open question how such a metabolic activation can contribute to cancer progression. Therefore, we set out to determine the role of glycolytic metabolism in the biology of GBM, especially focusing on the involvement of an intermediary metabolite acetyl-CoA in histone modification.

Methods: To uncover the functional consequences of cancer metabolism, we interrogated cell lines and clinical samples of GBM, the highly lethal brain cancer in human. We analyzed the effect of mTORC2 on the production of acetyl-CoA and the subsequent modification of nuclear histone proteins.

Results: Through metabolomics analyses, we discovered that mTORC2 reprograms cellular metabolism and promotes the production of acetyl-CoA. Increased production of acetyl-CoA in the cytoplasm promotes tumor growth and its resistance to molecularly targeted therapies through acetyl-CoA - dependent acetylation of Rictor, a core component of the mTORC2 signaling complex. Furthermore in the nuclei, mTORC2 facilitates histone acetylation through the production of acetyl-CoA, entailing the subsequent upregulation of oncogenic transcripts.

Conclusions: These findings indicate that mTORC2 promotes metabolic reprogramming which can be translated into the growth and therapy resistance of GBM through the post-translational modification of cytoplasmic as well as nuclear proteins.

Paper ID: 29

MTORC1 SIGNALING IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Aims: Mammalian target of rapamycin (mTOR) complex 1 (mTORC1) links to cell signaling in cellular proliferation, differentiation, metabolism, and survival. Although many studies have suggested the importance of mTORC1 in tumorigenesis, its role remains unclear in brain tumors other than glioblastoma. The aim of this study is to elucidate the relationship between mTORC1 and primary central nervous system lymphoma (PCNSL).

Methods: We evaluated activation of mTORC1 in 24 cases of PCNSL using immunohistochemical analysis. Because it is difficult to directly measure mTORC1 activity, expressions of downstream and upstream proteins were measured as an alternative method.

Results: Rheb, which is immediately upstream of mTORC1, was overexpressed in 20 cases of PCNSL. phospho-4E-BP1 (Thr37/46) and phospho-S6

(Ser235/236), which are mTORC1 downstream effectors, were overexpressed in 17 cases and 21 cases respectively. These results suggest that mTORC1 was activated in many cases of PCNSL.

Conclusions: Our data suggest that abnormal activation of the mTORC1 signaling pathway may cause tumor growth in patients with PCNSL.

Paper ID: 42

GLIOMA CELLS ADAPT METABOLIC STRESS BY REGULATING MIR-451 EXPRESSION

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Aims: Greedy tumors like glioblastoma, need to well adapt their changes in micro environment like hypoxia and/or hypo-glycaemia, to maintain their rapid growth and invasion. We report how glioma cells survive in poor environment by controlling the expression level of a microRNA and its transcription factor.

Methods: We have already reported microRNA-451 (miR-451) as one of the microRNAs which showed the most dynamic expression change between the proliferation and the invasion. MiR-451 was found to indirectly deactivate AMPK depending on glucose level, effecting the glioma cells to either proliferate or migrate. We used in silico analysis to identify the promotor candidates of miR-451, and confirmed them by molecular assays.

Results: MiR-451 was directly controlled its expression by one of the candidates, Oct1. S335 of Oct1 was phosphorylated depending on glucose level, and directly bound to DNA. Phosphorylated AMPK directly phosphorylated Oct1, giving indirect negative feedback to miR-451.

Conclusions: MiR-451 and AMPK reciprocal negative feedback loop was regulated by glucose level through phosphorylation of Oct1 transcription factor, allowing glioma cells to adapt metabolic stress from poor microenvironment.

Paper ID: 52

MUTANT IDH1-DRIVEN CELLULAR TRANSFORMATION INCREASES HOMOLOGOUS RECOMBINATION AND TEMOZOLOMIDE RESISTANCE.

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Aims: Isocitrate dehydrogenase 1 (IDH1) mutations occur in most lower grade glioma and not only drive gliomagenesis but are also associated with longer patient survival and improved response to temozolomideTMZ.

Methods: To investigate the effect of mutant IDH1 on the gliomagenesis and response to TMZ, we introduced wild-type (WT) or mutant IDH1 into immortalized, untransformed human astrocytes, then monitored transformation status and temozolomide response.

Results: By introducing mutant IDH1, immortalized astrocytes made colonies in soft agar. Parental cells and WT IDH1 introduced cells exhibited DNA damage and a prolonged G2 cell-cycle arrest beginning three days after TMZ exposure and persisting for more than four days. The same cells transformed by mutant IDH1 exhibited a comparable degree of DNA damage and cell-cycle arrest, but both events resolved significantly faster in association with increased, rather than decreased, clonogenic survival. The increases in DNA damage resolving, cell-cycle progression, and clonogenicity were unique to cells transformed by mutant IDH1, and were not noted in cells introduced by WT IDH1 or an oncogenic form (V12H) of Ras. Similarly, these effects were not noted following introduction of mutant IDH1 into Ras-transformed cells or established glioma cells. The cells transformed by mutant IDH1 showed increased homologous recombination (HR), compared to parental or WT IDH1 introduced cells. The unique response to TMZ in the cells expressed mutant IDH1 could be reversed by the genetic or pharmacologic suppression of RAD51, which is an important DNA repair protein.

Conclusions: Mutant IDH1 drives a unique set of transformative events that indirectly enhance HR and facilitate repair of TMZ-induced DNA damage and TMZ resistance. The results also suggest that inhibitors of HR may be a viable means to enhance TMZ response in IDH1-mutant glioma

Paper ID: 173

GENE EXPRESSION PROFILING REVEALS STEM CELL SIGNATURES AND THERAPEUTIC TARGETS FOR GLIOBLASTOMA AND GLIOSARCOMA

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Aims: (a) To examine gene expression profiles in human glioblastoma (GBM) and gliosarcoma (GSM); (b) to identify molecular determinants of glioma stem cells (GSCs), (c) to provide insight into the heterogeneity of these cancers and highlight potential therapeutic targets.

Methods: Fresh frozen human GBM and GSM patient specimens, six GBM and one GSM cell lines were analysed using qRT-PCR for genes related to stemness and

involved in cell proliferation and multilineage differentiation.

Results: Pluripotency transcription factor SOX2 was variably overexpressed in patient specimens and cell lines, however, core partner OCT4 and downstream target NANOG showed 90-180 times lower expression. GSC-associated marker CD133 was highly expressed in patient specimens but less so in cell lines. Similarly, pluripotency marker GDF3 was present in patient specimens, but undetectable in cell lines. Known cancer mediators EphA7, Notch receptor 4 and PTPRZ1 were highly expressed in both specimens and cell lines. Glial genes GFAP and S100B and neural genes MAP2 and GAP43 were variably expressed, with cell lines demonstrating significantly lower GFAP and GAP43 expression compared to normal human astrocytes ($P<0.01$). Endodermal marker (GATA4) was overexpressed in GBM. Mature epithelial signature cytokeratin 18 was observed in GSM and less so in GBM. Inversely, GBM showed significantly higher expression of epithelial gene E-cadherin than GSM ($P<0.05$).

Conclusions: Several potential therapeutic targets were identified including SOX2, EphA7, Notch receptor 4 and PTPRZ1. The presence of neural, epithelial and endodermal signatures in GBM and GSM implicates the multilineage potential of GSCs and supports the cancer stem cell theory. GSM demonstrate greater presence of different lineages and more heterogeneity than GBM, suggesting key differences from GBM. Additionally, the variability in expression of pluripotency markers between cell lines and patient specimens demonstrates the potential for selection *in vitro* and the importance of utilising both models in GBM and GSM research.

Paper ID: 53

DEVELOPMENT OF IDH1/2 MUTATION SCREENING ASSAY AS POSSIBLE DIAGNOSTIC TOOLS FOR GLIOMA USING DIGITAL PCR PLATFORM (O)

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Glioma is the most common malignant brain tumor of central nervous system. Many studies have shown that isocitrate dehydrogenase (IDH) mutations are observed in over 70% of low-grade gliomas and some cases of glioblastoma. Testing of the IDH status is highly relevant for the diagnosis of primary brain tumors. There are several IDH1/2 inhibitors under the drug development pipelines and expect to have molecular target drugs for the glioma patients near future. Moreover, coming or have come the new WHO classification of glioma, molecular biomarkers including IDH1/2 mutation have become more important to categorize glioma subtype. The combined interpretation of the molecular and tissue diagnosis may play more crucial roles in clinical decision. Driving up demand for molecular diagnostic of glioma, development of high sensitivity technologies for detection of IDH1/2 mutations is also essential. Digital PCR is one of promising technologies for liquid biopsy. It generates thousands of nanolitter-sized droplets, and each of which provides 1/0 counts and gives absolute quantification of the target gene. Here, we have developed hotspot-mutation screening probes for glioma liquid biopsy; IDH1 R132x (6 mutations) and IDH2 R172x (6 mutations). These highly specific and sensitive probe mixes in each tube are both cost- and time-effective for the screening of key mutations in disease and will help facilitate decisions on current and future therapy.

Paper ID: 184

COAGULATION PROFILE COMPARISON BETWEEN PRIMARY BRAIN TUMOUR AND SECONDARY BRAIN TUMOUR

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Aim: To compare of coagulation profile between primary and secondary brain tumour

Methods: This is a restrospective cross sectional study from medical records of adult brain tumor patients in Ciptomangunkusumo Hospital, Jakarta, from January 2009 - May 2015. Brain tumour was diagnosed based on clinical history, head CT scan/MRI, and histopathology of the brain or any other primary organs. Coagulation profile measurements include prothrombine time (PT), activated partial thromboplastin time (APTT), fibrinogen and D-dimer serum. Subjects were classified into primary and secondary brain tumour. Data regarding complications were obtained from patient's medial records.

Results: The study recruited 135 patients, with median age of 48 (18-68) years old. Women had higher proportion among subjects, with only minor difference. Primary brain tumour was slightly predominant than the secondary (52,6% vs 47,4%), among which astrocytoma was the most frequent (46,5%). Lung cancer as primary tumour had the highest fibrinogen level (424,70 (239,0-900,0; p 0,016), and highest incidence in the secondary brain tumour group (39,1%). The proportion of patients with abnormal fibrinogen in the secondary brain tumor group was higher than the primary brain tumor group (46,8% vs 27.7%, p 0,026). Among the confounding factors, sepsis significantly influenced the increase of APTT and fibrinogen levels (p 0,009 and 0,002).

Conclusions: Fibrinogen levels were higher in the secondary brain tumour compared to the primary brain tumour group. No significant differences were found between PT, APTT and D-dimer value in both groups.

Sepsis was the only confounding factor that influence coagulation markers.

Paper ID: 34

5-AMINOLEVULINIC ACID WITH IONIZING IRRADIATION STRONGLY ENHANCES DELAYED INTRACELLULAR PRODUCTION OF REACTIVE OXYGEN SPECIES IN GLIOMA CELLS.

Junkoh Yamamoto[1]
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Aims: 5-Aminolevulinic acid (ALA) is a prodrug used in fluorescence-guided resection of malignant gliomas due to its high cellular uptake in tumours. We previously showed that radiosensitizing effect of 5-ALA in experimental glioma in vitro and in vivo. However, the mechanism of radiosensitizing effect of 5-ALA remains unclear. In the present study, we assessed the effect of delayed production of intracellular reactive oxygen species (ROS) after ionizing irradiation in glioma cells pretreated with 5-ALA in vitro.

Methods: Delayed production of intracellular ROS 12 hours after ionizing irradiation was evaluated by flow cytometry (FCM) in glioma cells (9L, U251) pretreated with 5-ALA. Then, the subcellular localization of ROS in these glioma cells was determined by confocal laser scanning microscopy. Finally, the delayed production of ROS after ionizing irradiation at different times of 5-ALA treatment was also evaluated using FCM.

Results: Delayed intracellular production of ROS was significantly higher after 12 hours than that immediately following ionizing irradiation. However, pretreatment with 5-ALA strongly enhanced the delayed intracellular production of ROS in both glioma cells. Moreover, this increase in ROS production occurred mainly in the cytoplasm of glioma cells. The 5-ALA-induced increase in delayed ROS production was greater in glioma cells pretreated with 5-ALA before exposure to ionizing irradiation than in cells treated with 5-ALA after exposure to ionizing irradiation.

Conclusions: These results suggest that 5-ALA pretreatment increases delayed intracellular production of ROS up to 12 hours following ionizing irradiation, thereby enhancing the effect of ionizing irradiation on glioma cells.

Paper ID: 58

IDENTIFICATION OF GIC SPECIFIC MICRORNA (MIRNA), USING MIRNA PROFILING IN EXTRACELLULAR VESICLES

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Aims: Since most of analyses are just a method of utilizing isolated glioma tissues, there is no useful biomarker that can assess the disease state and the activity of glioma-initiating cells (GICs) with time. In the present study, we aimed to identify GIC specific microRNAs (miRNAs) in extracellular vesicles that can be a novel therapeutic tool.

Methods: The miRNAs in extracellular vesicle were extracted from the serum of five glioblastoma patients and three healthy volunteers, and also from the cell culture medium of eight cell lines, seven human GICs, and one human neural stem cell (NSC). Using miRNA microarray, we comprehensively analyzed the 2,006 miRNAs expression profiles, and aberrantly expressed (more or less than 2-fold) miRNAs were identified.

Results: 137 miRNAs (20 up-regulated and 117 down-regulated miRNAs) were aberrantly expressed in glioblastoma patients compared with healthy volunteers. On the other hand, 211 miRNAs (up 77 miRNA, down 134 miRNAs) were aberrantly expressed in human GICs compared with human NSC. Among these miRNAs, 19 miRNAs were defined as a GIC specific miRNA that ware down-regulated in common to all serums and mediums. In addition, all of these miRNA expression was decreased in all GICs and glioblastoma patients. Among them, 11 miRNAs (miR-18a, -18b, -30a, -30c, -128, -181a, -335, -340, -374a, -374b, -660) was identified as a "pure" GIC specific miRNA that contains target sequences for several genes named stem-cell marker.

Conclusions: Our results suggest that these miRNAs can be a good biomarker and useful therapeutic tool for improving the prognosis of glioblastoma.

Clinical Trials

Paper ID: 128

TUMOUR VOLUME REDUCTION WITH PET GUIDED INTENSITY MODULATED RADIATION THERAPY TO MINIMIZE EXTENT OF SURGERY REQUIRED FOR PATIENTS WITH FAVOURABLE MOLECULAR SUBGROUP ANAPLASTIC GLIOMA

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Aim: Assess reduction in tumour volume and outcome in favourable(FAV) anaplastic glioma(AG) following intensity modulated radiation therapy(IMRT).

Methods: Patients managed for AG with IMRT from 2008-2015 were classified as FAV or nonFAV cohort based on presence of oligodendroglial features, 1p19q co-deletion or IDH1mutation. From 2011 FAV received FET-FDGPET planning(PET-IMRT). Tumour volumes were created on representative T1/T2Flair MRI sequences using identical slice-levels in 3 planes for preIMRT, month+3 and month+12 postIMRT scans. Change in volumes was assessed between time periods. Progression-Free(PFS) was calculated from start RT. ECOG Scale and Employment status were recorded as surrogates for functional status postIMRT.

Results: 156 patients were included of which 124 FAV and 32 non-FAV. Median follow-up for survivors is 38.2 months. 18% received IMRT at second or later relapse. 66% received sequential chemotherapy. 50 relapses occurred for 5yPFS of 64.1%. Relapse was more frequent in nonFAV with 5yrPFS of 26.0% vs 75.3% for FAV ($p<0.001$).

56 FAV patients were managed with PET-IMRT since 2011, of which only 4 patients had no demonstrated residual disease on MRI/FET-PET. 12 patients relapsed for projected 3yr PFS of 74.4%; with only 5 relapses adjacent to initial surgical site. On MRI at month+3, the median volume for T1 and T2 reduced by 70.0% and 64.3% respectively; which further decreased to 82.8% and 81.0% at month+12. By month+12, 88.0% and 88.2% of patients had >60% volume reduction. 41 of 52 patients remain in paid employment, which was associated with improved ECOG and use of IMRT at diagnosis or first relapse, rather than delayed.

Conclusion: Patients with FAV AG achieve marked reduction in residual tumour volume with IMRT. With more than 75% patients progression-free at 5yrs, and relapses postIMRT at distant rather than local sites, decision-making for initial surgical therapy should aim to minimize the risks of intervention related morbidity.

Paper ID: 99

POSTOPERATIVE HYPOFRACTIONATED ACCELERATED INTENSITY MODULATED RADIOTHERAPY WITH CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN THE MANAGEMENT OF PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA: CLINICAL OUTCOME AND PROGNOSTIC FACTORS

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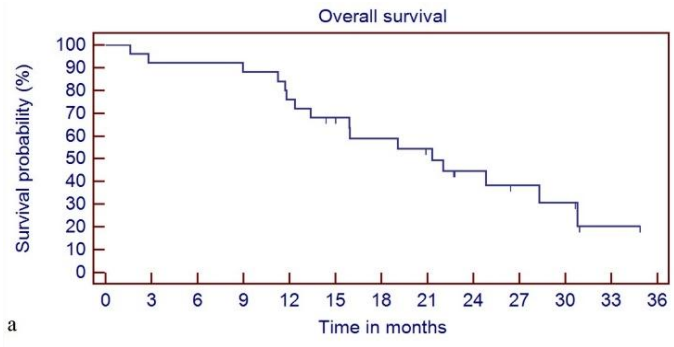
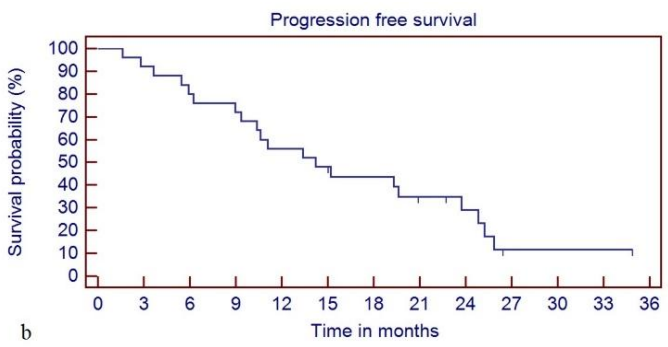
Aims: We intended to assess the feasibility and efficacy of hypofractionated accelerated IMRT with concurrent and adjuvant temozolomide(TMZ) in postoperative management of patients with glioblastoma.

Methods: In a single arm phase II study,25 patients with newly diagnosed, histologically proven glioblastoma(after maximal safe resection) with age 18-70 years and KPS≥70 were included. GTV was defined as enhancing tumour on post-contrast T1-W MR/CT images. CTV included GTV and perifocal oedema with an expansion of 2 cm. PTV and PTV boost encompassed CTV and GTV respectively with 0.5 cm expansion. IMRT-60Gy/25fractions/5weeks to PTV boost; 50Gy/25fractions/5weeks to PTV was delivered by simultaneous integrated boost technique with 4-9 coplanar beams. Concurrent and adjuvant TMZ was administered as per EORTC/NCIC protocol. Survival analysis was done by Kaplan Meier method.

Results: The median age was 50 years. Median KPS was 80. The extent of surgery was gross total, near-total and sub-total in 44%,24% and 32% of patients respectively. 23(92%) patients completed the planned RT course. Median number of cycles of adjuvant TMZ administered was 5. Grade 3/4 toxicities included acute CNS effects in 2(during RT), leucopaenia, neutropaenia and thrombocytopaenia in 1,3 and 2 patients(during adjuvant TMZ). After a median follow-up of 19.07 months, disease progression and death were observed in 80% and 64% of patients. The median PFS and OS were 14.2 months and 21.3 months respectively(2 year actuarial rate of PFS and OS-29.1% and 44.5% respectively). On univariate analysis, KPS≥80(P=0.03), gross or near-total excision(P=0.047) significantly improved OS whereas use of 6 cycles of adjuvant TMZ significantly improved both OS and PFS(P=0.003 and P=0.0001 respectively). Use of 6 cycles of adjuvant TMZ retained significance on multivariate analysis of OS and PFS(P=0.0067 and P=0.0007 respectively).

Conclusions: In patients with glioblastoma, postoperative hypofractionated accelerated IMRT with concurrent and adjuvant TMZ is well tolerated and leads to promising clinical outcome.





Paper ID: 109

10 YEARS REVIEW OF SURVIVAL AND MANAGEMENT OF MALIGNANT GLIOMA IN HONG KONG

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Aims: The study is to compare the survival of local Chinese GBM patients over a period of 10 years.

Methods: We retrospectively reviewed the brain tumour registry of the CUHK Otto Wong Brain Tumour Centre. Data of GBM patients were reviewed for the period of 1 Jan 2003 to 31 Dec 2005 and 1 Jan 2010 to 31 Dec 2012. Overall survival(OS) in these two periods of time were assessed by Kaplan Meier survival method. Risk factors of age, type and extent of resection, used of chemotherapy and methylation status of MGMT were also assessed.

Results: There were 26 GBM patients with mean age of 52.2 years old from the period of 2003-05. From 2010-12, there were 42 GBM patients with mean age of 55.1 years old. The overall survival was 221 days in 2003-05 and was 381 days in 2010-12 ($p<0.001$). The proportion of patients underwent surgical resection was similar of 69.3% (2003-05) and 78.6% (2010-12). There was a higher proportion of patients achieved total surgical removal 45.5% in 2010-12 compared to 11.1% in 2003-05. In the period of 2010-2012, patients received concomitant chemoradiotherapy (CCRT) showed definitively longer survival than those did not receive CCRT ($p=0.001$). Patients with 2 year-survival increase from 11.5% in 2003-05 to 21.4% in 2010-12.

Conclusions: Hong Kong has made substantial improvement in management of GBM with improvement of survival outcomes in recent 10 years. The combination of aggressive surgical strategy and CCRT are the driving force for the improvement.

Paper ID: 116

FIRST KOREAN EXPERIENCE OF DENDRITE CELL-BASED IMMUNOTHERAPY IN PATIENTS WITH PRIMARY GLIOBLASTOMA

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Objective: Dendritic cells are antigen presenting cells that recognize antigens and trigger an immune response in human immune system. Dendrite cell-based immunotherapy (DCI) has the potential to target and eliminate GBM cells. We evaluated the safety and efficacy of DCI in patients with primary glioblastoma.

Materials and methods: The dendritic cells sensitized with self-tumor lysate, WT1 and KLH are intradermal injected on upper arm. We administrated the dendritic cells four times every two weeks and twice at intervals of two weeks after the 4weeks of rest period. We followed up patients two years. Treatment response was evaluated with CT and MRI, and immune response was evaluated with T cell proliferation assay and ELISPOT test. The Control group was set up to histological reference (newly diagnosed, standard treatment completed 24 patients).

Results: Thirteen patients received this immunotherapy. The total 83 related adverse events occurred which were Grade I(82) and Grade II (1). Immune response (antigen specific IFN-γ and T-cell proliferation) was confirmed. The median progression free survival (PFS) was 15.6 months and the median overall survival (OS) was 28.4 months. DCI led to an extension of PFS (8.2 months; wilcoxon $p = 0.084$) and OS (16.1 months; wilcoxon $p = 0.029$) compared to control group. In IDH-1 non-mutation with gross total resection patients group, DCI showed 27 months of survival advantage (wilcoxon $p = 0.019$) compared to control group.

Conclusion: Dendritic cell-based Immunotherapy in patients with primary glioblastoma is comparative safe and had minor adverse reactions. DCI results in a longer PFS and OS compared to histological reference and well-tolerated. DCI is a good complementary treatment for primary glioblastoma.

Paper ID: 177

THE SUPRAORBITAL APPROACH FOR ANTERIOR SKULL BASE, SELLAR AND PARASELLAR TUMORS

Sung Jin Cho[1]

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Aims: Recently, the supraorbital(SO) approach is a mainstay surgical approach for providing access to the anterior skull base and suprasellar, parasellar, and retrosellar regions. We report our recent experience with this approach for neoplastic pathology.

Methods: Between March 2010 and December 2015, thirteen patients with neoplastic lesions underwent surgery by the SO approach. The clinical presentations, neuroradiological findings, microsurgical techniques, and outcome at discharge of these patients were analyzed. Seven (54%) patients were treated for meningioima; four (31%) patients for pituitary adenoma; and two (15%) patients for craniopharyngioma.

Results: The mean maximum tumor diameter was 2.5cm and seven patients(54%) had preoperative optic apparatus involvement with visual problem. Four patients(31%) had preoperative pituitary insuffiency. Total tumor removal was achieved in 9 patients(69%); There was no surgical mortality. One patient had temporary cerebrospinal fluid leakage. Two patient had new visual deficit and one patient had postoperative inflammation due to osteoconductive hydroxylapatite. Remnant tumor occurred in two pituitary adenoma and two craniopharyngoma. Two patients had temporary frontalis facial nerve palsy but improved within 6 months after surgery.

Conclusions: Compare with traditional pterional approach, the SO approach is a safe and effective keyhole method to remove both extraaxial and intraaxial skull base tumors, particularly lesions of the orbitofrontal region and parasellar area allowing for minimal disruption of normal brain parenchyma and promoting a rapid recovery and short hospital stay. The SO approach also provide better cosmetic result such as avoiding temporalis muscle atrophy.

Paper ID: 212

COMPARISON BETWEEN SITE AND CENTRAL RADIOLOGICAL ASSESSMENTS FOR PATIENTS WITH RECURRENT GLIOBLASTOMA ON A CLINICAL TRIAL

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Greg Fitt[3], John Simes[4], Anna Nowak[5], Elizabeth Barnes[4], Kate Sawkins[4], Christine Goh[1], Bradford A. Moffat[1], Simon Salinas[1], Lawrence Cher[3], Helen Wheeler[6], Elizabeth Hovey[7], Mark Rosenthal[1] and Pramit Phal[1]

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[3] *Austin Hospital, Melbourne*
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Aims: Assessment of magnetic resonance imaging (MRI) in glioblastoma can be challenging. In this study we compared assessments of disease status at hospitals where patients with recurrent glioblastoma were managed on a clinical trial, with subsequent blinded central expert radiological review of the same scans.

Methods: MRI conducted 8-weekly for patients on the CABARET trial was used to compare results of site versus central assessment of disease status. Clinical status was determined by the site for use in both site and central assessments. Response Assessment in Neuro-Oncology (RANO) criteria were used both by sites and the central reviewers. The trial's primary endpoint, progression-free survival (PFS), and response rates were compared between site and central assessments.

Results: Comparative data were available for 89 patients. Central review resulted in an earlier PFS date in 46% of patients (n=41). Where discrepancies occurred, median time difference between site and central date of progression was 1.8 months. Median PFS when comparing all central and site assessments was 3.6 versus 3.9 months (hazard ratio 1.6, 95%CI 1.3-1.8, $p<0.0001$) (Figure 1). Responses were documented more frequently by sites (n=16, 20%) than central reviews (n=10, 13%). Seven of 120 patients continued on trial as per site reviews for more than 6 months beyond the central review's determination of PD date.

Conclusions: While the comparison between site and central PFS dates was statistically significant, the difference in median PFS was ultimately not clinically relevant. Clinical benefit was obtained for a small proportion of patients well beyond when progression was determined centrally; reinforcing that off trial, clinical status in addition to radiology is an important determination of whether a therapy is effective for an individual.

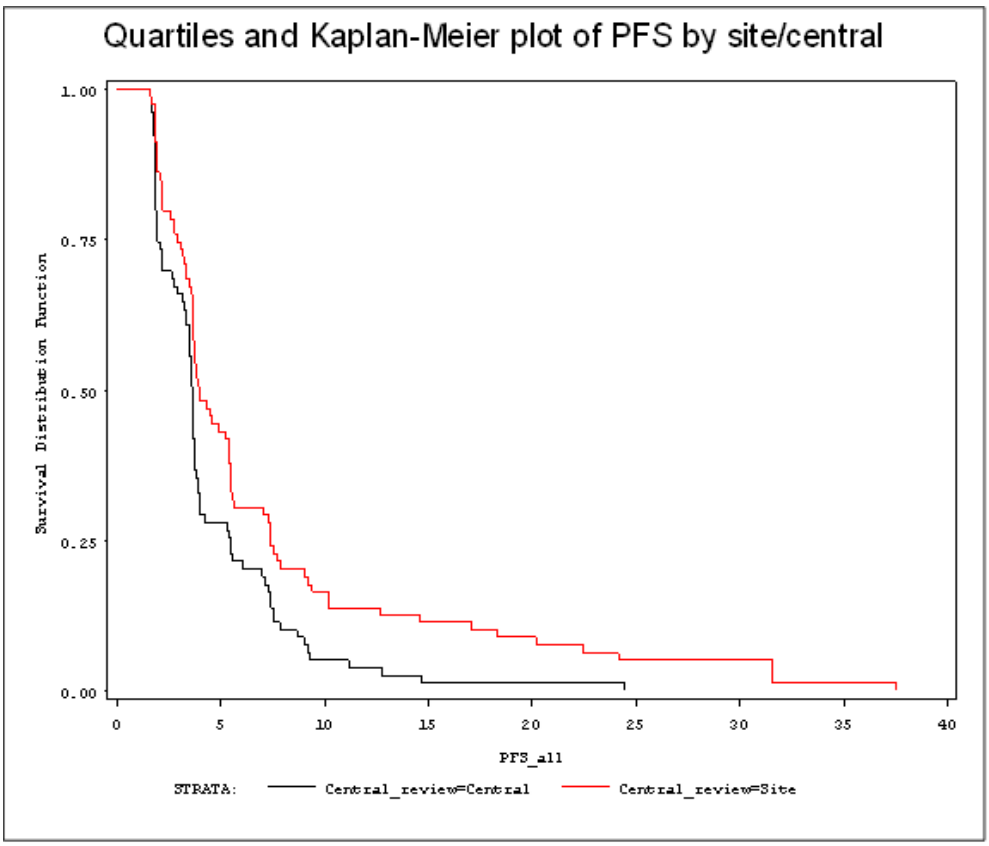

Figure 1: Kaplan-Meier curve comparing PFS (site review) with PFS (central review) for entire cohort

Paper ID: 31

MERITS OF THE ENDOSCOPIC SURGERY TO THE PITUITARY ADENOMAS

Tadateru Fukami[1]
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Aims: Now the major approach to the pituitary adenomas is endoscopic transsphemoidal surgery. Because of the development of various operative instruments, this approach may be more effective to preserve pituitary function, to improve visual function, and to increase resection rate of tumors than microscopic transsphenoidal approach. We exchanged the approach from microscopic to endoscopic in 2009. To evaluate the efficacy of endoscopic pituitary surgery for preservation of pituitary function and improvement of visual functions in our institute, we planned prospective one-arm observational study.

Methods: Our clinical cases of 60 pituitary adenomas were evaluated about the factors including the change of anterior pituitary lobe function, occurrence of diabetes mellitus, degree of tumor resection, improvement of visual functions, and control of functional pituitary adenomas. All our data were compared with previous reports which had described the result of operations for pituitary adenomas by microscopic surgery.

Results: In our series, there were no occurrence of anterior lobe deficiency and diabetes mellitus to the patients who did not have these symptoms. The rate of gross total resection, subtotal resection and partial resection were 60.5%, 21.1%, and 18.4%, respectively. Fully improvement, partially improvement, and deterioration of visual function were 66.7%, 8.3%, and 0%, respectively. Control rates of functional adenomas including PRLomas and ACTHomas were 100%. GHomas of Knosp grade 0-1 were controlled only by operation and those of other grade were controlled with following drug or/and radiation therapy. Postoperative epistaxis, meningitis, and CSF leakage which needed operative repair were 5.2%, 2.6%, and 2.6%, respectively.

Conclusions: Endoscopic transsphenoidal approach to the pituitary adenomas is minimally invasive and can be decrease the rate of postoperative severe complications.

Paper ID: 84

BEVACIZUMAB FOR BRAIN RADIATION NECROSIS

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Aims: Brain radiation necrosis is a serious adverse event of radiotherapy especially for malignant brain tumors,

which can deteriorate the quality of life in the patients. Since vascular endothelial growth factor is a forcible vascular permeability factor highly expressed in brain radiation necrosis, bevacizumab is expected be an alternative treatment to reduce its perilesional edema. We performed a prospective, multicenter, single-arm trial involving patients with symptomatic brain radiation necrosis to evaluate the safety and efficacy of bevacizumab.

Methods: Patients with surgically untreatable symptomatic brain radiation necrosis refractory to conventional treatments were enrolled. We judged that a major cause of perilisional edema was brain radiation necrosis, not tumor recurrence, on a basis of amino acid positron emission tomography (PET). 5mg/kg of bevacizumab was administrated 6 cycles biweekly. ≥30% reduction of perilesional edema lasting at least one month was specified as the primary endpoint.

Results: Forty-one patients were enrolled in this trial. Thirty patients (78.9%) reached to 30% ≤ reduction of perilesional edema. The median time to 30% ≤ reduction was 3.03 months. Sixteen patients (42.1%) experienced improvement of Karnofsky performance status. Corticosteroid could be reduced in 29 patients (76.3%). Twenty-seven patients (71.1%) aggravated perilesional edema (25% increase) with the median time of 9.31 months. Adverse events with grade ≥3 occurred in 10 patients (24.4%).

Conclusions: Bevacizumab treatment offers certain clinical benefits for patients with surgically untreatable symptomatic brain radiation necrosis. The determination using amino acid PET, not biopsy, is valid and less invasive for eligibility to administrate bevacizumab.

Paper ID: 219

EFFICACY OF A NOVEL ANTIBODY-DRUG CONJUGATE (ADC), ABT-414, AS MONOTHERAPY IN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AMPLIFIED, RECURRENT GLIOBLASTOMA (GBM)

Hui Gan[1,2]
Martin van den Bent[3], Andrew B. Lassman[4,5], Priya Kumthekar[6], Ryan Merrell[7], Nicholas Butowski[8], Zarnie Lwin[9,10], Tom Mikkelsen[11], Louis B. Nabors[12], Kyriakos P. Papdopolous[13], Marta Penas-Prado[14], John Simes[15], Helen Wheeler[16], Erica Gomez[17], David Reardon[18], Ho-Jin Lee[17], Lisa Roberts-Rapp[17], Hao Xiong[17], Earle Bain[17] and Kyle Holen[17]

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Background: Recurrent GBM (rGBM) has dismal prognosis. Almost 50% GBM tumors harbor amplified (amp) EGFR. ABT-414 is a tumor specific ADC combining an antibody targeting a unique conformation of EGFR (ABT-806) to a microtubule cytotoxin, monomethyl auristatin F.

Methods: M12-356 is an open-label, phase 1, 3-arm study: Arm-A (ABT-414+radiation/temozolomide (TMZ) in newly-diagnosed GBM (nGBM)), Arm-B (ABT-414+TMZ in nGBM as adjuvant-therapy, or in rGBM) and Arm-C (ABT-414 monotherapy in rGBM). Each arm had escalation cohort to determine RPTD and expansion cohort to establish safety/preliminary efficacy at RPTD. Results of Arm-C expansion cohort at 1.25 mg/kg RPTD (IV infusion) are shown here. Eligible patients (pts) were adults with KPS score ≥70, EGFR amp (confirmed centrally), rGBM, normal end-organ function and no prior bevacizumab.

Results: As of 7Jan2016, 48 EGFR amp, rGBM pts were treated in this cohort. Median age was 59 years (range, 35-80). Most pts had prior therapies: 40% had 1, 48% had 2, 10% had ≥3 prior therapies. Most common treatment emergent adverse events (TEAEs) (≥25% pts) were blurred vision (60%), headache, photophobia (29% each), dry eye, eye pain, fatigue (27% each). Most common serious AE (>1 pt) was seizure (8%). Grade 3/4 TEAEs (>1 pt) were keratitis (15%), corneal epithelial microcysts (8%), hemiparesis, hyperglycemia, muscular weakness, seizure (6% each), blurred vision, ulcerative keratitis (4% each). No dose-limiting toxicities were reported. Best RANO responses of 44 pts with complete data were: 2 partial responses, 18 stable disease, 24 progressive disease. The 6-month progression-free survival (PFS6) estimate was 30% [95% CI=17, 44].

Conclusions: ABT-414 monotherapy, at 1.25 mg/kg RPTD, displayed frequent yet reversible ocular toxicities. An encouraging tumor stability/response and PFS6 were observed in this highly refractory EGFR amp, rGBM. A global randomized trial of ABT-414, alone or with TMZ, vs. TMZ or lomustine, is underway in EGFR amp, rGBM (NCT02343406).

Paper ID: 110

COMPARISON OF CONSOLIDATIVE EFFECT OF THREE MYELOABRATIVE HIGH-DOSE CHEMOTHERAPIES FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Aims: Although high-dose methotrexate and whole-brain radiation therapy (WBRT) is the current standard for primary central nervous system lymphoma (PCNSL), it is associated with high rates of relapse and severe neurotoxicity. In an attempt to improve survival and functional outcome, we treated 15 patients with PCNSL with methotrexate, cyclophosphamide, doxorubicin, vincristine, and prednisolone (M-CHOP) followed by consolidative high-dose chemotherapy and autologous stem cell rescue without WBRT. We compared the consolidative effect of three high-dose protocols.

Methods: Fifteen patients with newly diagnosed PCNSL who achieved complete response after M-CHOP without WBRT were enrolled. Patients were treated with one of three myeloabrative protocols: busulfan and thiotepa (BT), busulfan and L-PAM (BM), or MCNU, CBDCA, VP-16, and CPA (MCEC). Overall survival and recurrence-free survival (RFS) were analyzed.

Results: In the BT group (5 patients), one patient died of recurrent disease and one patient died of nonrelated disease. Three patients were alive without recurrence and maintained 100% Karnofsky performance status (follow-up period: 14-77 months). The median of survival had not yet been reached. In the BM group (6 patients), all patients experienced recurrence (RFS = 11 months), and two patients were alive. Median survival time was 45 months (follow-up period: 27-46 months). In the MCEC group (4 patients), three patients experienced recurrence (RFS = 12 months); one patient died of recurrent disease and three patients were alive. The median of survival had not yet been reached (follow-up period: 13-29 months). There were no severe toxicities related to high-dose chemotherapies.

Conclusions: Myeloabrative high-dose chemotherapies were well tolerated in all patients, including patients over 65 years of age. Only high-dose protocol with busulfan and thiotepa has a consolidative effect; that involving busulfan and melphalan or MCEC did not. The addition of consolidative chemotherapy and the deferring of WBRT is a promising strategy for PCNSL.

Paper ID: 44

FACIAL NERVE FUNCTIONAL RECOVERY : THE USEFULLNESS OF DIFFUSION TENSOR IMAGING TRACTOGRAPHY FOR PREOPERATIVE IDENTIFICATION OF FACIAL NERVE IN VESTIBULAR SCHWANNOMA SURGERY

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Introduction: Facial nerve palsy is a common complication in treatment of vestibular schwannoma (VS) but preserving facial nerve(FN) function is important. The preoperative visualize the course of FN in relation to VS could help preventing injury to the nerve during the surgery and shortening of operation time. In this prospective study, we present the usefulness of diffusion tensor imaging tractography(DTI) for FN to preoperative identification and evaluation of postoperative functional outcomes.

Materials and methods: We prospectively studied 20 patients with VS from July 2011 to April 2016. Four patients were Koos grade II, and seven were grade III, other nine were grade IV. All patients performed preoperative DTI for FN. And postoperative DTI was performed at postoperative 1 day, 3 month and 1 year. We checked electroneuronography for evaluation for FN. Clinically FN function was evaluated according to the House-Brackmann grade.

Results: FN course on preoperative DTI were correlated with intraoperative findings in 90%(18/20 patients). Facial nerve was located on the anterior of the tumor surface in 5 cases, on anteroinferior surface in 8, anterosuperior surface in 4, posterosuperior surface in 1, superomedial surface in 1 and posteroinferior surface in 1 case. Eighteen of twenty preserved the FN but in two patient, FN was transected during removal of tumor and immediate repair of FN was performe. In postoperative facial nerve DTI, preservation of FN were confirmed in all patients. Immediate postoperative facial nerve palsy were grade III in six patients, grade IV in six patients. FN function at 3 months after surgery was clinically improved and then all of them recovered to grade II after 1year.

Conclusion: DTI for preoperative identification FN in VS surgery is very useful in order to preserve FN and we could predict the nerve function recovery with the help of postoperative DTI and electroneuronography.

Paper ID: 45

SURGICAL RESULTS OF ATYPICAL AND MALIGNANT MENINGIOMA : SURVIVAL AND PROGNOSTIC FACTORS

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Objective: This retrospective study analyzed the prognostic factors, the effect of different methods of

treatments and the behavior of atypical meningioma and malignant meningiomas.

Methods: Thirty three patients were diagnosed as atypical or malignant meningioma, among 273 patients who were given a diagnosis of meningioma in the period of 2002 to 2015. Age, gender, tumor location, Ki 67, Simpson grade and treatment received were analyzed. We studied the correlation between these factors with recurrence, overall survival rate and progression free survival.

Results: Mean patient ages was 57.8 ± 13.4 (27 to 80years) and mean follow up period was 63.9 ± 55.4 (12 to 158 months). Mean overall survival rate and progression free survival rate are 73.6 ± 55.2(12 to 160 months) and 60.9 ± 52.6(8 to 160 months). Of 33 patietns, 27 cases (72.9%) were still alive.

Better survival was observed for patients less than 50 years old but with no statistical significance (P = 0.096). And patients with total resection (Simpson grade 1-2) compared with subtotal resection (Simpson grade 3-4) also better survival rate but no statistical significance (P < 0.720). Patients with a tumor located in brain convexity, parasagittal and skull base also no statistical significance (P = 0.386). Progression-free survival showed a significant relationship with total resection compared with subtotal rescection (P = 0.008).

Conclusions: Independent prognostic factors affecting overall survival is not founded in our study. But we confirmed that Simpson grade was significant factor for statistically affect to progression free survival. Overall survival was not affected statistically by patient age, gender, tumor location, Ki 67, Simpson grade and treatment received. in this study. This is may be due to most of patients are still alive. With long-term follow up period, it would be able to observe more independent prognostic factors clearly.

Paper ID: 38

ACUTE HEMATOLOGICAL TOXICITY DURING CRANIO-SPINAL IRRADIATION: IS IT UNDER-REPORTED?

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Aim: To analyze treatment interruptions due to acute hematological toxicity in patients of medulloblastoma receiving cranio-spinal irradiation (CSI)

Methods: In our department, blood counts are monitored twice a week during CSI and spinal fields are interrupted for patients with ≥ grade 2 hematological toxicity. Spinal irradiation is resumed after recovery to grade 1 level (TLC > 3000; platelet count > 75,000). Case records of 52 patients of medulloblastoma treated between 2011 and 2014 were retrospectively analyzed for hematological toxicity and treatment interruptions.

Results: Median age was 11 years. All patients received adjuvant CSI of 36 Gy, followed by boost of 18 Gy to posterior fossa, at 1.8 Gy per fraction. Concurrent chemotherapy was not given. Adjuvant chemotherapy was given after CSI.

Spinal fields were interrupted in 73.1% of patients. Cause of first interruption was leucopenia in 92.1%, thrombocytopenia in 2.6%, and both in 5.3%. Median number of fractions at first interruption was 8.5, with 63.2% of interruptions before 10 fractions. Median duration for hematological recovery was 10 days. Half of the patients had at least 2 interruptions, and 20% subsequently developed grade 3 toxicity.

On multivariate analysis, significant correlation with duration of delay was observed for pre-treatment hemoglobin (p=0.018), number of fractions at first interruption, grade and duration of recovery of leucopenia (p<0.0001).

Conclusion: Acute hematological toxicity with CSI is frequently under-reported. Even after interrupting spinal irradiation at grade 2 levels, 20% of patients developed grade 3 toxicity subsequently. Frequent monitoring and timely intervention for acute hematological toxicity are recommended during CSI.

Paper ID: 95

EFFICACY OF POSTOPERATIVE INTRACRANIAL PRESSURE MONITORING AFTER BRAIN TUMOR SURGERY IN ELDERLY

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Aims: Although intracranial pressure (ICP) monitoring is useful for managing brain swelling after trauma, hemorrhage, or surgery, the efficacy of ICP monitoring after surgery in the elderly still remains to be determined. Therefore, we investigated the efficacy of postoperative ICP monitoring after brain tumor surgery in the elderly.

Methods: Between January 2010 and December 2015, 103 patients underwent ICP monitoring after brain tumor surgery. Among them, 28 consecutive patients aged >65 years, who underwent elective brain surgery, were retrospectively reviewed. The patients were divided into an increased ICP group (n=11) and a stable ICP group (n=17), and the postoperative status of the two groups were compared.

Results: Among the 28 patients, 11 (39.3%) had ICP elevation. All patients who presented increased ICP underwent immediate CT scan and postoperative hemorrhages were observed. The patients were treated with mannitol infusion for reducing the ICP. In contrast, 17 patients (60.7%) had stable ICP, among which 8 (47.1%) had postoperative hemorrhage. The

hospitalization period of the increased ICP group was significantly greater than that of the stable ICP group (43.4 days versus 26.1 days; $p<0.05$). Amount of postoperative subdural hemorrhage of the increased ICP group was significantly greater than that of the stable ICP group (5.9 cc versus 0 cc; $p<0.05$). In addition, postoperative epidural hemorrhage of the increased ICP group was significantly greater than that of the stable ICP group (6.4 cc versus 0.9 cc; $p<0.05$).

Conclusions: ICP monitoring may be advantageous in immediate postoperative management of the elderly after elective brain tumor surgery.

Paper ID: 30

LONG-TERM RESULTS OF PRIMARY NOVALIS RADIOSURGERY FOR INTRACRANIAL MENINGIOMA.

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Background: The principle treatment for meningioma is surgical resection. However, radiosurgery is also an important treatment modality for primarily or adjuvant for residual or recurrent. In this study, we evaluated the effectiveness and long-term results of primary radiosurgical treatment for meningioma in our institution.

Methods: We studied 95 patients (23 men and 72 women) who underwent Novalis radiosurgery for primary treatment modality of intracranial meningioma, which is radiologically diagnosed, from Nov 2000 to Mar 2013. We included only patients with followed up more than 3 years with imaging and clinical examination. Patients with high-grade meningioma was excluded. Seventy-three patients and 97 meningiomas were included and 8 patients have multiple meningiomas. We analyzed each of the factors associated with long term results.

Results: The mean patient's age was 58.6 years-old. Mean 80% marginal dosage was 14.5 Gy. Mean follow-up period was 5 years 10months.The overall tumor control rate was 96%; no tumor growth in 52%, decreased tumor size in 44%. Four patients (4.1%) showed evidence of tumor growing. Three patients (3%) developed peritumoral edema (PTE) after Novalis radiosurgery; two of them (2%) underwent surgical resections due to PTE and tumor growth.

Conclusion: Primary Novalis radiosurgery for intracranial meningioma has proven to be a safe and effective treatment modality with successful long-term outcomes. Radiosurgical treatment of deep seated large meningiomas should be careful for tumor necrosis with PTE.

Keywords: Meningioma; Radiosurgery; Primary therapy

Paper ID: 157

ACCREDITED MGMT METHYLATION ANALYSIS FOR USE IN MOLECULAR DIAGNOSTICS

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Aims: Methylation of the promoter region of *MGMT* occurs frequently in glioma, in particular glioblastoma and *IDH*-mutated low-grade glioma. *MGMT* methylation status has prognostic as well as predictive value. The value of testing for MGMT protein expression by immunohistochemistry staining as an alternative is controversial, and *MGMT* methylation remains the gold standard for clinical decision making. We thus have established a workflow for DNA methylation analysis of *MGMT* suitable for use in molecular diagnostics to support neuro-oncologists in their decision making processes.

Methods: Tumour-rich and tumour-free areas are identified by a pathologist on H&E stained sections of formalin-fixed, paraffin-embedded (FFPE) tumours. DNA is extracted from the macrodissected material and bisulfite-modified for DNA methylation analysis. The sample is then tested for DNA methylation in the promoter region of the *MGMT* gene using methylation sensitive-high resolution melting analysis (MS-HRM). A quantitative score can be obtained using bisulfite pyrosequencing after MS-HRM if required.

Results: MS-HRM allows the reliable detection of *MGMT* methylation in FFPE-derived DNA and gives results consistent with bisulfite pyrosequencing. The assay allows an easy and unambiguous interpretation of results, even when methylation patterns are clearly heterogeneous.

Conclusions: The workflow established for *MGMT* methylation analysis meets the requirements for routine use in molecular diagnostics. An independent study showed that this assay outperformed methylation-specific PCR in predicting progression-free survival and overall survival for high-grade glioma patients. Standardised testing procedures and stringent quality control procedures ensure high-quality and reproducible results as well as a fast turn-around-time. Our laboratory at the Olivia Newton-John Cancer Research Institute is NATA accredited for performing *MGMT* methylation testing.

Paper ID: 18

A PROSPECTIVE MULTICENTER SINGLE-ARM CLINICAL TRIAL OF BEVACIZUMAB FOR PATIENTS WITH SURGICALLY UNTREATABLE SYMPTOMATIC BRAIN RADIATION NECROSIS

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Aims: Brain radiation necrosis (BRN) can be a complication of radiation therapy for brain tumors. Since VEGF is also a vascular permeability factor in the brain, bevacizumab, a humanized antibody that inhibits VEGF, would be expected to reduce perilesional edema that often accompanies BRN.No study was attempted what a kind of BRN patients and how long can they be benefited from bevacizumab treatments. We performed this nationwide multi-center clinical trial for on-label use of bevacizumab for symptomatic BRN.

Methods: Patients with surgically untreatable symptomatic BRN refractory to conventional medical treatments (e.g., corticosteroid, anticoagulants, or hyperbaric oxygen therapy) were enrolled. We judged that a major cause of perilesional edema with a lesion/normal brain ratio ≤1.8 on 11C-methionine or ≤2.5 on 18F-boronophenylalanine PET was BRN, not tumor recurrence, and six cycles of biweekly bevacizumab (5 mg/kg) were administered. The primary endpoint was a ≥30% reduction from the patients' registration for perilesional edema continuing for ≥1 month. This and other endpoints were evaluated from historical control of non-bevacizumab medical treatment.

Results: Of the 41 patients enrolled, 38 were fully eligible for the response assessment. The primary endpoint was achieved in 30 of the 38 (78.9%) patients at 3.03 months (median) after enrollment. Sixteen patients (42.1%) experienced improvement of their KPS. Corticosteroid could be reduced in 29 patients (76.3%). These endpoints were achieved with statistical superiority in comparison with the historical control.

Conclusions: Bevacizumab treatment offers clinical benefits for patients with symptomatic BRN, irrespective of radiation modalities and original cancer diseases. Amino-acid PET, not biopsy, is adequate and less invasive for eligibility to receive bevacizumab. Six cycles of biweekly bevacizumab is very potent and promising for the treatment of symptomatic BRN, however the effectiveness was temporarily and repetitive treatments with bevacizumab should be considered in some cases.

Paper ID: 169

RESULTS OF THE INTERIM ANALYSIS OF THE EORTC RANDOMIZED PHASE III CATNON TRIAL ON CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN ANAPLASTIC GLIOMA WITHOUT 1P/19Q CO-DELETION, AN INTERGROUP TRIAL (O)

Anna Nowak[1]
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Aims: The benefit of adding chemotherapy to radiotherapy (RT) in newly diagnosed anaplastic glioma without 1p/19q co-deletion is unknown. CATNON investigated adjuvant and/or concurrent chemotherapy with temozolomide (TMZ) in these tumours.

Methods: Eligible patients had newly diagnosed WHO grade III glioma without 1p/19q co-deletion, ≥ 18 years, WHO performance status (PS) 0-2. All patients received RT 59.4 Gy in 33 fractions, and in a 2 x 2 factorial design were randomized to i. RT alone; ii. RT with concurrent daily TMZ 75mg/m2; iii. RT then 12 cycles adjuvant TMZ 150-200mg/m2 day 1-5/4 weeks; or iv. RT with both concurrent and 12 cycles adjuvant TMZ. Stratification factors included MGMT promoter methylation and PS. Primary endpoint was overall survival (OS). 748 patients and 534 events were needed to detect a HR of 0.775 for both concurrent and adjuvant TMZ. Planned interim analysis after 219 events required a p value of 0.0084 to reject the Null hypothesis of no OS difference.

Results: 748 patients were randomised (12/2007 to 8/2015). Interim analysis 10/2015 was based on 221 events (median follow-up: 27 months). OS: HR=0.645 (95% CI 0.450-0.926; p= 0.0014) with adjuvant TMZ (arms iii and iv). MGMT status could be determined in 74% of patients (42% methylated)and was prognostic for OS (HR 0.54, 95% CI 0.38-0.77; p= 0.001), but at this stage not predictive of adjuvant TMZ outcomes. Progression free survival (PFS): HR=0.586 (95% CI 0.472-0.727; p < 0.0001) for adjuvant TMZ. OS at 5 years: no adjuvant TMZ 44.1%; adjuvant TMZ 55.9%. With adjuvant TMZ median PFS increased from 19.0 to 42.8 months.

Conclusions: 12 cycles adjuvant TMZ improved OS in anaplastic glioma without 1p/19q co-deletion. Further follow-up will elucidate the role of concurrent TMZ . Molecular studies to address the impact of isocitrate dehydrogenase (IDH) mutational status and methylation profiling are ongoing.

Paper ID: 111

AN MULTIVARIATE ANALYSIS FOR PROGNOSTIC SURVIVAL OF 121 ELDERLY PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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Objective: In order to verify the role and impact of extent of resection on elderly patients with newly diagnosed GBM for survival.

Methods: The medical data like gender, age, symptom, symptom duration, preoperative Karnofsky performance statusKPS, preoperative Charlson combidity index[21], preoperative Performance status of ECOG (PS), preoperative American Society of Anesthesiologists index (ASA), preoperative comorbid disease, tumor location, tumor size, extent of resection (EOR), adjuvant therapy, interval of adjuvant-treatment administration after operation and immunohistochemistry, duration for anesthesia and surgery, and volume of bleeding of 121 patients aged ≥65 years treated between 2007 January to 2015 June was systematically collected.

Results: The mean survival for 121 patients(2 excluded) was 15.50 months. Age (p =0.028), KPS (p0.0001), ASA (p0.0001), Tumor located (p < 0.0001), extent of resection(p 0.0001), stupp schedule (p = 0.031) was significantly difference between groups. COX hazard models identified KPS (HR 1.977 [95% CI 1.118 - 3.312]; p = 0.01), Extent of resection(HR 0.97 [95% CI 0.95 - 0.99]; p = 0.0082) and stupp schedule or not (HR 0.485 [95% CI 0.329 - 0.717]; p 0.001) was independent predictors of survival. **Conclusion** We consider that the elderly patients with newly dignosed GBM can also benefit from extending resection and stupp schedule. Patients with bad performance status, low preoperative KPS couldn't achieved more OS benefit though extending resection, but still achieved increasing OS compared to patients who under partial resection. Age is not a significant prognosis factor for survival in elderly patients.

Keywords: Elderly patients; Extent of resection; Glioblastoma multiforme; prognosis

Paper ID: 192

CYBERKNIFE RADIOSURGERY FOR CAVERNOUS SINUS MENINGIOMAS

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Aims: To present results of cavernous sinus meningiomas treated with CyberKnife radiosurgery.

Methods: Six patients (Sex: male 1, female 5, Age: median 43.5 years (range, 37-58 years)) were treated in 3-5 fractions with CyberKnife radiosurgery for meningiomas of the cavernous sinus between Oct. 2002 and Oct. 2010 at author's institute. Histology was WHO grade I in one lesion, and undetermined in 5 lesions. Median target volume was 9.45 cm3.

Results: The follow-up periods ranged from 38 to 151 months (mean, 86 months; median, 74.5 months). The tumor volume decreased in all 6 patients. Two patients underwent repeated radiosurgery, one of them recurred 62 months later, and surgical operation revealed atypical meningioma. The other one recurred 138 months after radiosurgery had large tumor volume of 17 cc, In 4 patients with neurological symptoms, a significant improvement was observed in all 4 patients (disappeared diplopia in 2, restored visual acuity in 2). No radiation induced optic neuritis was observed.

Conclusion: These small data set suggests that hypofractionated radiosurgery with CyberKnife might be reliable technique for the management of symptomatic cavernous sinus meningiomas patients.

Paper ID: 122

DOSE AND CYCLE MODIFICATION OF HIGH-DOSE METHOTREXATE FOR PRIMARY CNS LYMPHOMA; AN EARLY EXPERIENCE OF A SINGLE CENTER

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Dose and cycle modification of high-dose methotrexate for primary CNS lymphoma; an early experience of a single center.

Introduction: Primary central nervous system lymphoma (PCNSL) is relatively good response to high-dose methotrexate (MTX). But MTX have toxicities to affect the bone marrow and intestinal epithelium, with risks of bleeding, infections, and severe mucositis. Here we report an early experience of dose and cycle modification of high-dose MTX for PCNSL according to the renal function and early radiologic response.

Method: From 2010 to 2012, eleven immunocompetent PCNSL patients were treated with high-dose MTX monochemotherapy. MTX was given at a schedule with 3 cycles of induction chemotherapy (8 g/m^2) and 6 cycles of maintenance chemotherapy (3.5 g/m^2). But MTX dosage was reduced by the percentage reduction in creatinine clearance, and a number of induction cycles were changed by radiologic response after the third cycle.

Results: Six (55%) patients required dose reduction and 4 (36%) patients were performed more than 4 cycles at the induction chemotherapy. In 10 evaluable patients, the overall radiologic response rate was 80%, with 6 compete response (60%) and 2 partial response (20%). Median overall survival was 22 months but median progression-free survival was not reached. Age and radiologic response after induction chemotherapy were significant prognostic factor in clinical outcome. MTX-related toxicities were

observed in 8 of 11 patients with hypersensitivity (grade II) in 3 patients, hematological complications (grade II) in 1 patient, gastrointestinal disturbance (grade I) in 1 patient, and viral skin infection (grade III) in 1. Two patients died due to grade V toxicities.

Conclusion: In spite of a limited data, dose and cycle modification of high-dose MTX is well tolerable method for PCNSL.

Epidemiology

Paper ID: 94

LONG TERM SURVIVORS OF GLIOBLASTOMA - A CLOSER LOOK

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Aims: Glioblastoma has a poor prognosis with median survival of 12-14 months. Long-term survivors (LTS) are defined as those alive at least 2 years from diagnosis, representing 10% of this population. This study aims to provide a clinical profile of LTS at a single Melbourne institution.

Methods: Retrospective audit of consecutive adult patients with a histological diagnosis of glioblastoma from 1st January 2006 to 31st December 2012. Demographic, treatment and survival characteristics were recorded, with follow-up to 31st December 2015. Independent sample t-test, chi-squared and fisher exact were used to identify differences between LTS and those surviving less than 2 years, with survival estimated by Kaplan-Meier method.

Results: 444 patients were identified with 77 patients (17%) surviving >2 years. Compared with patients surviving less than 2 years, LTS were more likely to be younger (53 vs 64yrs, p<.0001), have ECOG 0-2 (90% vs 48%, p<.0001), past history of low-grade glioma (23% vs 8%, p<.0001), unilateral tumours (95% vs 78%, p<.0001), gross tumour resection (64% vs 21%, p<.0001) and receive radiotherapy plus concurrent temozolomide followed by adjuvant temozolomide (74% vs 15%, p<.0001). In LTS, the most common presenting symptoms were headache (38%) and seizure (23%), with confusion present in 10%. Fourteen patients remained disease-free, whilst 56 patients (73%) progressed at a median of 18.9 months from diagnosis. Twenty-nine patients underwent a second craniotomy, with 11 undergoing 3 or more. Temozolomide was the most common second line treatment (42%), followed by investigational treatment (11%), and 26% received third line treatment. ECOG deteriorated with repeated recurrence. The median overall survival for LTS was 37.6 months, compared with 8.6 months (entire cohort).

Conclusions: LTS of glioblastoma (17%) are more likely to be younger, have previous low-grade glioma, unilateral tumours and good performance status. These data begin to assist prospective identification of these patients.

Paper ID: 182

EVOLVING IMPROVEMENTS IN PROGNOSIS AND SURVIVAL OF PATIENTS WITH GLIOBLASTOMA MULTIFORME MANAGED WITH ADJUVANT CHEMORADIOTHERAPY: BUILDING STEADILY ON ESTABLISHED CLINICAL TRIAL DATA.

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Helen Wheeler[2,3,4], Raymond Cook[2,4], Charles Teo[5], David Brazier[2,3], Geoff Schembri[2,3], Marina Kastelan[2,4], Lesley Guo[2] and Michael Back[2,6,3,4]

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Aims: Evaluate survival of patients diagnosed with Glioblastoma Multiforme (GBM) managed with adjuvant intensity modulated radiation therapy (IMRT) and temozolomide (TMZ) since the introduction of the EORTC-NCIC protocol and to determine the extent that improved survival in the literature has translated to clinical practice.

Methods: All patients with GBM managed between May 2007 to December 2014 with EORTC-NCIC protocol were entered into a prospective database. The primary endpoint was the median survival (MS). Univariate predictors of survival were evaluated with respect to tumour resection, age, and ECOG performance status (PS) using log-rank comparisons.

Results: 233 patients were managed under the protocol and analysed for outcome. The median age was 57 years; the rate of gross total resection(GTR), subtotal resection(STR) and biopsy(Bx) were 47.2%, 35.2% and 17.6% respectively. At progression 49 patients had re-resection, and in addition to second-line chemotherapy, 86 patients had Bevacizumab including 26 with re-irradiation.

The median survival was 17.0 months (95%CI:15.4-18.6). On univariate evaluation, independent predictors of survival included extent of resection (p = 0.001), age, ECOG PS and RPA class III were shown to significantly improve survival (p<0.0001). The median survival for GTR, age<50, ECOG 0-1 and RPAclassIII were 21, 27, 20, and 47 months respectively.

Median survival was analysed over the time period in adjacent two yearly blocks; 2007-8, 2009-10, 2011-12 and 2013-14. The median survivals were 14,17,18,18 months respectively (p=0.71)

Conclusion: This study confirms the significant improvement in median survival in GBM that has occurred in recent years since introduction of the EORTC-NCI Protocol. Further additional improvements have occurred presumably related to subspecialised care, improved resection rates, sophisticated RT targeting and early systemic salvage therapies. However, the burden of the

disease within the community remains high and the median survival improvements over time have plateaued.

Paper ID: 197

A PATTERN OF RECURRENCE AND CAUSE OF DEATH IN GLIOBLASTOMA PATIENTS TREATED WITH CHEMORADIOTHERAPY WITH TEMOZOLOMIDE

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Aims: Intracranial dissemination of a tumor is more common in glioblastoma (GBM) patients. A pattern of recurrence and cause of death in GBM patients were examined.

Methods: One hundred seventeen patients with GBM have been treated with chemoradiotherapy with temozolomide in our hospital from 2005 until 2013. Patient background, MGMT promoter methylation status, MRI, clinical course and cause of death for each patient were reviewed from clinical records. Local or distant recurrence was defined as an increased tumor within the FLAIR high lesion of the initial tumor or a new appearance outside the initial tumor, respectively. Dissemination was defined as a distant recurrence, an appearance of subependymal space or subarachnoid space and leptomenigeal metastases.

Results: GBM patients with multiple lesions at initial diagnosis was found in 13/117 cases (11.1%). Among 102 patients with a single lesion, 48 patients (47.1%) and 27 patients (26.5%) had a local recurrence and dissemination at the first progression, respectively. Among these 48 patients with a first local recurrence, 28 patients (58.3%) and 10 patients (20.8%) had a local recurrence and dissemination at the second recurrence, respectively. Finally 47 cases (46.1%) of patients had dissemination. Time to dissemination of the patients with MGMT promoter methylation (MGMT(+)) and unmethylation (MGMT(-)) were 48.6 and 12.7 months, respectively ($p<0.001$). Among patients with MGMT(+), 50% and 10% of patients were died of an uncontrolled local recurrence and dissemination, respectively. Among 44 patients with MGMT(-), 50% and 30% of patients were died of an uncontrolled local recurrence and dissemination, respectively.

Conclusions: GBM patients had often dissemination disease but a local recurrence was the most cause of death in GBM patients. To improve the prognosis of GBM patients, control of an initial tumor is very important.

Paper ID: 198

STATISTICAL REPORT OF CENTRAL NERVOUS SYSTEM TUMORS HISTOLOGICALLY DIAGNOSED IN SICHUAN PROVINCE IN CHINA FROM 2008 TO 2013: A WEST CHINA GLIOMA CENTER REPORT

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Aims: Sichuan is a province in the west of China with a population of 81.4 million. This is the first statistical report of central nervous system (CNS) tumors, which were operated on and histologically diagnosed, in a large Chinese population.

Methods: All of the patient data were obtained from 86 medical facilities, which covered the Sichuan province population. Data from patients operated on between 2008 and 2013, and corresponding histology samples were re-reviewed in the major pathology centers. All of the CNS tumors were categorized according toICD-10 and ICD-O-3 classifications, and were reviewed manually. The tumor distribution was analyzed and stratified by gender, age, race, and tumor sites. Tumors in some ethnic minorities, such as the Tibetan people, were also analyzed.

Results: The final analytic dataset included 35,496 records. The top four histological tumors were meningioma (28.51%), pituitary adenoma (15.00%), nerve sheath (13.77%), and glioblastoma (11.82%).There was a dramatically high incidence of malignant tumor in males. The median age at diagnosis ranged from 13(pineal region tumors) to 56 (metastatic brain tumors) years. Most tumors in the insular lobe or cerebellum were low grade, whereas those in the thalamus or basal ganglia were likely to be high grade. The incidence of malignant tumors or high-grade gliomas in the Tibetans was significantly lower than that in the Chinese Han population.

Conclusion: This report is a preliminary statistical analysis of brain and spinal tumors in a large Chinese population, and may serve as a useful resource for clinicians, researchers, and patients' families.

Genomics and Epigenomics

Paper ID: 54

THE ROLE OF P53 GENE MUTATIONS IN DRIVING MIGRATION AND INVASION IN A MULTICENTRIC GLIOBLASTOMA

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Aims: In a single glioblastoma (GBM) patient, two spatially separated tumours (left thalamic and left temporal) arose almost simultaneously, but displayed no connecting T2/FLAIR signal abnormality. Both tumours were collected and patient derived cell lines (PDCLs) were established. The aim of this study was to characterise the two tumours genomically and examine their physiological properties *in vitro*.

Methods: The 2 tumour samples were sent to Caris Life Science for tumour profiling. PDCLs were established for the left thalamic (G52) and left temporal (G53) lesions. Immunohistochemistry (IHC) staining for the proliferation marker Ki67 was performed on the G52 and G53 cell lines. Both cell lines were tested in real time for cell proliferation, migration and invasion using the xCELLigence Real-Time Cell Analysis (RCTA) system. A clonogenic assay of cells *in vitro* was also performed on each cell line.

Results: Genomically, G52 (thalamic lesion) and G53 (temporal) lesion were identical with the exception of p53. G52 was wild-type for the p53 gene while G53 harboured a mutation. Sanger sequencing confirmed a homozygotic substitution of C/T in exon 8 of the p53 gene in G53 cells. Physiologically, the 2 tumours differed in proliferation (measured by Ki67 and xCelligence) with G53 showing significantly higher proliferation. G53 also showed significantly higher migration and invasion when compared to G52. Interestingly, G53 could initiate colonies whereas G52 could not.

Conclusions: Mutations in the *p53* tumour suppressor gene are a genetic hallmark of human astrocytic neoplasms, but their predictive role in GBM progression is still poorly understood. This study demonstrates that mutations of the *p53* gene may enhance the tumourgenic nature of GBM, contributing to increased proliferation and migration, and in its ability to form clonal sub-populations. Moreover, GBM is highly heterogeneous and careful analysis of multiple lesions; multi-centric, multifocal and recurrent is required to advance personalised treatment.

Paper ID: 202

A COMBINED GENOME, EPIGENOME AND TRANSCRIPTOMIC ANALYSIS IN PRIMARY CENTRAL NERVOUS SYSTEM GERM CELL TUMOURS SUGGESTS A PRIMORDIAL GERM CELL ORIGIN FOR GERMINOMA

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Aims: Central nervous system germ cell tumours (CNS GCTs) are the second most common paediatric brain tumours in Japan. The WHO Classification recognizes 5 sub-types, which are often subdivided into two classes, germinomas and non-germinomatous GCT (NGGCT). CNS GCTs often display mixed histology as a mixed-GCT or sometimes interchange histology at recurrence, the mechanism of which is unknown. The unexpected localization of GCTs to brain has invoked several hypotheses as to the origin of CNS GCTs, however their pathogenesis is largely unexplored. In this study, we aim to explore the pathogenesis and potential cell of origin(s) of CNS GCT by means of combined genome and epigenome analysis.

Methods: Forty-one CNS GCTs were analysed by whole exome sequencing and 83 additional tumours examined by targeted sequencing using an Ion Torrent system. DNA methylation of 59 CNS GCTs were studied by Illumina HumanMethylation 450 BeadChip. RNA sequencing was performed in 61 GCTs.

Results: By means of a genome-wide methylation analysis, we show that germinoma, but not NGGCT, is characterized by massive global DNA hypomethylation. The pattern of methylation strongly resembles that of primordial germ cells (PGC) at the migration phase, indicating that PGC is the cell of origin for germinoma but not for NGGCTs. Unlike PGC, hypomethylation in germinomas involves LINE1 retrotransposons as well. Microdissected germinoma and NGGCT components of mixed-GCTs showed distinct methylation profiles but shared identical somatic mutations of the MAPK or PI3K pathways. A transcriptomic analysis using RNA-sequencing revealed that germinomas and PGCs were clustered together while NGGCTs were clustered with embryonic stem cells.

Conclusions: These results suggest that CNS GCTs develop through acquisition of MAPK/PI3K mutations during early embryogenesis prior to or during PGC development followed by epigenetic diversion, the phenotypic fate of tumors being determined by the timing of mutations.

Paper ID: 155

MUTATIONAL ANALYSIS AND METHYLATION PROFILING REVEAL FEW CONSISTENT THERAPY-INDUCED MARKS IN PRIMARY GLIOBLASTOMA

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Aims: Glioblastoma present as a heterogeneous disease with poor prognosis despite the use of multimodal therapy. The aim of this study was to pinpoint the genomic and epigenomic changes that occur in tumours between initial diagnosis and recurrence in response to standard treatment with radiation and temozolomide. Additionally, we were able to compare these alterations with those observed in the natural progression of tumours from untreated patients.

Methods: A study cohort of 21 patients with primary glioblastoma were examined between diagnosis and first recurrence; eighteen patients were treated with standard dose radiation and temozolomide and the remaining three patients had elected not to receive any intervention other than surgery. The DNA from paired primary and first recurrent glioblastoma FFPE tumour specimens were profiled using the Comprehensive Cancer Panel (Life Technologies) which sequenced 409 cancer-associated genes to a mean depth of 1200x. The Infinium HumanMethylation450K BeadChip array (Illumina) was used for methylation profiling of the same specimens.

Results: In this cohort, the recurrent tumour of only one patient displayed an increased mutation rate attributable to a temozolomide-associated hypermutator phenotype. Mutations with predicted functional impact clustered in genes involved in the regulation of cyclin-dependant protein kinase activity, cellular senescence and a range of DNA repair and epigenetic regulation roles. Network analysis revealed further enrichment of functional groups associated with DNA damage and repair in recurrent samples of treated patients.

The number of CpGs differentially methylated between matched specimens ranged from 126 to 20096, however there was no significant difference between treated and untreated patients overall. Across the cohort, there were no consistent differences observed in differential methylation patterns between diagnosis and recurrence.

Conclusion: Little evidence for consistent selection pressure toward any mutation or methylation pattern due to standard radiation or temozolomide treatment was observed in this primary glioblastoma cohort.

Paper ID: 78

INTEGRATED ANALYSIS OF METHYLATION OF MGMT PROMOTER AND ALTERATION OF MISMATCH REPAIR ENZYMES IN GLIOBLASTOMA

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Aims: Temozolomide (TMZ) is known to induce mutations in mismatch repair (MMR) genes in glioblastoma with methylated O6-methylguanine-DNA methyltransferase (MGMT), thereby could potentially transform to hypermutator phenotype at recurrence. Mutations in MMR genes at initial presentation may also be associated with TMZ resistance. Here we investigate molecular genetic status of MGMT/MMR genes in glioma specimens including those with paired samples from initial and recurrent tumors, and analyze relationship of the molecular status and changes by recurrence with outcome of the patients with glioblastoma.

Methods: TMZ-treated newly-diagnosed glioblastomas (137 cases) and gliomas whose initial and recurrent specimens were available (36 cases) are eligible for this study. MGMT methylation status, mutations in IDH1/2 and MSH6 genes, and protein expression of MMR genes (MLH1, MSH2, MSH6, and PMS2) were determined by methylation-specific PCR (MSP), Sanger sequencing, and immunoblots/immunohistochemistry staining, respectively. Correlation of changes in MGMT and MMR status at recurrence with malignant progression as well as molecular status with clinical outcome were statistically analyzed.

Results: Protein expression of MLH1, MSH2, MSH6, and PMS2 was defective in 10.5%, 9.7%, 36.6%, and 11.9%, respectively, in newly-diagnosed glioblastomas. Expression level of MMR proteins did not correlated with prognosis. In MGMT unmethylated glioblastomas, low expression of MLH1 or MSH6 was a significant prognosticator for OS ($p<0.05$), while MMR expression was not associated with outcome in MGMT methylated glioblastomas. After recurrence, there was no correlation between MGMT methylation status of recurrent tumors and prognosis, whereas patients with reduced MMR protein expression at recurrence tended to have better survival than those with stable MMR expression.

Conclusions: Defective MMR may be involved in TMZ resistance in newly-diagnosed glioblastoma with unmethylated MGMT. Whether MGMT methylation and MMR status and their changes at recurrence could serve as molecular determinants for therapeutic selection in gliomas needs further investigation.

Paper ID: 132

GENETIC ANALYSIS OF MALIGNANT TRANSFORMATION IN OLIGODENDROGLIOMA WITH 1P19Q LOH

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Purpose: Glioma is a CNS tumor resulting from accumulation of genetic alterations. In the process of malignant change in low grade gliomas another genetic alterations are supposed to be accumulated. In this study we analyzed the accumulation of genetic alterations in grade 2 or 3 oligodendroglioma with 1p19q LOH.

Patients and methods: We examined genomic alterations of whole chromosome using an Snip-microarray in grade 2 & 3 gliomas and found 66 cases with 1p19q LOH tumor. We focused on several genetic alterations such as loss of heterozygosity (LOH) and amplification in all chromosomes. IDH1 mutation was also examined by direct sequencing method. Furthermore we analyzed the mutation of 48 cancer-related genes. We compared the genetic alterations in between the primary tumors and the recurrent tumors with malignant transformation.

Results: There were 5 patients with oligodendroglioma with 1p19q LOH demonstrating the malignant change at their recurrence. In 3 of 5 patients we could compare the genetic alterations between the primary tumors and the recurrent tumors. We found LOH in chromosome 18 and a mutation in PIK3CA gene as the additional common genetic change. IDH1 mutation was also found at both primary and recurrent tumors in all 3 cases.

Conclusion: Although there are various genetic alterations at recurrence, PIK3CA and a gene in chromosome 18 may play a key role in malignant transformation.

Paper ID: 83

STANNIOCALCIN-1 EXPRESSION IN GLIOBLASTOMA IS ASSOCIATED WITH LEPTOMENINGEAL DISSEMINATION OR METASTASIS.

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Aims: Dissemination or metastasis (D/M) occasionally occurs in glioblastomas (GBMs), and those cases have very poor prognosis. MicroRNAs (miRs) have been shown to involve metastasis in various tumors. The aim of this study is to clarify the miRs which promote D/M and to find a target molecule associated with them in GBMs.

Methods: Twenty-two supratentorial GBMs with D/M to spinal cord or medulla oblongata and 53 GBMs without D/M were analyzed. The expression levels of 22 miRs which were known to be related to GBM were examined by real-time RT-PCR, and miRs which were statistically upregulated or downregulated in GBM with D/M compared to GBM without D/M were determined. Then, we analyzed targets of these miRs by a search on the web site of "microRNA.org". Then, we analyzed the association of miRs with target molecule by real-time PCR and Western blot. Furthermore, we analyzed the functions and the expressions of the target molecule in GBMs.

Results: Eight miRs (miR-7, miR-29b, miR-34a, miR-101, miR-124, miR-128a, miR-137, miR-218) were statistically decreased in GBM with D/M, and mimic RNAs of these miRs inhibited cell proliferation and migration in glioma cells. As the most predictive target of these miRs, we focused on stanniocalcin-1 (STC1), a secreted homodimeric glycoprotein. We confirmed that the mimic RNAs of these miRs (miR-24b, miR-34a, miR-101) decreased the expression of STC1. Knockdown of STC1 inhibited the cell proliferation and migration. The expressions of STC1 in GBM were increased when compared with peripheral brains. GBMs with D/M had statistically higher expression levels of STC1 than those without D/M.

Conclusions: STC1 may be the target of miRs downregulated in GBM with D/M, and may be one of the key molecules of metastasis or dissemination in GBMs.

Paper ID: 191

GENE EXPRESSION PROFILING OF BEVACIZUMAB-INDUCED GLIOMA INVASION

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Aims: Data showing that bevacizumab in combination with temozolomide and radiotherapy improved progression-free survival in patients with newly diagnosed glioblastoma have highlighted the potential of bevacizumab as a glioma therapy. However, while bevacizumab potently suppresses angiogenesis, it has also been reported to cause invasive proliferation. This study examined gene expression in glioma cells to analyze the mechanisms of bevacizumab-induced invasion.

Methods: Human glioma U87ΔEGFR cells were stereotactically injected into the brains of nude mice. Bevacizumab was administered intraperitoneally three times per week. At 18 days after tumor implantation, the brains were removed for histopathology observations and

RNA was extracted from the orthotopic U87ΔEGFR glioma cells. Gene expression was compared between the bevacizumab-treated group and the control group using qRT-PCR arrays, which included factors such as adhesion molecules. *In vitro*, expression of gene A was compared between the bevacizumab and the control group. The cytotoxicity of bevacizumab was evaluated, and its effects on U87ΔEGFR invasiveness by scratch wound assay.

Results: *In vivo*, bevacizumab treatment increased glioma cell invasion, despite reducing angiogenesis. QRT-PCR array analysis revealed up-regulation of gene A and several other factors. *In vitro*, gene A was significantly upregulated by bevacizumab treatment. The low dose of bevacizumab did not have cytotoxicity, but cell motility was increased in scratch wound assays.

Conclusions: The increase in invasion induced by anti-VEFG therapy was associated with up-regulation of gene A in invasive tumor cells. *In vitro* studies suggest that gene A is related to tumor invasion or migration.

Paper ID: 37

GENETIC AND HISTOLOGICAL STABILITY OF 1P/19Q CO-DELETED GLIOMAS AT RECURRENCE (O)

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Aims: 1p/19q co-deleted gliomas, mostly WHO grades 2 and 3, are distinct gliomas showing response to chemotherapy(Chemo) as well as radiatiotherapy(RT), leading to significantly better prognosis. The mechanism underlying such clinical features is not well understood. To gain insights into the mechanism of their favorable behavior, we retrospectively analyzed molecular alterations at recurrence after treatment of 1p/19q codeleted gliomas.

Methods: 12 pairs of original and recurrent 1p/19q co-deleted gliomas with matched constitutional DNA samples were analyzed. Of those, 1 had RT, 2 had RT/Chemo, and 9 had Chemo only as the initial treatment. Copy number aberrations and whole exom sequencing were performed.

Results: WHO grades remained 2- 3 in all cases, indicating histological progression was rare in those tumors in contrast to astrocytic gliomas. Additional copy number aberrations were mostly deletions, and amplifications were rare. Number of point mutations did not increase significantly, with many initial mutations not observed at recurrence.

Conclusions: Those results may indicate that 1p/19q co-deleted gliomas are relatively stable genetically, and selective pressure within the tumor is not very high without strong driver mutations. Those features may contribute to the better prognosis of 1p/19q co-deleted gliomas.

Paper ID: 208

THE RELATIONSHIP BETWEEN 1P19Q LOH STATUS AND IMMUNOHISTOCHEMISTRY WITH NKX2.2 AND OLIG2

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Aims: Immunohistochemistry using antibody against NKX2.2 or olig2 is known to be useful for diagnosis of oligodendroglioma. 1p19q codeletion is specific feature of oligodendroglioma, however, it is unknown whether 1p or 19q status including partial deletion have an impact on morphologic feature of oligodendroglioma. The aim of this study is to confirm the relationship between 1p19q LOH status and immunohistochemistry with NKX2.2 and Olig2

Methods: 40 patients with glioma were enroled. 6 oligodendrogliomas, 9 anaplastic oligodendrogliomas, 2 oligoastrocytomas, 7 anaplastic oligoastrocytomas, 1 anaplastic astrocytoma and 14 glioblastomas were included. All the patients were diagnosed by neuropathologists by H.E. and immunohistochemistry. To know LOH status, Fish and/or Microsatellite Marker Analysis were performed.

Results: Positivity for NKX2.2 or Olig2 almost covered 1p or 19q abnormality. Sensitivity is 84.8% and specificity is 14.3%. True positive rate is 82.4% and true negative rate is 16.6%.

Conclusions: Immunohistochemistry with NKX2.2 and Olig2 tends to overestimate the 1p and 19q LOH status.

Health Services Research and Health Economics

Paper ID: 159

KNOWLEDGE, ATTITUDES, AND PRACTICES OF NEUROLOGIST TOWARDS CANCER PAIN

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Aims: To evaluate knowledge, attitudes, and practices of neurologist working with cancer patients in Indonesia regarding the management of cancer pain.

Methods: In a descriptive study, 175 randomly selected neurologist practicing in various type of hospital in Indonesia participated in this study. They have provided their demographic characteristics and completed a questionnaire, based on their "knowledge", "attitude" and "practice" regarding cancer pain and its management.

Results: Of 250 surveys distributed, 175 were returned. Our data indicates that 85,1% neurologists have sufficient knowledge that cancer pain was included in neurooncology area. However, most respondents (87,4%) dealed with only <10% cases of cancer pain in their practice, and most cases were refferal cases. The most common etiology of cancer pain they handled were mass effect (46,8%) and bone metastases (46,8%). Only very few caused by chemotherapy effect (3,4%).

Regarding opioid uses in patient with cancer pain, 61,1% respondents gave opioid to <50% of their patient, and another 33,2% gave opioid to ≥ 50% of their patients. Social phobia regarding opioid dependence might be the main factors of opioid delay in most cases. Our data also indicates that only 6,8% respondents ever used morfine injection, which possibly sustainable with narcophobia.

Most respondents (76%) gave anticonvulsants as adjuvant therapy for pain management. Likewise, most respondents (88,5%) used pain intensity rating as screening and compehensive pain assessment related with analgetics given.

Conclusion: The results of this survey reflect some knowledge deficiencies regarding opioid uses along with appropriate principles of cancer pain management. Concerning anticonvulsant adjuvant therapy and the use of compehensive pain assessment, neurologist in Indonesia already have sufficient knowledges, attitudes, and practices. The study may indicate the need for a continuing education programs in the area of cancer pain management.

Keywords: Attitudes; Cancer Pain; Clinical Practice; Knowledge; Neurologist.

Paper ID: 183

SURVIVAL OUTCOME OF ELDERLY PATIENTS TREATED WITH ADJUVANT RADIOTHERAPY WITH A DIAGNOSIS OF GLIOBLASTOMA MULTIFORME IN THEIR SEVENTY-FIFTH YEAR OR OLDER. (O)

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Aim: Assess outcome of the most elderly cohort of patients diagnosed with Glioblastoma Multiforme (GBM) after management with Intensity Modulated Radiation Therapy (IMRT).

Methods: Patients with GBM managed with IMRT from May 2007 to December 2015 were entered into a prospective database. Analysis was performed on patients diagnosed in or after their seventy-fifth year of life with the primary endpoint being median survival. Univariate analysis was performed with respect to survival for age 75-80 vs >80 years, ECOG Performance status (PS) of 0-1 vs 2-3, high dose of radiotherapy (60Gy) vs any hypofractionated schedule and the use of temozolomide (TMZ) vs no TMZ.

Results: Of the 108 patients diagnosed with GBM, 41 were managed with best supportive care, 4 were managed with primary chemotherapy with TMZ, 69 received IMRT and were included in the analysis. Two patients receiving primary chemotherapy received IMRT after early progression and were included in the analysis. IMRT was delivered with a hypofractionated technique (40Gy) in 60 patients and long course RT (60Gy) in 9 patients.The median age was 79 years with 59% of patients being 75-80yrs and 41% >80 yrs.

There were 61 deaths on follow-up with a median survival of 10 months (95%CI:8.1-11.9), with a projected 12-month survival of 31.1% and 24-month survival of 7.3%.

On univariate evaluation, independent predictors of survival included younger age of 75-80 years (p=0.24) and TMZ use (p<0.0001). PS and RT dose showed no significant difference between the groups.

Conclusion: The current literature underrepresents elderly patients over the age of 75 years with GBM. Despite these elderly patients having a worse prognosis, this study suggests the presence of survival benefits with IMRT in selected patients that can be further extended with addition of TMZ. Further study of this cohort and understanding of appropriate selection criteria is clearly warranted.

Paper ID: 215

NEURO-ONCOLOGY PATTERNS OF CARE IN MANDALAY GENERAL HOSPITAL, MYANMAR: A RETROSPECTIVE REVIEW

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Aims: Mandalay General Hospital (MGH) is a 1000 bed public tertiary care centre and serves as the main teaching hospital for the University of Medicine, Mandalay, Myanmar. MGH treats an estimated 12,000 general patients per day. Neuro-Oncology services provided at MGH include neurosurgery, medical oncology, radiation oncology, diagnostic imaging, pathology and neurology. We explored the Neuro-Oncology case-load and patterns of care over a 13 month period.

Methods: The Cancer Registry for MGH was interrogated to identify Neuro-Oncology patients who received care at the MGH radiation oncology clinics. All Neuro-Oncology cases registered from November 2014 to December 2015 were then selected and a retrospective chart review was conducted. Data regarding patients' age, sex, date of diagnosis, imaging results, surgical procedures performed, histological diagnosis obtained, primary brain tumours vs. secondary metastases, and treatment received were captured. Summary statistics were used to describe results.

Results: A total of 80 patients were identified; 38 (48%) male and 42 (52%) female. Median age was 45 years (range 4 months-86 years). There were 41 (51%) histology proven primary brain tumours, 31(39%) classified as secondary metastases, and 8 unclassified or data missing. In the primary brain tumour group 12(29%) had either a meningioma, schwannoma or ependymoma. Twenty eight(68%) had a glioma, and 14 had either temozolomide or radiation. Among the 31 patients in the secondary brain tumour group 11(32%) had chart documentation of attempted tissue diagnosis of their brain metastases, 20(64%) had radiation treatment, 4 had chemotherapy, and 10(32%) received supportive care only.

Conclusions: MGH case-load reflected a mix of primary and secondary tumours. A significant number of Neuro-Oncology patients had secondary metastases, and more than half proceeded to radiation. Strategies to develop resources and better clinical documentation are needed to improve Neuro-Oncology care.

Paper ID: 216

NEURO-ONCOLOGY PATTERNS OF CARE IN YANGON GENERAL HOSPITAL, MYANMAR: A RETROSPECTIVE REVIEW

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Aims: Yangon General Hospital (YGH) is a 1500 bed public tertiary care centre and the main teaching hospital for the country's premier medical school; the University of Medicine (1) Yangon, Myanmar. Neuro-Oncology services provided include neurosurgery, medical oncology, radiation oncology, diagnostic imaging, pathology, and neurology. YGH encompasses a vast catchment area, therefore patients travel variable distances to seek specialist cancer care. We explored the Neuro-Oncology case-load and patterns of care over a 16 month period.

Methods: The YGH Cancer Registry was interrogated to identify Neuro-Oncology patients who received out-patient care in either medical oncology or radiation oncology clinics at YGH. All Neuro-Oncology cases registered from September 2014 to February 2016 were then selected and a retrospective chart review was conducted. Data regarding patients' demographics, place of residence, presenting symptoms, time to presentation, imaging modality performed, histological diagnosis obtained, and treatment received, were captured. Distances travelled in kilometres were calculated. Summary statistics were used to describe results.

Results: A total of 55 patients were identified; 36 male (65%) and 19 (34%) female. Median age was 44 years (range 7-79). Duration of symptoms at time of presentation were only documented in 20 patients (36%) and ranged from 2 days to 7 months. Diagnostic imaging was performed in 53 (96%) with either CT or MRI brain. Tissue diagnosis was obtained in 31 (56%). Of those with a histological diagnosis 9 (31%) were primary glioma, of which 7 received radiation, 4 received radiation plus temozolomide, 1 received temozolomide alone. There were 25 (45%) patients with brain metastases of which 4 received supportive care only. Furthest distance travelled was 887 kilometres.

Conclusions: Majority of Neuro-Oncology patients received diagnostic imaging but only 56% could proceed to tissue diagnoses. Strategies to develop resources and better clinical documentation are needed to improve Neuro-Oncology care.

Paper ID: 172

PATIENT EVALUATION OF THE CARE EXPERIENCE FOLLOWING TREATMENT AT THE GAMMA KNIFE CENTRE OF QUEENSLAND, PRINCESS ALEXANDRA HOSPITAL.

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Aims: To assess patient satisfaction of the service provided by Gamma Knife Centre of Queensland (GCQ), Australia's first public provider of this technology. Based on the feedback received, current practice will be reviewed and service delivery optimised to ensure optimal care delivery. It is not known whether patients with benign versus malignant diseases have the same expectations and/or care needs.

Methods: Patient satisfaction surveys have been developed to assess experience and levels of satisfaction relating to interaction with clinicians, clinical and Telehealth Services, educational resources and support, day of treatment processes and follow-up care. Surveys include questions that are answered using Likert scale, supplemented with free-text comments. In early May 2016, surveys were posted to all alive patients who have completed Gamma Knife since the day of commencement of service in October 2015 (n=108). Responses are invited anonymously and returned via an enclosed self-addressed envelope. All patients receive the same survey but a simple code allows the investigators to distinguish those with benign from malignant diseases.

Results: Data collection and analysis is expected to be complete in August. Both qualitative and quantitative data will be reported to describe current patient experience and level of satisfaction with the service. Differences between the two cohorts (malignant and benign) will be explored.

Conclusion: This evaluation will give valuable information about patient satisfaction and guide subsequent changes to practice to ensure the provision of optimal patient care in Australia's first public Gamma Knife service.

Paper ID: 210

ACUTE HOSPITAL-BASED SERVICES USED BY ADULTS WITH PRIMARY OR SECONDARY BRAIN CANCER DURING THE LAST YEAR OF LIFE IN NEW SOUTH WALES, AUSTRALIA: A RETROSPECTIVE, POPULATION-BASED COHORT STUDY

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Aims: To describe patterns of acute hospital-based health services utilisation during the last year of life for adults dying with primary or secondary brain cancer.

Methods: Linked, routinely collected administrative data were analysed for all adults who died with primary or secondary brain cancer in 2007 in New South Wales. Measures were hospital and intensive care(ICU) admissions, emergency(ED) presentations, inpatient palliative care received and place of death.

Results: Of the 1,825 adults who died with brain cancer, the majority had at least one hospital episode, particularly during their final month(Table). Those with primary brain cancers spent longer in hospital, less commonly had >5 episodes and were more likely to spend time in ICU. ED presentations were similar but more of those with secondary cancer presented in the last month. Palliative care information was limited but clear involvement with inpatient palliative care services was recorded for 41% with primary and 48% with secondary brain tumours and 65% and 69% respectively had any mention of hospital-based palliative care.

	PRIMARY BRAIN CANCER (n=465)	SECONDARY BRAIN CANCER (n=1,360)
	%	%
Median age at death(IQR)	67 (57-76)	67 (58-76)
Hospitalisations		
At least one	97	99
>5 episodes	14	21
Final month of life	80	89
Median days (IQR)	42 (22-74)	33 (18-54)
>3 months	14	9
ICU admission	26	11
ED Presentations		
At least one	86	88
Median (IQR)	2 (1-3)	2 (1-3)
>3 presentations	22	23
Final month of life	37	49
Place of Death		
Hospital/hospice	68	78
Home	12	10
Nursing home	13	8

IQR - Interquartile range

Conclusions: This is the first Australian study to describe statewide, acute hospital-based health service utilisation during the last year of life for all people who died with brain cancer. Our findings provide a foundation for planning health services and optimal data collection for brain cancer patients nearing end-of-life.

Paper ID: 145

INITIAL CLINICAL EXPERIENCE AT THE GAMMA KNIFE CENTRE OF QUEENSLAND, PRINCESS ALEXANDRA HOSPITAL

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Aims: To describe the early clinical experience at Australia's first public Gamma Knife (GK) facility.

Methods: The Gamma Knife Centre of Queensland, Princess Alexandra Hospital (GCQ) was established as a statewide service and commenced treatment on 26/10/2015. All patients discussed at our multidisciplinary meeting (MDM) are recorded in a prospectively-maintained database which was analysed in May 2016.

Results: Of the 230 patients (69% benign and 31% malignant) referred, 101 patients have been treated with GK and 17 more are booked for treatment. Sixty-one (61) patients with benign disease have received GK and 55% were considered equally amenable to open surgery. There were 24 (39%) acoustic neuroma, 12 (20%) meningioma, 10 (16%) pituitary, 5 (8%) arteriovenous malformation, 6 (10%) trigeminal neuralgia and 4 (7%) other. Median interval from MDM discussion to treatment was 42 days (range 7-106). Forty (40) patients with malignant disease have received GK including 38 patients with brain metastases (42% non-small cell lung cancer, 32% melanoma, 10% breast, 5% colorectal, 8% renal and 3% other primaries), 1 recurrent glioma and 1 recurrent atypical meningioma. Median interval from MDM discussion to treatment was 12 days (range 0-35).

Referring doctors are Neurosurgeons (30%), Radiation Oncologists (20%), Medical Oncologists (14%), other specialists (30%) and General Practitioners (6%). Of the 230 patients referred, 78 live at least 100km from GCQ and 42 have utilised the Statewide TeleHealth Service for consultations.

Conclusions: The case mix observed in the first six months contains more benign disease than might be expected internationally. This likely reflects an accumulation of non-urgent cases prior to opening and may change with time. Over half of patients with benign disease previously would have been considered for open surgery. Many patients live outside the immediate metropolitan vicinity thus it appears GCQ is meeting its goal to provide a statewide service.

Paper ID: 149

KNOWLEDGE AND ATTITUDES OF NEUROLOGIST TOWARDS PRACTICE IN NEURO-ONCOLOGY

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Aims: To evaluate knowledge, attitudes, and practices of neurologist working with oncology patients in Indonesia regarding practice in neuro-oncology.

Methods: In a descriptive study, 175 randomly selected neurologist practicing in various type of hospital in Indonesia participated in this study. They have provided their demographic characteristics and completed a questionnaire, based on their "knowledge", "attitude" and "practice" regarding practice in neuro-oncology.

Results: A total of 175 neurologists responded to the survey. It was found that 85,1% neurologists have sufficient knowledge about neuro-oncology. However, most subjects (62,6%) only dealed with less than 5 cases per month. They were the main clinician treating patients with brain tumor (72%).

Amongst its distribution, most subjects (76,5%) dealed mainly with patient with primary brain tumor (>50% of their patients). Only a few treated the metastatic one. Most subjects also rarely dealed with brain tumor patients with cognitive impairment. Regarding the choices of emergency treatment, 78,2% respondents gave dexamethasone. In the case of elevated intracranial pressure, 50,8% subjects used mannitol.

Neurologist should have sufficient knowledge and skills for intrathecal chemotherapy. However, only 11,4% subjects perform intrathecal chemotherapy. Most subjects performed funduscopy (68%), electromyography for neuropathy cases (46,2%), electroencephalography for patients with seizure (64,5%), and mini mental state examination for patients with cognitive impairment (54%).

Most subjects also have sufficient skill of breaking the bad news. As much as 41,4% subjects were involved in multidisciplinary team for neuro-oncology and only 26,2% subjects have palliative team in their hospital.

Conclusion: This study indicates that knowledges regarding neuro-oncology field and interventions were adequate. Most neurologist had appropriate attitudes towards neurological examination and adequate skill of breaking the bad news. Many also involved in multidisciplinary and palliative team.

Keywords: Attitudes; Clinical Practice; Knowledge; Neuro-oncology; Neurologist.

Paper ID: 174

THE AUSTRALIAN ADOLESCENTS AND YOUNG ADULTS (AYAS) PATTERN OF CARE (POC) STUDY-CENTRAL NERVOUS SYSTEM CANCERS (O)

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Aims: 10% of adolescent and young adult (AYA) cancers involve the CNS. Improvements in cancer outcomes for AYAs have lagged behind both adult and paediatric populations. This study describes the management of a retrospective cohort of AYAs with CNS tumours treated over a 6 year period.

Methods: 15-24 year-olds diagnosed between 1/1/2007 and 31/12/2012 were identified through population-based cancer registries (Victoria, Queensland, Western Australia, Tasmania) or hospital medical records (New South Wales, South Australia). Trained data abstractors extracted diagnostic and treatment information from patient hospital records.

Results: Data was collected from 322 cases, with tumour subtypes shown in Table 1.

Table 1. CNS tumour subtypes

	%
Low Grade Glioma	37
High Grade Glioma (AA/GBM)	23
Medulloblastoma/PNET	11
Oligodendroglioma	6
Ependymoma	6
Other	17

83% were treated at adult hospitals (AH) and 17% at paediatric hospitals (PH). Interval between symptom onset and first consultation was <1 month for 51% of patients, 1-3 months for 21% and >3 months for 28%. Initial consultation was with an Emergency Department in 30%. Patients treated at a PH were more likely to have a baseline CSF sample (31 % vs 17%, $p<0.05$). Other staging investigation rates were similar across hospital type. 58% of AA/GBM and 65% of Medulloblastoma/sPNETs had surgery, radiotherapy and chemotherapy with treatment not related to hospital type. Fertility discussions for chemotherapy patients were similar across hospital types (AH 36%; PH 29%). Psychosocial screening was documented more commonly in PH (16%) than AH (4%) ($p<0.01$). Only 14 patients were enrolled on a clinical trial. Outcome data is currently being analysed.

Conclusions: This is the largest population-based study of the POC for AYAs with CNS tumours in Australia. Diagnostic and treatment approaches appear to be similar across hospital types. The low rate of clinical trial participation is concerning in the context of known poor outcomes for patients with high-grade CNS tumours.

Immunology

Paper ID: 133

IMMUNOTHERAPY WITH WT1 PEPTIDE FOR GLIOMAS; SURVIVALS, BIOMARKERS AND RESPONSE ASSESSMENT

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Aims: To report the results of clinical trials on WT1 vaccination against gliomas.

Methods: We have completed clinical trials on WT1 peptide vaccination against gliomas; phase II trial for recurrent ones (Izumoto, Hashimoto et al., J Neurosurg, 2008) and phase I for newly diagnosed glioblastomas focusing on the safe combination with temozolomide (Hashimoto et al., Cancer Immunol Immunother, 2015). Survival data were updated and biomarkers were extensively explored. Surgical samples of 20 patients who underwent surgery after vaccination were immunohistochemically analyzed on those cells and factors influencing immune function. MRI data of 60 patients in phase II trial were retrospectively re-evaluated using MRI-based response assessments of RECIST, Macdonald, irRC, RANO and iRANO, to see what is the best assessment criterion as a surrogate of survival.

Results: Although survival data was published in the papers, updated data for longer follow-up period will be presented. Especially, WT1 vaccination combined with Stupp regimen in the latter trial against glioblastomas produced progression free survival over 48 months in 5 of 7 patients recruited. We found that high level of WT1 protein and HLA class I expression on tumor cells were predictive of longer survival. Immunologically, increased WT1-specific T cells and WT1 antibody in peripheral blood after the vaccination were also predictive, and positive change of delayed type hypersensitivity (DTH) in early phase was also a biomarker. Samples from 20 non-responders revealed that tumor cells might have escaped from immunological attack by decreasing WT1 and HLA expression. Among MRI-based response assessments, RANO and iRANO were the most appropriate surrogate of survivals in early phase, as compared with other criteia.

Conclusions: From the survival data of WT1 peptide vaccination clinical trials, immunological biomarkers and mechanism of escape from immune system were revealed. We recommend using RANO and iRANO when performing clinical trials of immunotherapy against gliomas.

Paper ID: 156

A PROGRAMMED CELL DEATH BIOMARKER PREVALENCE IN PEDIATRIC MALIGNANT BRAIN TUMORS FROM KOREA: ITS POTENTIAL CLINICAL IMPLICATION (O)

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Aims: PD-L1 protein expression has been evaluated as one of prognostic biomarker in patients with several tumor types. However, there are very limited data available on the expression pattern of ligands for PD-1 and gene expression in pediatric cancers, especially highly malignant pediatric brain tumors such as AT/RT, ependymoma, medulloblastoma, and high grade gliomas; these data are needed to guide immunologically rationale design of clinical trials for immune checkpoint inhibitor in certain pediatric tumors.

Materials and methods: Pediatric patients diagnosed with AT/RT, ependymoma, medulloblastoma, and HGGs receiving standard of care from 1990 to 2014 in Seoul National University Children's Hospital and Seoul National University Bundang Hospital, and and with sufficient archival tumor specimen for immunohistochemistry (IHC) and gene expression profiling (GEP) were enrolled. Prototype assay and primary antibodies (anti-PD-L1 clone 22C3, Merck & Co.) were used for the PD-L1 IHC staining. To characterize the GEP, immune gene panel were used with nCounter system (Nanostring®).

Results: Total 89 patients were included in this study: AT/RT, 20 patients; ependymoma, 20; HGG, 21, and medulloblastoma, 28. PD 1 and PD-L1 expression were graded on a 0 to 5 scale evaluating prevalence of positive cells. Samples with scores ≥2 were considered positive. PD 1 expression was positive in 7 patients (35%) in AT/RT, 7 (35%) in ependymoma, 4 (19%) in HGG, 3 (10.7%) in medulloblastoma. PD-L 1 expression was positive in 8 patients (40%) in AT/RT, 4 (20%) in ependymoma, 4 (19%) in HGG, while all medulloblastoma samples were negative. Although it was not statistically significant, PD-L1 positive patients showed relatively poorer survival data. (GEP data will be update.)

Conclusion: AT/RT would show relatively higher expression rate of PD-L1 compared to other evaluated tumor types, and might be a candidates for treatment by immune checkpoint inhibitors targeting the PD-1 axis.

Neuroimaging and Novel Technologies

Paper ID: 35

POSITRON EMISSION TOMOGRAPHY WITH 11C-METHYL-L-METHIONINE SUPPLEMENTS MAGNETIC RESONANCE IMAGING FOR ASSESSMENT OF RESPONSE AFTER INITIATING BEVACIZUMAB IN RECURRENT GLIOBLASTOMA

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Aims: Restoration of the brain-blood barrier after administering bevacizumab (BEV) makes assessment of therapeutic response using magnetic resonance imaging (MRI) difficult. The aim of this study was to clarify whether positron emission tomography with ^{11}C-methyl-L-methionine (MET-PET) would supplement MRI for assessment of response after initiating BEV in glioblastoma.

Methods: Twenty-two patients with recurrent glioblastoma were treated with biweekly BEV plus temozolomide. Both MRI and MET-PET were performed before treatment (baseline), and 4 and 8 weeks after starting treatment. Results on MRI (response or non-response) according to RANO criteria were compared with those on MET-PET, with response defined as a tumor-to-normal brain ratio of standardized uptake value ($SUV_{T/N}$) < 1.6. Progression-free survival (PFS) was compared between responders and non-responders on MRI alone and MET-PET alone. PFS was also compared between patients showing response on both MRI and MET-PET and patients showing response on MRI but non-response on MET-PET at each time point.

Results: Frequencies of both types of patient showing response on both modalities (true-responders) and patient showing response on MRI but non-response on MET-PET (pseudo-responders) were 20-30% during 8 weeks. PFS was significantly longer in responders than non-responders on both MRI at 4 and 8 weeks and MET-PET at 8 weeks, whereas MET-PET at 4 weeks provided no information regarding outcomes. Combined assessment with MRI and MET-PET at 4 weeks did not provide any prediction of PFS, whereas the true-responders showing response on both modalities at 8 weeks exhibited significantly longer PFS than pseudo-responders showing response on MRI but non-response on MET-PET.

Conclusions: Combined assessment of MRI and MET-PET at 8 weeks can differentiate true- responders who are predicted more favorable prognosis from pseudo-responders. MET-PET supplemented MRI at 8 weeks after initiating BEV in glioblastoma.

Paper ID: 81

CCL2 INHIBITION DECREASES MACROPHAGE RECRUITMENT AND INCREASES ANTI-ANGIOGENIC EFFECT IN GLIOBLASTOMA: APPLICATION OF DSC MRI FOR IN VIVO MONITORING

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Glioblastoma multiforme (GBM) is one of the most dismal tumors in the brain, and still has poor long term survival. To overcome this problem, an alternative strategy is to target cells in the glioma microenvironment, such as tumor-associated macrophages and microglia (TAMs) (1). Macrophages depend on Chemokine (C-C Motif) Ligand 2 (CCL2/MCP-1) for differentiation.

Dynamic susceptibility contrast (DSC) MR imaging is advanced technique that provides cerebral blood volume (CBV) and can be used for the assessment of tumor response to therapy, especially for antiangiogenic therapy such as bevacizumab.

To investigate the therapeutic effect of TAM modulation, we used a CCL2 inhibitor, mNOX-E36 in an athymic rat GBM model, which significantly increased antiangiogenic effect of bevacizumab. In MRI, both tumor volume ratio (%) and relative CBV decreased in CCL2 expressing tumors with combination drug treatment (bevacizumab+mNOX-E36) compared with mono drug treatment (bevacizumab). In histology analysis, more MVD formatted by bevacizumab resistance and more macrophages recruited by CCL2 cytokine were observed in CCL2 expressing tumors with mono drug treatment than those with combination drug treatment. With these results, we believe that CCL2 inhibitor can increase the therapeutic effect of antiangiogenic treatment, which can be assessed noninvasively with DSC MR imaging.

References: 1. Nat Med. 2013 October; 19(10): 1264 - 1272

Paper ID: 79

PREOPERATIVE ASSESSMENT USING CT-BASED VIRTUAL ENDOSCOPIC IMAGES FOR ENDOSCOPIC TRANSSPHENOIDAL RESECTION OF RECURRENT PITUITARY TUMORS

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Endoscopic transsphenoidal surgery (ETSS) for pituitary tumors is quite familiar to neurosurgeons, however re-operation for recurrent cases is still challenging because of altered normal anatomy and adhesions.

Aims: To report the efficacy of CT-based virtual endoscopic images (VEIs) in preoperative noninvasive diagnosis and simulation of surgical tasks especially for recurrent pituitary tumors.

Methods: Sixteen patients with recurrent pituitary adenomas who underwent ETSS from March 2012 to April 2016 were included in this study. Prior operations were performed using microscopic transsphenoidal surgery via the sublabial approach in all cases. Preoperative DICOM CT data with and without contrast medium was transferred to a workstationSynapse Vincent, Fuji Film, Tokyo, Japanand VEIs were reconstructed. Intraoperative endoscopic surgical views were compared subjectively with the VEIs of the nasal phase and the sphenoidal phase of ETSS by the primary surgeons and assistants.

Results: Time required to reconstruct the VEIs was approximately thirty minutes. The VEIs correlated well with the intraoperative view, especially for the structures in the nasal cavity, the remnant septum and mucosa of the sphenoid sinus, the remnant sella turcica, and the course of the internal carotid arteries. However, it was difficult to reconstruct these structures for cases of large pituitary adenoma with considerable bone destruction.

Conclusions: The present study is the first report of preoperative simulation with VEI for recurrent pituitary tumors. According to our study, VEI was a valuable tool in ETSS for teaching and training purposes, as well as for preoperative planning especially for difficult re-operative cases. VEI was relatively easy to use, had a relatively short learning curve by novice as well as experienced pituitary surgeons, and was able to accurately depict individual patient anatomy for improved intraoperative orientation and potentially better outcomes.

Paper ID: 153

ECCHORDOSISPHYSALIPHORA: TYPICAL AND ATYPICAL RADIOLOGIC FEATURES

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Objective: Ecchordosisphysaliphora (EP) is a distinct clinical entity defined as a notochordal remnant found on the dorsal surface of the clivus, occurring in about 2% of autopsies. The aim of this study is to introduce the typical and atypical imaging features of EP that can be confusing with a clivalchordoma.

Methods: Forty-one patients clinically suspicious of clivalchordoma visited the outpatient clinic from June 2007 to August 2015. A retrospective review was performed with magnetic resonance imaging (MRI) and computed tomography (CT) studies to revise the diagnosis to EP.

Results: Eight of 41 patients (19.5%) manifested lesions on the dorsal surface of the clivus that were well-circumscribed, homogenous with no septations or osteolysis. The lesions were all hypointense on T1, hyperintense on T2-weighted MRI and no enhancement with gadolinium. Distinct T2-hypointense pedicle, which is the hallmark of EP was seen in 5 patients (62.5%) and defined as typical EP. Characteristic T2-hypointense rim was observed in 3 patients and defined as atypical EP (37.5%). The mean largest diameter of the lesions was 1.1 cm (0.6-1.8 cm). Size of the lesions did not change in all patients who were followed for a mean 3.6 years (1.4-8.2 years) by separate MRI scans done every 6 months to 1 year.

Conclusion: EP and clivalchordoma represent different spectrum of the same pathology. As the two lesions have a completely different prognosis, precise knowledge of the imaging features of EP is very important. Accurate diagnosis is essential for proper treatment planning.

Keywords: Clivalchordoma,Computed tomography, Ecchordosisphysaliphora, High-resolution imaging, T2-weighted magnetic resonance imaging

Paper ID: 178

PREDICTING PATTERNS OF FAILURE IN TEMPORAL LOBE GLIOBLASTOMA MULTIFORME: IMPLICATIONS FOR NOVEL RADIATION THERAPY TARGET VOLUME PROTOCOLS.

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Aims: Radiation therapy(RT) target volume protocols for high-grade glioma are based on determination of gross tumour volume (GTV) with uniform (isotropic) expansion to a Planning Target Volume (PTV). However infiltration may occur along neural pathways that are non-isotropic from initial tumour site. To aid design of novel RT protocols, patterns of failure(PoF) of Temporal Lobe(TL) Glioblastoma Multiforme(GBM) following treatment was

assessed in relation to normal TL anatomy and neural pathways.

Methods: Patients managed with IMRT for GBM between 03/2007 and 07/2014 were analysed for TL location and failure pattern. Of 335 patients, 100 were located in TL and 86 had radiological progression. Tumour location and subsequent relapse were subdivided into 5 local TL sites (anterior, lateral, medial, posterior and superior); 5 adjacent regional sites (occipital lobe, inferior frontal lobe, caudate or internal/external capsules, fornix and trigone of ventricle or thalamus), and 5 distant failure sites (ventricles, contralateral hemisphere, brainstem, leptomeninges and spine). Infiltration sites were correlated with a standard trachtography atlas and broadly categorised into anterior, superior, medial and posterior pathways. Analysis was conducted on PoF in relation to initial location, failure sites and neural pathways.

Results: At diagnosis, 98% of tumours were confined to the TL though 29% involved more than one TL subsite. At first recurrence, 41% of failures were confined to the TL sites alone; 33% extended to regional sites; and 26% failed at distant sites. Whilst only 19% of patients had extension along neural pathways at diagnosis, at relapse this had increased to 53%. Initial tumour location within TL predicted for local subsite recurrence ($p<0.0001$), regional site recurrence ($p=0.004$) and neural pathway recurrence ($p=0.005$), but not distant sites ($p=0.081$).

Conclusion: TL GBMs relapse with predictable pattern related to initial TL subsite and along neural pathways. This knowledge can be utilised in design of novel RT Protocols.

Paper ID: 139

MAGNETIC RESONANCE SPECTROSCOPY DETECTION OF HIGH LIPID LEVELS IN INTRAAXIAL TUMORS WITHOUT CENTRAL NECROSIS: A CHARACTERISTIC OF MALIGNANT LYMPHOMA

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Aims: The differentiation of malignant lymphomas from gliomas or malignant gliomas by conventional MRI can be difficult. The authors studied Gd-enhanced MR images to obtain a differential diagnosis between malignant lymphomas and gliomas without central necrosis or cystic changes and investigated the diagnostic value of single-voxel proton MR spectroscopy ((1)H-MRS) using different parameters, including lipid levels.

Methods: This was a retrospective study of patients with primary malignant CNS lymphoma (n = 17) and glioma (n = 122 [Grades I, II, III, and IV in 10, 30, 33, and 49 patients, respectively]) who were treated between 2007 and 2013. The authors focused on 15 patients with homogeneously enhanced primary malignant CNS lymphomas and 7 homogeneously enhanced gliomas. Images of all the included tumors were acquired with (1)H-MRS at 3 T, and the diagnoses were histologically confirmed.

Results: Using a short echo time (1)H-MRS, large lipid peaks were observed in all 17 patients with a malignant lymphoma, in 39 patients (79.6%) with a Grade IV glioma, and in 10 patients (30.3%) with a Grade III glioma. A focus on homogeneously enhanced tumors revealed large lipid peaks in 15 malignant lymphomas that were free of central necrosis on Gd-enhanced T1-weighted images. Conversely, in the 7 homogeneously enhanced gliomas (glioblastoma and anaplastic astrocytoma, n = 2 each; anaplastic oligodendroglioma, diffuse astrocytoma, and pilomyxoid astrocytoma, n = 1 each), lipid peaks were small or absent.

Conclusions: Large lipid peaks on (1)H-MRS images of tumors without central necrosis were characteristic of malignant lymphomas. Conversely, small or absent lipid peaks in intraaxial tumors without central necrosis were strongly suggestive of glioma.

Paper ID: 61

PREOPERATIVE MUSCLE WEAKNESS AND DEMYELINATION OF THE CORTICOSPINAL TRACT IN PATIENTS WITH BRAIN TUMOR – USING DIFFUSION TENSOR IMAGING

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Aims: Diffusion tensor imaging (DTI), a magnetic resonance technique, has recently been applied to evaluate white-matter degeneration in patients with brain tumor. Recent reports have shown that the presence of motor weakness of the patients having brain tumor is significantly related to a low fractional anisotropy (FA) value in the corticospinal tract on the affected side. The aim of this study was to investigate whether FA of the posterior limb of internal capsule (PLIC) is associated with FA of the cerebral peduncle (CP) in patients with brain tumor.

Methods: Thirteen patients who have hemiparesis caused by brain tumor were included in this retrospective study. Only those tumors located close to the PLIC but without involvement of the motor cortex. Preoperatively, all patients underwent MRI. Two regions of interest on PLIC and CP were set bilaterally using DTI. FA values were assessed using FSL. For comparisons between affected and unaffected sides of FA, paired t-tests were separately performed PLIS and CP. In subsequent analyses, the ratio FA values (rFA) between in both sides of the PLIC-rFA and CP-rFA were calculated. Correlations between PLIC-rFA and CP-rFA were also calculated using Spearman rank-correlation coefficient. Statistical significance was defined as $P<0.05$.

Results: The values of FA (PLIS and CP) in the affected side were significantly lower than those of the unaffected side, respectively ($p<0.05$). PLIC-rFA showed a significant positive correlation with CP-rFA($r=0.57 p<0.05$).

Conclusions: These results suggested that reduced FA values in PLIS were attributable to infiltrated or compressed by tumor. Reduced FA values in CP could have been due to axonal loss and /or demyelination of the corticospinal tract. Assessing the FA values of the CST before surgery may be useful in predicting the muscle strength after surgery.

Paper ID: 103

THE SURGICAL STRATEGY OF MANAGEMENT FOR SOLID HEMANGIOBLASTOMAS INVOLVED MEDULLA OBLONGATA

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Objective: Hemangioblastomas involved medulla oblongata present the most challenge for neurosurgeon because of high disability and mortality in patients. This article's aim is to describe and analyze the presentation, radiographic features, surgical management, and outcomes of patients with pathologically proven hemangioblastomas located in medulla oblongata.

Material and methods: We retrospectively reviewed and analyzed the medical recorders of 35 patients with solid hemangioblastomas located in medulla oblongata in the past 10 years.

Results: Sixteen female and 19 male patients with solid hemangioblastomas located in medulla oblongata (mean 42.5 years) were included in the study, represented 12.2% of all single intracranial hemangioblastoma in the same period. Primary manifestations included headache (82.1%), paraesthesis (75.3%), ataxia (59.1%), and pyramidal sign (62.8%). The disease often attacked young adults, and the diagnosis often is relying on MR imaging and DSA. Tumors located in the medullary oblongata (17/35), ponto-oblongata (8/35), and cervicomedulla (11/35). The diameter was small (2cm), large (2-4cm), giant (4cm) in 8, 20, 7 cases, respectively. Preoperative embolization was performed in 16 cases. Total tumor removal was accomplished in all patients. Postoperative death occurred in 3 cases (8.57%), long-term follow-up (mean 89.5 months) revealed good quality of life in 28 cases, and recurrence in 4 cases.

Conclusion: Surgical removal for hemangioblastoma in medulla oblongata is still a high risk and a challenge for neurosurgeon. With full understanding of the characteristics of lesion, combine with preoperative embolization, intraoperative excellent microsurgical techniques and perioperative management, is helpful to total removal and can improve the quality of life.

Paper ID: 105

MICROSURGICAL MANAGEMENT OF BRAINSTEM NON CYSTIC HEMANGIOBLASTOMAS

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Objective: Non cystic Hemangioblastomas of the brainstem is one of the most challengeable surgeries for the neurosurgeon. In an attempt to clarify some of the uncertainty about the operative treatment under the guide of DTI and electrophysiological monitoring of these lesions and its outcome, the authors reviewed all cases in which resection of brainstem hemangioblastomas was performed at West China hospital during a 7-year period.

Methods and results: 28 consecutive patients (16 male and 12 female patients [mean age 41.3 years; range 16 - 49 years]) with brainstem hemangioblastomas were included in this study (mean follow-up period, 46.3 months; range 17-72 months). Serial examinations, hospital charts, magnetic resonance images, and operative records were reviewed. To evaluate clinical course, clinical grades were assigned to each patient before and after surgery. Preoperative neurological function was the best predictor of long-term outcome. In addition, patients who underwent CNS surgeries for hemangioblastomas were more likely to improve or to remain neurologically stable under the guide of DTI and electrophysiological monitoring. Tumor size or the location of the tumor did not affect outcome. No patient was neurologically worse after brainstem surgery. At long-term follow-up review (mean 46.3 months), only 2 patient had declined neurologically.

Conclusions: Brainstem non cystic hemangioblastomas in patients can be removed safely; they generally should be resected when they become symptomatic or when the tumor has reached a size such that further growth will increase the risks associated with surgery, or in the presence of bleeding. Magnetic resonance imaging and DTI for preoperative evaluation and intraoperative electrophysiological monitoring are both important. Presurgical embolization is unnecessary. The goal of surgery is complete resection of the lesion before the patient experiences a disabling neurological deficit.

Paper ID: 25

BEVACIZUMAB TREATMENT FOR THE MASSIVE LESION EMERGING AFTER THE RADIOTHERAPY FOR MALIGNANT GLIOMA

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Aims: Because blocking vascular endothelial growth factor from reaching leaky capillaries is a logical strategy for the treatment, we reasoned that bevacizumab might be an eective treatment on recurrent malignant glioma and

radiation necrosis (RN). In this study, the authors examined to dierentiate RN from recurrent malignant glioma, and evaluated the results of bevacizumab treatment in each diagnosis.

Methods: Four patients of malignant glioma (2 glioblastomas and 2 anaplastic astrocytomas), which demonstrated symptomatic massive lesion after radiotherapy, were involved in this study. All four patients were treated with bevacizumab on a 10 mg/kg biweekly (one cycle), for a total dose of 30 mg/kg (3 cycles) or furthermore. RN was dierentiated from local recurrence in all four patients on the basis of 11C-methionine positron emission tomography and/or clinical course. Clinical evaluation and MRI studies were obtained after bevacizumab treatment in all cases repeatedly as possible.

Results: Two patients were diagnosed as RN, and another two patients as tumor recurrence. Of the two patients with RN, neurological dysfunction was distinctly alleviated after bevacizumab treatment. Other two patients demonstrated no remarkable improvement in neurological dysfunction after bevacizumab treatment. Of all the two patients with RN, post-treatment MRI performed after the bevacizumab therapy showed a significant reduction of the massive lesion.

Conclusions: We concluded that bevacizumab could control the symptomatic massive lesion occurring after radiotherapy, and it might be more eective with the patients of RN, than with those of recurrent tumor.

Paper ID: 97

FLUORESCENCE GUIDED RESECTION OF INTRACRANIAL GLIOMAS

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Chao Ke[1], Ke Sai[1], Zheng-he Chen[1], Yin-sheng Chen[1], Ji Zhang[1], Xiao-bing Jiang[1], Zhen-qiang He[1], Hao Duan[1], A-du Fu[1] and Yang Wang[1]

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Aims: To investigate the role of fluorescence guidance in the resection of intracranial gliomas.

Methods: Sodium fluorescein-guided resection under Zeiss Pentero 900 microscope was performed in 24 patients with intracranial glioma between March 2015 and March 2016. The demarcation and residue of gliomas were decided with fluorescein guidance. The correlation between the histological characters and fluorescence intensity was analyzed. The extent of resection (EOR) was also explored.

Results: Clinical data of 24 patients with glioma (10 glioblastoma multiformes, 3 anaplastic oligodendrogliomas, 1 anaplastic ependymoma, 3 astrocytomas, 4 oligodendrogliomas, 3 pilocytic astrocytomas) were analyzed. Among 24 patients, total resection was achieved in 22 cases and subtotal resection in 2 cases. No allergic reactions and surgery-related neurological complications such as hemiplegia and aphasia were recorded. Among 11 patients who were followed up for 10 months, no recurrence was found. The intensity of fluorescence of the tumor tissue was correlated with the histological grade.

Conclusions: Fluorescence guided surgery facilitates the demarcation and resection of glioma. Tumour tissue with strong fluorescence should be resected.

Paper ID: 66

DIFFERENTIATING PRIMARY CENTRAL NERVOUS SYSTEM MALIGNANT LYMPHOMA FROM GLIOMA BY MAGNETIC RESONANCE SPECTROSCOPY

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Aims: Primary central nervous system lymphoma (PCNSL) is an uncommon tumor that represents 3-5% of primary brain tumors. PCNSL is highly sensitive to chemotherapy and radiotherapy. The impact of the extent of resection in survival is relatively low. On the other hand, in glioma (especially in high grade glioma), the treatment preference is a maximal safe resection, followed by chemotherapy and radiotherapy. Therefore, thenoninvasive differentiation of these tumors may be useful in the clinical management. However radiographic differentiation of PCNSL from glioma on conventional imaging is challenging. The aim of this study is to assess whether 1H-MRS may be useful to discriminate glioma and PCNSL.

Methods: Fifty seven patients with glioma (astrocytic tumor 47 and oligodendroglial tumor 10) and 14 patients with PCNSL underwent conventional single voxel short echo time MRS prior to surgery. We also conducted integrated analyses of clinical samples (48 glioma and 39 PCNSL tumor samples) to examine expressions of various metabolic enzyme (ISYNA1, etc.) in gliomas and PCNSLs. Differences between glioma and PCNSL were assessed using the Mann-Whitney U nonparametric test.

Results: A MRS analysis demonstrated lower levels of *myo*-inositol in PCNSL. Interestingly, *myo*-inositol levels were significantly decreased in PCNSL compared to astrocytic tumor ($p < 0.001$). Through an analysis of metabolic enzyme in *myo*-inositol pathways, the expressions of inositol 3-phosphate synthase (ISYNA1) were reduced in PCNSL compared to astrocytic tumor ($p < 0.05$).

Conclusions: Our study provides new insight into *myo*-inositol metabolism alteration in gliomas and PCNSLs. The detection of *myo*-inositol by MRS may be useful in differentiation in glioma and PCNSL patients.

Keywords: MR spectroscopy, glioma, primary central nervous system malignant lymphoma, *myo*-inositol

Paper ID: 48

PRE AND INTRAOPERATIVE PREDICTIVE FACTORS THAT DIFFERETIATE GENETIC SUBGROUPS OF ADULT SUPRATENTORIAL GLIOMAS

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Kazuhiro Murayama[2], Hikaru Sasaki[3], Masanobu Kumon[1], Yuya Nishiyama[1], Shigeo Ohba[1], Joji Inamasu[1], Masato Abe[4], Mitsuhiro Hasegawa[1] and Yuichi Hirose[1]

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Introduction: Clinical significance of genetic subgrouping of gliomas has been validated by its strong association with prognosis of patients. Recently, we investigated *IDH1/2* and *TP53* mutations via Sanger sequencing for adult supratentorial gliomas and reported that PCR-based sequence analysis classify gliomas into three genetic subgroups in widely available methods; *IDH* mutant gliomas without *TP53* mutations, *IDH* and *TP53* mutant gliomas, and *IDH* wild-type gliomas. In the present study, we investigated the correlation radiological features including computed tomography (CT) and magnetic resonance imaging (MRI) with genetic subgroups.

Methods: We examined 167 adult patients with supratentorial glioma who underwent an initial surgery at Fujita Health University between 2005 and 2015. The tumor characteristics were preoperatively evaluated using CT and/or MRI including MR spectroscopy (MRS). We collected clinical information for preoperative factors including gender, age at onset, laterality, location of tumors, calcification on CT, contrast enhancement (CE) on MRI, quantification of tumor metabolites analyzed by MRS, and intraoperative 5-aminolevulinic acid (5-ALA) fluorescence.

Results: Age at diagnosis, location of tumor, CE, and 5-ALA fluorescence were highly statistically significant predictive factors to distinguish *IDH* mutant and wild-type gliomas ($p < 0.0001$ for all factors). On the other hand, calcification and laterality were statistically significant predictive factors for separating *TP53* wild-type and *TP53* mutation in *IDH* mutant gliomas ($p = 0.0023$ and 0.0009, respctively). In addition, quantification analysis based on MRS showed that lipid13/tCho ratio can be a statistically significant marker to differentiate *TP53* wild-type and *TP53* mutation in *IDH* mutant gliomas ($p = 0.0255$).

Conclusions: In this study, we showed several pre and intraoperative statistically significant predictive factors for supratentorial gliomas. These results could help us to plan appropriate management including surgery and adjuvant therapy for glioma patients.

Paper ID: 36

ATYPICAL FEATURES ON MAGNETIC RESONANCE IMAGING OF PILOCYTIC ASTROCYTOMA

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Pilocytic astrocytoma, which is classified as a grade I astrocytic tumor by the World Health Organization, is the most common type of glioma in children and young adults. Pilocytic astrocytoma generally appears as a well-circumscribed, contrast-enhancing lesion, frequently with cystic components on magnetic resonance imaging (MRI). However, it has been reported that the MRI appearance of pilocytic astrocytoma may be similar to that of high-grade gliomas in some cases. We here report on 6 cases of pilocytic astrocytoma with atypical MRI findings, including small cyst formation, heterogeneously enhancing tumor nodules, irregularly enhancing tumor nodules, and enhancing tumor nodules with internal hemorrhage. All tumors were successfully resected, and the histological diagnoses were pilocytic astrocytoma. When the tumor is located near a cerebral cistern or ventricle, the risk of leptomeningeal dissemination is increased. Furthermore, partial resection has also been associated with a higher risk of recurrence and leptomeningeal dissemination. To date, all but one patient are alive and recurrence-free. Because the preoperative diagnosis influences the decision on the extent of resection and because of the high risk of leptomeningeal dissemination associated with these tumors, careful and correct diagnosis by MRI is important.

Paper ID: 47

ANALYSIS OF 11C-METHIONINE 4D DYNAMIC PET FOR GLIOMA

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Aims: This study assessed whether dynamic imaging of 11C-methionine (MET) uptake on positron emission tomography (PET) is useful for differential diagnosis of brain tumour histology.

Methods: 139 patients diagnosed with brain tumours between March 2012 and October 2015 were enrolled. No patients received prior surgery, and diagnoses were made from tumour specimens obtained during surgery. Patients with newly diagnosed brain tumours [8 diffuse astrocytoma (DA), 27 oligodendroglioma (OD), 21 oligoastrocytoma (OA), 23 anaplastic astrocytoma (AA), 10 anaplastic oligodendroglioma (AO), 19 anaplastic oligoastrocytoma (AOA), and 31 glioblastoma multiforme (GBM)] underwent a MET-PET study. In dynamic MET-

PET studies, we started a 35-minute emission scan in 3-dimensional mode at the time of tracer administration. Emission recording consisted of 14 time frames. Maximum MET SUV tumour/normal frontal cortex uptake ratio (T/N ratio) was calculated by dividing maximum SUV for tumour by mean SUV of contralateral normal frontal cortex, respectively, and evaluated semi-quantitatively.

Results: The time activity curve of the MET T/N ratio was divided into three patterns. Type 1: dynamic decrease of early phase and plateau of late phase was seen in DA; Type 2: dynamic increase of early phase and plateau of late phase was seen in AA and GBM; Type 3: dynamic increase of early phase and gradual decrease of late phase was seen in OD, OA, AO and AOA. Maximum T/N ratio was significantly higher for GBM than for AA ($p<0.0002$). Setting the maximum T/N ratio of 3.486 as the cut-off for differentiating GBM from AA, sensitivity was 74.2%, specificity was 90.0%. One-way repeated measures ANOVA showed maximum T/N ratio was significantly higher for AOA than OA ($p<0.043$) in Type 3.

Conclusions: These results suggest that dynamic imaging of MET-PET in addition to evaluation of the MET T/N ratio could make the differential diagnosis of brain tumour histology.

Paper ID: 65

AUTOMATIC AND QUANTITATIVE ANALYSIS TOOL FOR CROSSOVER NEURAL CELL IN HIGH THROUGH-PUT SCREENING

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Aims: The analysis of neural cell images acquired from High Through-put Screening (HTS) experiments is tedious and labor intensive routine work for biologists, especially in the drug discovery for neuro-oncology study. Automatic neural cell quantitative analysis software tools are essential and desired by biologists. Hence, we propose an automatic and quantitative solution for crossover neural cell in HTS experiments.

Methods: We present an automatic neural cells quantitative software tool named ***NeuronCyto II***. The software has a well-designed graphical user interface (GUI) with only few selected parameters for biologists to manipulate as shown in **Fig. 1**. The software package implemented with interactive viewer to help biologists for the image processing. Hence, the analysis becomes easy and convenient. Result inspector is designed to allow biologists to interact every single neurite and their measurements in the viewer as shown in **Fig. 2**. In the software framework, two different neurite tracing algorithms are integrated. The processing of short neurites without crossovers is based on our previous work of topological dependence, and our solution for the crossovers long neurite is based on recently published directed graph theory.

Results: We compare our solution with NeuriteQuant using ground truth that annotated using NeuronJ from experience biologists. Our results show significant correlation compared to NeuriteQuant for crossovers and non-crossovers neurons.

Conclusions: ***NeuronCyto II*** is freely available for the problem of neural cells quantitative analysis in high through-put screening (https://sites.google.com/site/neuroncyto/). It is especially suitable for long and crossovers neurite outgrowth in neuro-oncology study

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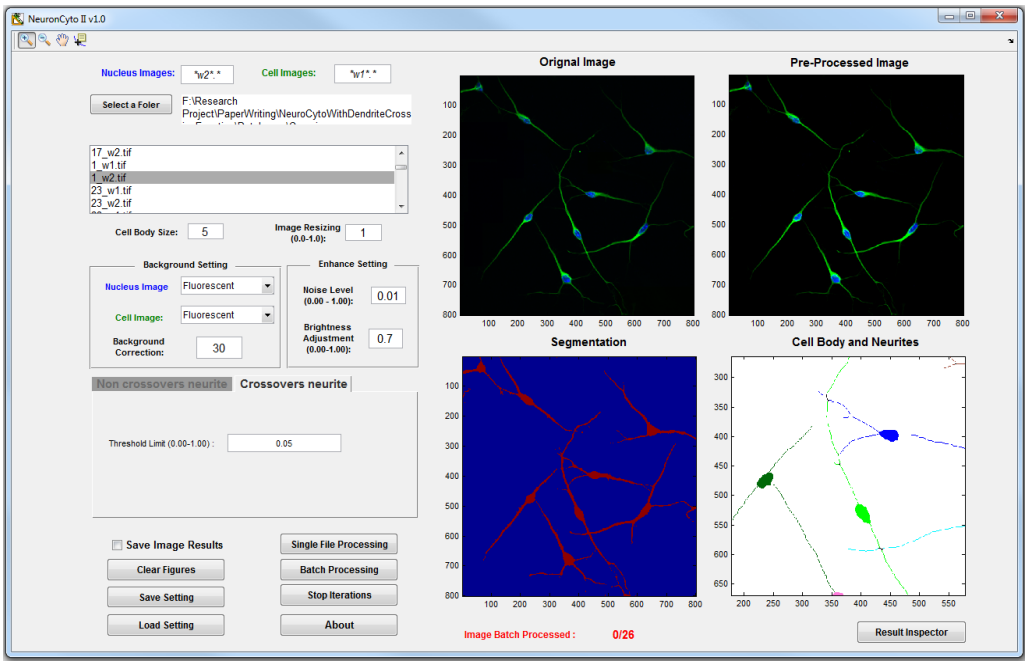

Figure 1. *NeuronCyto II* software GUI with crossovers neural cells processed.

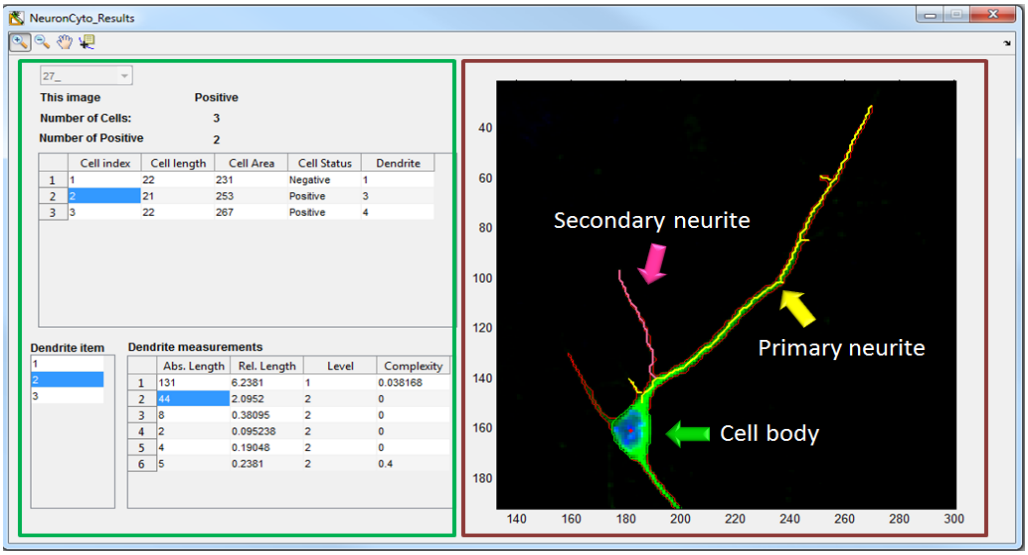

Figure 2. Neurites with their measurements using Result Inspector viewer. Green rectangle indicates numerical results and red rectangle indicates selected cell with their neurite in image viewer.

Paper ID: 72

MAPPING MOLECULAR GENETIC FACTORS IN HIGH-GRADE GLIOMA PATIENTS: A VOXEL-BASED NEUROIMAGING ANALYSIS

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Aims: Tumor location is a prognostic factor for high-grade gliomas, which may reflect the phenotype of molecular genetic factors of tumor initiate cells and predict tumor origin. Thus, the purpose of this study is to combine radiographic atlases and tumor biomarkers though a voxel-based neuroimaging analysis approach.

Methods: Sixty-five newly diagnosis and histological confirmed high-grades glioma patients' preoperative MRIs were collected. TP53 mutation, MMP-9.PTEN, MGMT, EGFR, IDH1 status of these samples were analyzed using statistical voxel-based lesion-symptom mapping (VLSM) method, which correlated the anatomical location of HGGs with the molecules profile.

Results: Vlsm analysis identified the periventricular white matter regions in the lift hemisphere, containing P53 mutation, IDH wild type and EGFR overexpression, can be predicted with a short overall survival from the time of diagnosis, in the deep region of right frontal lobe can be identified as poor prognosis region because lack of MGMT promoter methylation.

Conclusions: Our study demonstrated different phenotypes of molecules and seizure activity were related to certain brain regions. In addition, the survival associated factors-related brain regions based on structural MRI could be used in glioma operation planning and clinical survival predictions.

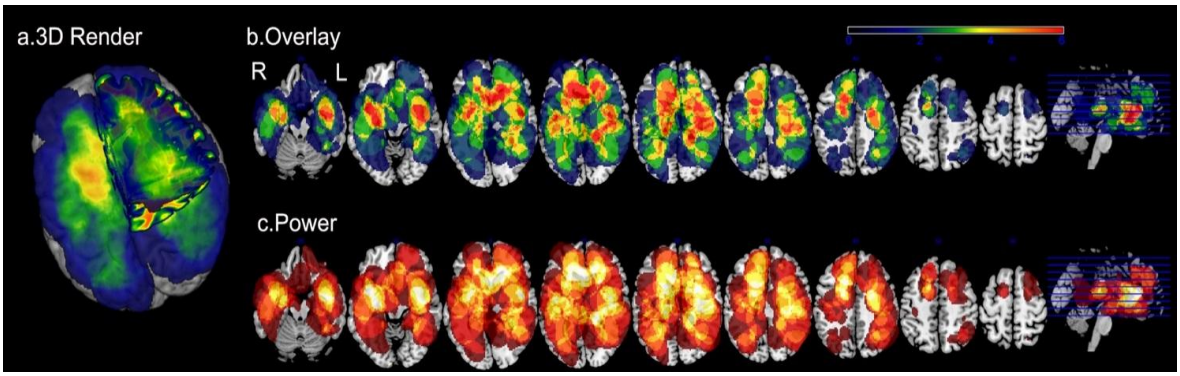

Fig 1 Overlap of lesions and power map. a. Overlaps of the brain lesions for 65 glioma patients in 3D view. b. Overlaps of the brain lesions in axial view. c. Power distribution map of all brain lesions.

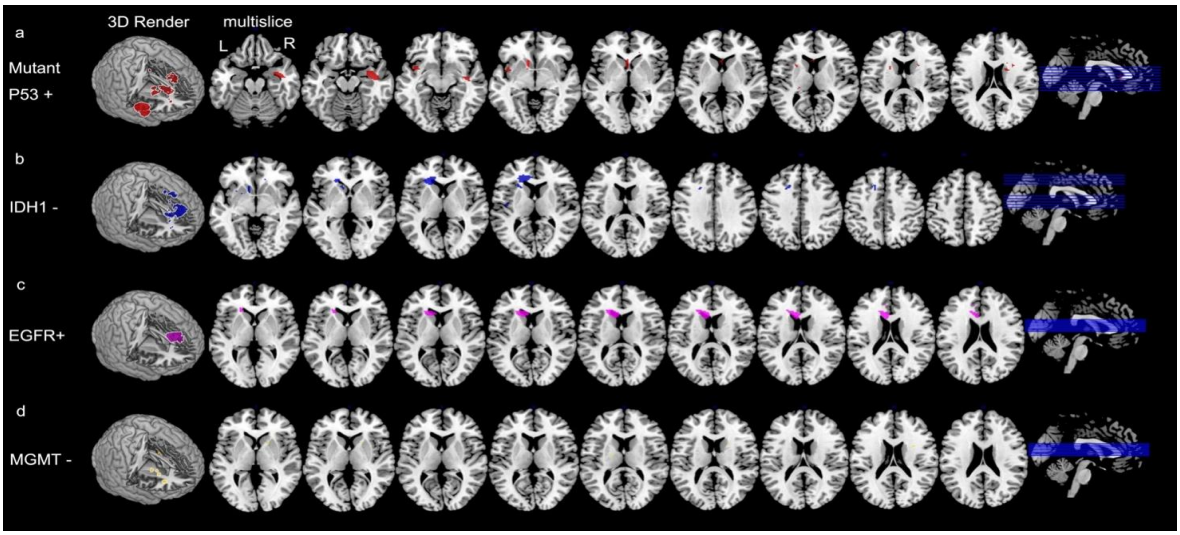

Fig2 Vlsm analyze of molecular genetic factors based on structural MRI.

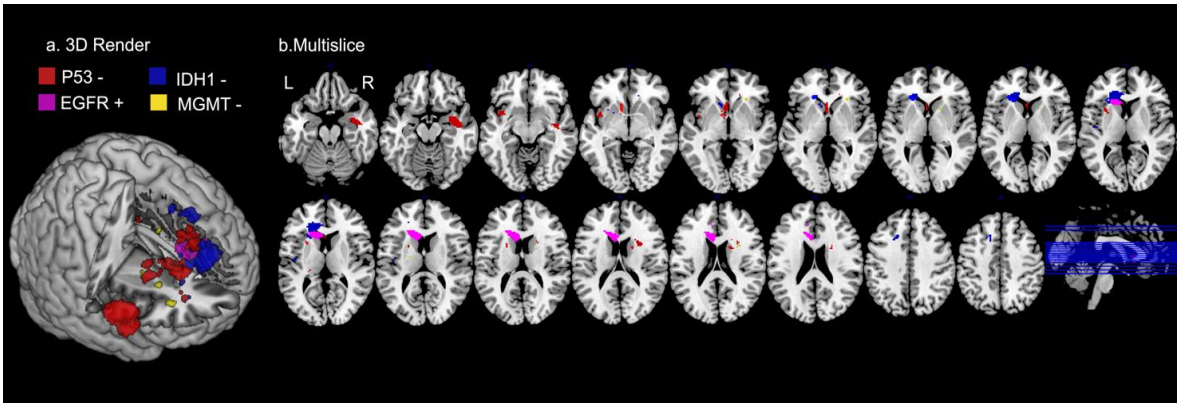

Fig 3 The merged images for VISM analysis results.
Left panel shows 3D re-construction image, right panels show mutislice in axial view.

Paper ID: 165

PROBING THE BARRIERS TO EFFECTIVE TREATMENT IN GLIOMA PATIENTS USING 18F-FDOPA AND 18F-FMISO PET IMAGING (O)

Stephen Rose [1]
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[4] *University of Newcastle*

Aims: To improve our understanding of the biological and physical barriers impacting the effective delivery of drugs and radiation therapy, we are investigating the clinical utility of FDOPA and FMISO PET imaging in patients with high-grade glioma (HGG).

Methods: To date we have acquired serial imaging data from twelve patients with newly diagnosed HGG. Patients were scanned (MRI and PET) after resection at approximately one week before the commencement of standard therapy (RT/TMZ) and at four and twelve weeks post treatment. Follow-up MRI and PET images (SUVR normalised) were registered to the first time point images. Barriers to treatment were investigated by comparing patterns of change in infiltration and hypoxia (volumes and tracer uptake) across patients with respect to treatment outcome and survival. MGMT methylation status for each patient was also measured.

Results: Despite maximal safe resection using intraoperative 5-aminoevulinic acid, nine patients presented with regions of elevated FDOPA uptake prior to commencement of therapy, indicating possible tumour regrowth. Of these patients, four exhibited increased levels of tumour hypoxia as evidenced by enhanced FMISO uptake. Regions of hypoxia were spatially coincident with regions of FDOPA uptake. Follow-up post treatment FDOPA imaging, a method we have shown to be reliable for measuring early treatment response and predicting overall survial,[1] revealed treatment failure localised to areas of tumour hypoxia pre-treatment.

Conclusions: This study highlights that tumour hypoxia, and to a lesser extent tumour regrowth before therapy, significantly impacts current treatment strategies. Molecular imaging with FDOPA and FMISO may provide a novel mechanism to better stratify patients for inclusion into clinical trials. Our preliminary findings support the potential use of a combination of PET-image guided vascular normalisation, high dose hypofractionated radiotherapy and possible follow-up neurosurgical interventions for patients presenting with hypoxic tumours.

[1] Dowson et al., Current Oncology 2014;21(1):e172.

Paper ID: 33

PET STUDIES FINDINGS CORRELATE WITH MULTI-DRUG RESISTANT GENES IN THE HUMAN GLIOMAS

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Aims: Molecular imaging modalities such as L-[methyl-^{11}C]methionine (MET) positron emission tomography (PET), [^{18}F]-fluoro-3'-deoxy-3'-l-fluorothymidine (FLT) PET, and [^{18}F]-fluoromisonidazole (FMISO) PET have revealed intra-tumoral heterogeneity in the human gliomas. Especially, imaging hypoxia with FMISO PET may predict poor response to chemotherapy. The objective of this study was to evaluate the relationship between the high-uptake regions of MET, FLT, or FMISO and the expression of multi-drug resistant genes in the malignant gliomas.

Methods: Forty-one patients with gliomas (7 WHO grade II, 14 WHO grade III, 20 WHO grade IV) were investigated with MET, FLT and FMISO-PET studies. MET, FLT and FMISO uptake studies were combined with navigation system or stereotactic localization techniques and used as a guide for stepwise histopathological evaluation (Ki-67 labeling index) throughout the tumor space. In tumors with heterogeneous PET findings, the expressions of multi-drug resistant genes

(MDR1, MRP1-5, ABCG2 and MGMT) were determined at high uptakes of some or all PET studies.

Results: All glioblastomas showed tumor uptake of MET, FLT, and FMISO. In all patients, the uptakes of each PET tracers showed intra-tumoral heterogeneity. Analysis of the histological correlation of tissue samples demonstrated the highest expression of Ki-67 labeling index within the high-uptake areas of all tracers. Overexpressions of MDR1 and ABCG2 were identified within the high-uptake areas of FLT and FMISO PET studies. The expressions of these genes were detected in the intra-tumoral microvessels and tumor cells. However, MRP 1-5 and MGMT were not influenced by these areas.

Conclusions: The maps of all PET uptakes strongly correlated with histopathology in malignant gliomas. Malignant foci can be accurately identified, and these findings have implications for prognostic evaluation and decision making for surgery and chemotherapy.

Paper ID: 60

USEFULNESS OF PRESTO-MRI STUDY FOR GRADING OF GLIOMAS

Yusuke Tomogane[1]
Yuki Miyaji[1], Tomoko Iida[1] and Shinichi Yoshimura[1]
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Aims: The principles of echo-shifting with a train of observations (PRESTO) MR imaging technique employs an MR sequence that sensitively detects susceptibility changes in the brain. Susceptibility-weighted MR imaging and PRESTO MR imaging show intracerebral hemorrhages, ferrugination, vessels, and calcification as void spots. We investigated the usefulness of the PRESTO sequence for the distinguishing between astrocytic tumors.

Methods: A total of 57 astrocytic tumors, 14 with astrocytomas, 12 with anaplastic astrocytomas and 31 glioblastomas, were included in this study. PRESTO images contained spotty signal voids within astrocytic tumors, which were defined as intratumoral hypointense dots. We counted the number of spotty signal voids and classified into the following 3 grades: grade 0 as tumor contained no spot, grade 1 as tumor contained three and under spots, grade 2 as tumor contained more than three spots or over 1 cm diameter large spots. We compared this classified grades with astrocytic tumors and Mib-1 labeling index of these tumors.

Results: The patients with astrocytomas classified 13 patients as Grade 0 and 1patient as Grade1. The patients with anaplastic astorocytomas classified 7 patients as Grade 0, 1 patient as Grade 1 and 4 patients as Grade 4. The patients with glioblastoma classified 3 patients as Grade 0, 6patients as Grade 1 and 22 patients as Grade 2. Fisher's exact tests demonstrated significant difference between each tumor groups ($P<0.05$). Mean MIB-1 labeling index of Grade 0 tumors is 11.38 (6.80-16.00). Mean MIB-1 labeling index of Grade 1 tumors is 16.49 (8.66-24.33). Mean MIB-1 labeling index of Grade 2 tumors is 22.11 (17.76-26.45). One-way ANOVA followed by Tukey's multiple comparison tests demonstrated high grade tumors had significantly high Mib-1 index.

Conclusions: Our classification of spotty signal voids within the intratumoral portion imaged by PRESTO was useful for distinguishing astrocytic tumors.

Paper ID: 74

MAPPING SEIZURE FOCI AND TUMOR GENETIC FACTORS IN GLIOMA ASSOCIATED SEIZURE PATIENTS

Yang Yuan[1]
Mao Qing[1]
[1] *West China Hospital Of Si Chuan University*

Aims: Epilepsy, which is the most common symptom accompanying gliomas, was reported as an independent favorable prognosis factor for glioma patients. However, the correlation between glioma location and epilepsy prognosis, genesis and genetic phenotypes of the glioma associated seizure (GAS) patients is far from clear, the purpose of the current study was to provide probabilistic radiographic atlases reflecting seizure susceptible regions, relationship between tumor associated biomarkers and seizure initiation and poor epilepsy prognosis areas.

Methods: Preoperative MRIs were collected from 119 newly diagnosed patients with histologically confirmed gliomas. These samples were analyzed for seizure status and tumor genetic makers (TP53 mutations, MMP-9.PTEN, MGMT, EGFR and IDH1) using a statistical voxel-based lesion-symptom mapping (VLSM) method.

Results: We found bilaterally that the frontal lobe containing regions were associated with GAS for low grades gliomas, moreover lesions with the PTEN mutation and IDH1 mutation and seizure susceptible regions were located close together and partially overlapped, Patients with preoperative tumor involving the right frontal lobe may have good seizure control; however, for the glioma-infiltrated regions in front of the precentral regions in the left hemisphere, the epilepsy prognosis is poor.

Conclusions: The current results of seizure associated molecules and specific regions on structural MRI could be used in preoperative surgical planning, seizure prognosis predictions and anti-epilepsy drug usage.

Fig 1

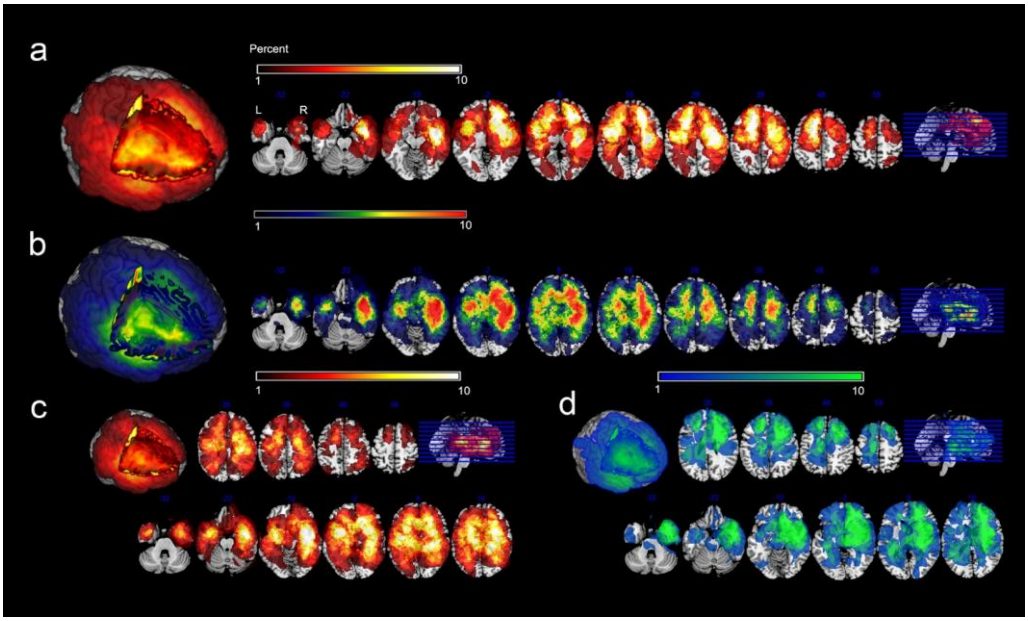


Fig 2

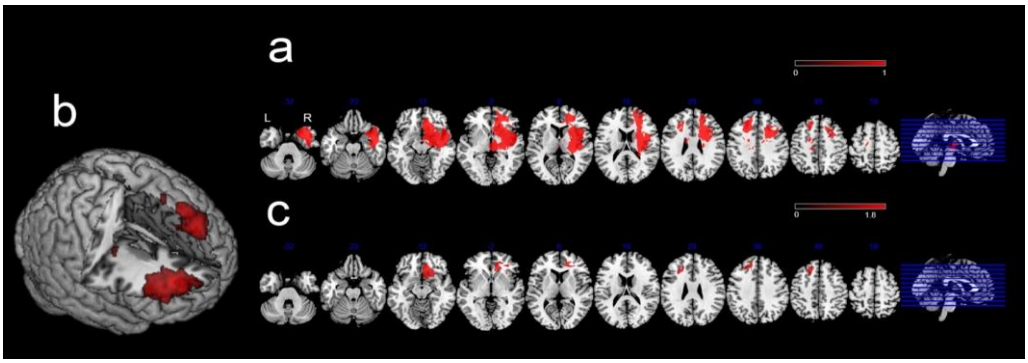


Fig 3

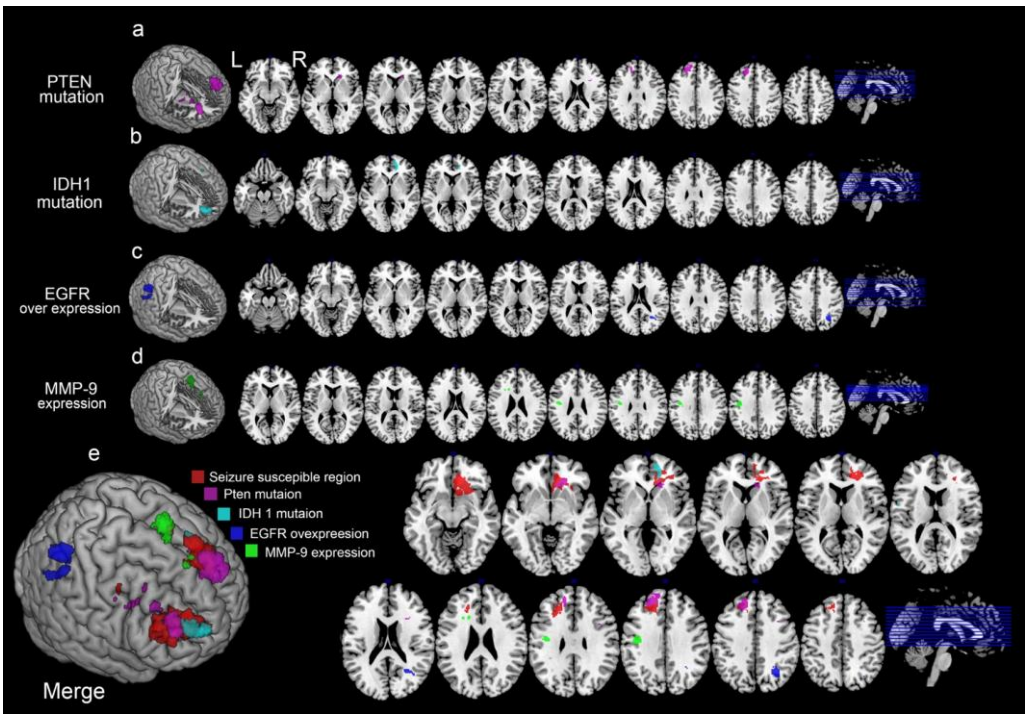
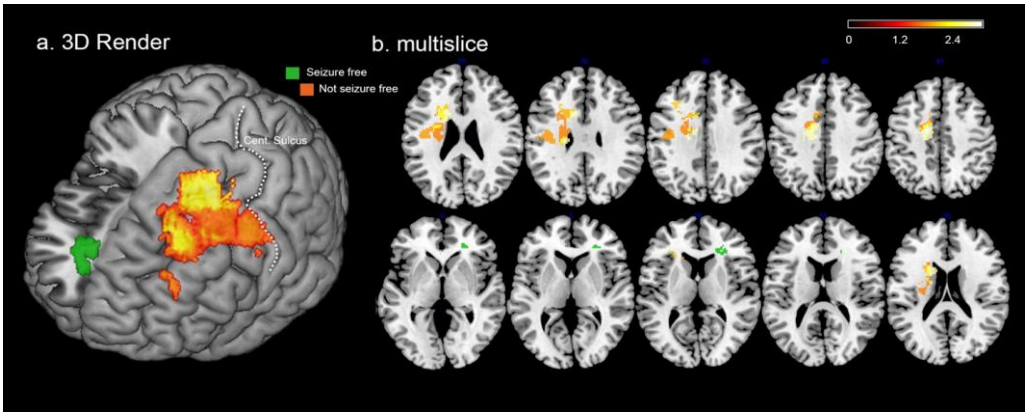


Fig 4


a. 3D Render
b. multislice
Seizure free
Not seizure free
Cent. Sulcus
0
1.2
2.4

Novel Therapeutics and Preclinical Studies

Paper ID: 188

HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR ELDERLY GLIOBLASTOMA

Yoshiki Arakawa[1]
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Objective: Several reports suggest that hypofractionated stereotactic radiotherapy (HFSRT) is effective for elderly patients with newly diagnosed glioblastoma. In the present study, we investigated the feasibility of HFSRT plus concomitant and adjuvant temozolomide (TMZ) for elderly glioblastoma.

Subjects and methods: We retrospectively analyzed 15 patients ≥ 70 years of age with newly diagnosed glioblastoma in our institution between 2011 and 2015. Patients with KPS ≥70 underwent radical resection of tumor. All patients received HFSRT with 33-42.5Gy/10-11fractions and TMZ (75mg/m2/day or 150-200 mg/m2), in combination of bevacizumab (10mg/kg, every 2 weeks) in only two patients.

Results: Eight patients underwent tumor resection and seven did biopsy. Median progression free survival (mPFS) and median overall survival (mOS) was 8.2 and 13.0 month, respectively. The grade 4 adverse events were identified in only one patient. Ten patients were treated with BEV after tumor recurrence.

Conclusion: Although this analysis was performed in a small number of patients, it demonstrate that its efficacy may not be inferior to that of the standard radiotherapy and it can shorten periods of the initial treatment. HFSRT plus concomitant and adjuvant temozolomide could be a feasible treatment for elderly patients with glioblastoma.

Paper ID: 117

TARGETING GLIOBLASTOMA'S SWEET TOOTH

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Aims: The prognosis of patients with glioblastoma (GBM) is dismal with a median survival of less than 14 months. The aim of this study is to assess the efficacy of metabolic modulation of radiotherapy.

Methods: In vitro assays were performed on a panel of commercial and primary cell lines. These include cell proliferation, colony survival, cell cycle analysis, mitochondrial superoxide production, extracelluar flux assays as well as western blotting and PCR microarray. In vivo studies were performed using an orthotopic mouse xenograph model.

Results: Metabolically, the elevated glycolysis in GBM cells was observed post-RT together with upregulated hypoxia inducible factor (HIF)-1α and its target pyruvate dehydrogenase kinase 1 (PDK1). Dichloroacetate (DCA), a PDK inhibitor currently being used to treat lactic acidosis, can modify tumor metabolism by activating mitochondrial activity and forcing glycolytic tumour cells into oxidative phosphorylation. DCA alone demonstrated anti-tumour effects both *in vitro* and *in vivo* models and could reverse the RT-induced glycolytic shift when given in combination. *In vitro*, an enhanced suppression of clonogenicity in a panel of GBM cells when DCA was combined with RT was observed. Further mechanistic investigation revealed that DCA sensitized GBM cells to RT by inducing cell cycle arrest at the G2/M phase, reducing mitochondrial reserve capacity, and increasing the oxidative stress as well as DNA damage together with RT. *In vivo*, the combined treatment of DCA and RT significantly improved the survival of orthotopic GBM-bearing mice by 48%.

Conclusion:This provides proof of concept that DCA can sensitize GBM cells to RT by modulating the metabolic state of tumour cells and improve survival in vivo. Since DCA has already completed a Phase I Study in patients with GBM, further evaluation of the combination of DCA and RT is warranted.

Paper ID: 93

EXTENDED MAINTENANCE TEMOZOLOMIDE BEYOND 6 CYCLES IS FEASIBLE AND SAFE FOR PATIENTS WITH GLIOBLASTOMA

Sonia Yi Pin Hsieh[1,2,3]
Danny TM Chan[1,2,3] and Wai Sang Poon[1,2,3]

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[2] *Prince of Wales Hospital*
[3] *The Chinese University of Hong Kong*

Aims: To compare outcomes of GBM patients received standard 6-cycle adjuvant Temozolomide to those of patients continued Temozolomide for more than 6 cycles (6+cycle).

Methods: We reviewed our brain tumour registry for identification of GBM patients during 2009-2013. The 14 eligible patients completed standard 6-cycle

Temozolomide without disease progression. They were all provided the advice of continue Temozlomide according to local practise. Progression free survival (PFS) were calculated respectively. Impacts of age, extent of resection, MGMT status and cycles of Temozolomide on PFS were analyzed. Those with a p-value less than 0.05 after univariate and multivariate analyses were considered as prognostic factors.

Results: The seven patients treated with 6+cycles of Temozolomide had a markedly improved PFS (45.5 months versus 17.0 months, p=0.003). All factors were well balanced except for extent of resection, yet no individual distinct impact on PFS was observed. Increased cycles of Temozolomide was independently in association with a significantly better PFS (HR=0.67, 95% CI 0.47-0.95, p=0.024). Two patients in 6-cycle group and one in 6+cycles group encountered with CTC Grade 1 toxicity and recovered after dose adjustment. Median overall survival for patients with 6-cycle Temozolomide was 30.6 months. Five out of seven patients in 6+cycle group were alive thus no OS data could be presented by March 2016.

Conclusions: Extended cycles of Temozolomide improved PFS with a satisfying toxicity profile.

Paper ID: 163

INHIBITION OF GLIOBLASTOMA TUMORSPHERES BY COMBINED TREATMENT WITH 2-DEOXYGLUCOSE AND METFORMIN

Eui Hyn Kim[1]
Ji-Hyun Lee[1], Yoonjee Oh[2], Ilkyoo Koh[2], Jin-Kyung Shim[1], Junseong Park[1], Junjeong Choi[3], Chang Ki Chang[1], Jong Hee Chang[1], Sun Ho Kim[1], Pilnam Kim[2], Jae-Ho Cheong[4] and Seok-Gu Kang[1]

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[2] *Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology*
[3] *Departments of Pharmacy, Yonsei University College of Pharmacy*
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Aims: Deprivation of tumor bioenergetics by inhibition of multiple energy pathways has been suggested as an effective therapeutic approach for various human tumors. However, this idea has not been evaluated in glioblastoma (GBM). We hypothesized that dual inhibition of glycolysis and oxidative phosphorylation could effectively suppress GBM tumorspheres (TSs).

Methods: Effects of 2-deoxyglucose (2DG) and metformin, alone and in combination, on GBM TSs were evaluated. Viability, cellular energy metabolism status, stemness, invasive properties, and GBM TS transcriptomes were examined. In vivo efficacy was tested in a mouse orthotopic xenograft model.

Results: GBM TS viability was decreased by the combination of 2DG and metformin. ATP assay and positron emission tomography showed that cellular energy metabolism was also decreased by this combination. Sphere formation, expression of stemness-related proteins, and invasive capacity of GBM TSs were also significantly suppressed by combined treatment with 2DG and metformin. A transcriptome analysis showed that the expression levels of stemness- and epithelial mesenchymal transition-related genes were also significantly down-regulated by combination of 2DG and metformin. Combination treatment also prolonged survival of tumor-bearing mice and decreased invasiveness of GBM TSs.

Conclusions: The combination of 2DG and metformin effectively decreased the stemness and invasive properties of GBM TSs, and showed a potential survival benefit in a mouse orthotopic xenograft model. Our findings suggest that targeting TS-forming cells by this dual inhibition of cellular bioenergetics warrants expedited clinical evaluation for the treatment of GBM.

Paper ID: 16

CENTRAL-HOLLOWING RADIATION PLANNING FOR DECREASING RADIATION DOSE

Hyo Joon Kim[1]

[1] *Presbyterian Medical Center NS dept.*

Aims: Radiosurgery to the brain tumor has limit regarding with its size and volume. Usually big sized tumor, radiosurgery is thought as harmful due to overdosed normal tissue exposure. As we know, one of important factors for treating and predicting prognosis is bioactivity in tumor marginal area. In this study, we tried central-hollowing radiation planning for decreasing total radiation dose and at the same time, suppressing tumor activity

Methods: We planned using Elekta volumetric modulated arc therapy (VMAT) and an anatomy-based treatment planning system (TPS) for single high-dose radiosurgery (SRS-VMAT) of large size brain tumor. Planning was done with both manners, conventional whole taget radiation(CR) and central hollowing(HR) radiation. And prepared total dose, its marginal dose and normal tissue exposure

Results: CR show critical exposure more than 3 cm diameter tumor size. HR show under critical radiation until 70 mm in tumor diameter with 4mm thick radiation

Conclusions: Central hollow radiation planning show possibility in radiosurgery with bigger size brain tumor.

Paper ID: 162

A BRAIN TUMOUR ORGANOTYPIC CULTURE PLATFORM TO BRIDGE THE GAP OF LEAD COMPOUND DISCOVERY AND DRUG VALIDATION

Yi Chieh Lim[1]
Kathleen Ensbey[1], Zara Bruce[1], Brett Stringer[1] and Bryan Day[1]

[1] *QIMR Berghofer Medical Research Institute*

Aims: Glioblastoma is a lethal cancer known to limit the efficacy of radio- and alkylating-based drug treatment as a result of radioresistant, a known mechanism associated with DNA repair activation. Currently, there is a lack of translatable inhibitors in the clinic to improve patient survival. Cell-based *in vitro* culture employed for drug screen programme lacks the cellular microenvironment to reflect the disease origin, leading to inconsistent lead discovery. While orthotropic animal model validates treatment modalities, the approach is slow and costly for compound library screen. The organotypic slice platform is an alternate proposal to fill the gap in the current work flow of drug discovery to reduce the attritions rate of candidate compounds by simulating an *in vivo*-like tumour engraftment. When integrated with an image-based high content screen, candidate drugs can be tested rapidly.

Methods: The image-based high content screen first identifies compounds that improves the effect of DNA damage. This is followed by further functional analysis of drug efficacy in patient-derived glioblastoma stem cells growth on coronal slides of mouse brain to recapitulate tumour recurrence.

Results: Confocal imaging is used to determine the drug efficacy by viewing the cellular changes of the tumour progression in organotypic slice culture. Several biological assays such as cell invasion, growth potential, tumour-death and DNA repair properties can be investigated in-parallel to determine the interaction of tumour cells and the microenvironment while studying the effect of cytotoxicity in the brain.

Conclusions: Organotypic culture slide model is a proposed platform to bridge the gap between cell-based drug discovery and complex animal model validation. By providing a controlled environment in which cell behaviour and novel treatment options can be manipulated, data obtained can further explore the detail mechanisms underlying the potential role in improving malignant brain tumour targeting.

Paper ID: 112

ESTABLISHING THE ROLE OF ARGININE DEPRIVATION IN CANCER TREATMENT THROUGH PRE-CLINICAL ACTIVITY OF THE RECOMBINANT HUMAN ARGINASE PEG-BCT-100 IN GLIOMAS

Herbert Loong[1]
C T Choy[1], H T Cheong [1], Y Li[1], Aden Chan[1], K P U[2] and C H Wong[1]

[1] *The Chinese University of Hong Kong*
[2] *Bio-Cancer International Limited*

Background: Arginine deprivation is a novel approach to limit arginine-dependent tumour growth. The presence of enzymes involved in the *de novo* synthesis of arginine from citrulline, argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and ornithine transcarbamylase (OTC), can influence the sensitivity of tumour to arginine depletion. We studied the preclinical efficacy of PEG-BCT-100 (also known as rhArg1peg5000), a PEGylated recombinant human arginase 1 on glioma cell lines.

Methods: Cells from 5 representative glioma cell lines (A172, M059J, M059K, T98G and U-87 MG) were either incubated in full culture medium (control), arginine free medium or PEG-BCT-100 (1U/ml) treated medium. Their corresponding IC_{50} were determined by cell viability assay. Additionally, an analysis of ASS1, ASL and OTC expression in adult gliomas determined from archival samples.

Results: All cell lines were sensitive to PEG-BCT-100 and demonstrated significant cell proliferation inhibition. Their IC_{50}, as determined by cell viability assay were 0.156 U/ml, 0.300 U/ml, 0.312 U/ml, 0.415 U/ml, and 0.522 U/ml for T98G, M059J, A172, U-87 MG and M059K respectively. In particular, cell death with both apoptosis and necrosis were observed in T98G, M059K and A172

cells. When cultured in arginine free medium, growth inhibition were only observed in M059J, M059K and T98G cells, indicating that these cells may be more auxotrophic to arginine. Determination of basal ASS1 and OTC expression in archival samples of adult gliomas showed complete absence of ASS1 (0%) and low incidence of OTC (8.3%) over-expression.

Conclusions: Arginine deprivation by PEG-BCT-100 is effective in suppressing glioma cell growth in vitro, suggesting arginine auxotrophism in gliomas and STS. Low expression of OTC, instead of ASS and ASL, may be a more important predictive biomarker for response to treatment. Confirmed absence of ASS1 and low-levels of OTC expression in archival glioma patients' samples confirm a potential target population for future clinical development.

Paper ID: 102

USING REVISED FAR LATERAL APPROACH RESECTING THE VENTRAL ASPECT OF BRAIN STEM AND OCCIPITAL MAGNUM AREA LESIONS

Lu Ma[1]

[1] *Dept. of Neurosurgery, West China Hospital*

Using Revised Far Lateral Approach resecting the ventral aspect of brain stem and occipital magnum area lesions

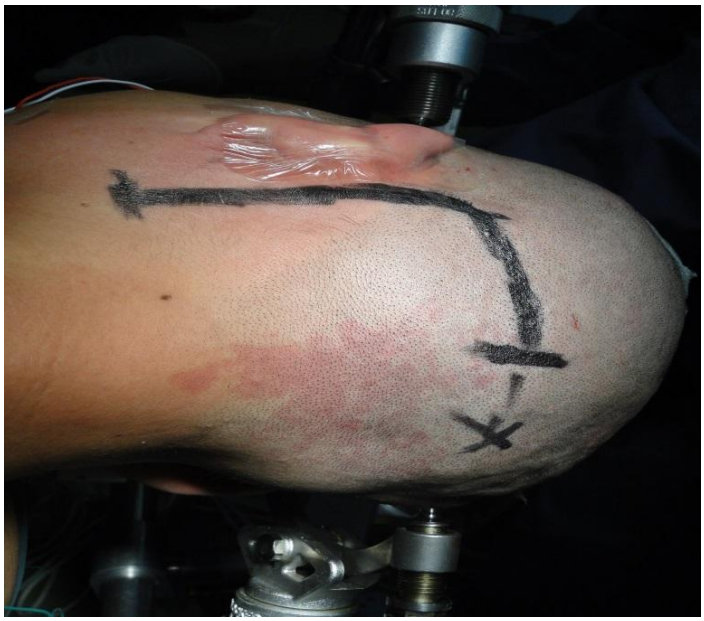
Objective: Far lateral approach is used in the lesion which locates in the ventral aspect of brain stem and occipital magnum area (OM-C1-2), for example the meningioma, schwannoma and vertebral and PICA aneurysms. We used the revised far lateral approach to evaluate the surgical outcome in the ventral aspect of brain stem and occipital magnum area lesions.

Methods: We collected 12 patients from 2013 Jan to 2015 Dec and analyse the mortality and morbidity of the cases. The complete surgical procedure is presented in this article including the presurgical Diffused Tensor image (DTI), intraoperative electrophysilogical monitoring and anatomical exposure and repair. The data was analysed to find out the relationship between the revised surgical procedures and mortality.

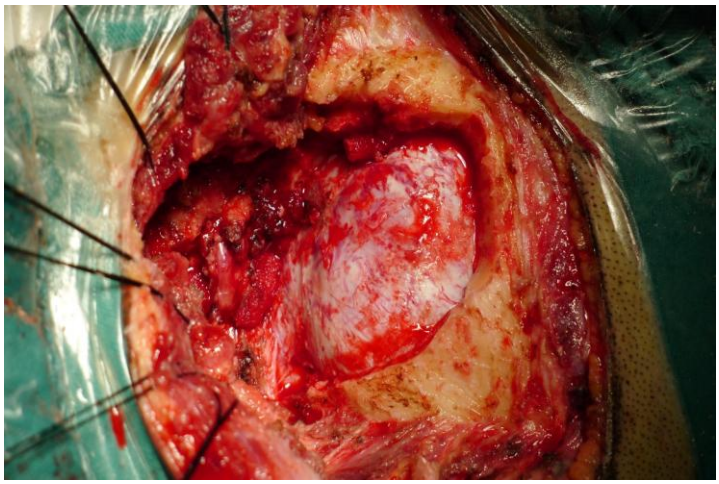
Results: The Female and Male ratio is 8/4 in our series. The 12 cases include 10 Meningiomas, 1 Arachnoid cyst, 1 Chondroma. All the patients recovered well after surgery without severe complications through the revised far lateral approach. Only two cases existed the mild symptoms of IX-XII cranial nerves.

Conclusions: Revised far lateral approach requires the carefully anatomy in the head-neck junction area. This approach is optimal depending on its ZERO traction and adequate exposure to the ventral aspect of brain stem area. It supplies the utmost protection to the brain stem, nerves and blood vessles. Less heat injury is the key during the whole surgery. Perioperative DTI evaluation and intraoperative electrophysilogical monitoring are necessary to judge the outcome of surgery.

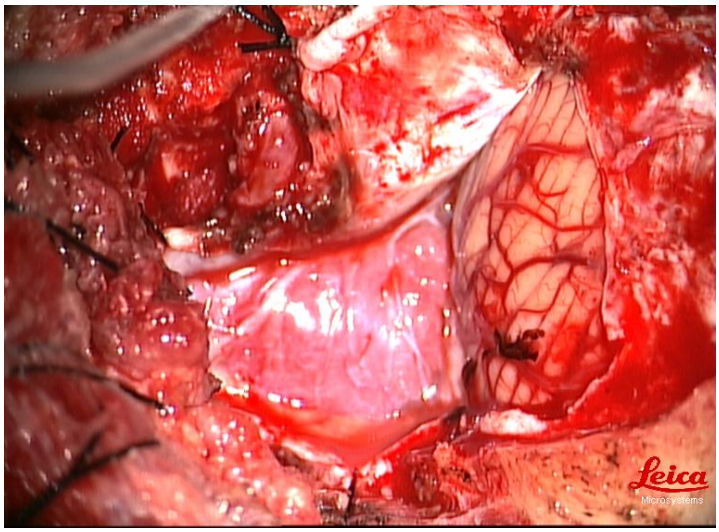
Exemplary case:



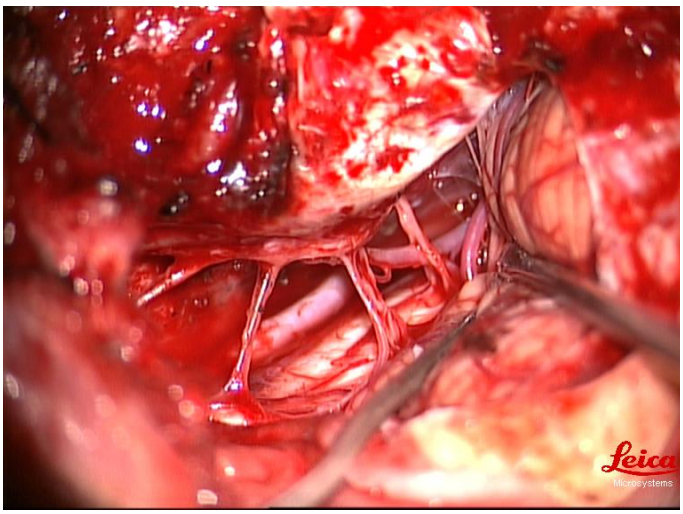
pic 1 incision design



Pic2 exposing of VA



Pic3 exposing of the tumor



Pic4 total resection of the tumor

Paper ID: 104

USING COMBINED SUPRA-INFRA TENTORIAL APPROACH RESECTING THE GIANT PETROSAL APEX INVOLVING MIDDLE AND POSTERIOR SKULL BASE LESIONS

Lu Ma[1]

[1] *Dept. of Neurosurgery, West China Hospital*

Objective: Combined supra-infra tentorial approach usually means combination of the subtemporal and presigmoid approach. It is used in the lesion which locates in the petroal apex involving middle and posterior skull base, for example the meningioma, trigeminal schwannoma. We used the combined supra-infra tentorial approach to evaluate the surgical outcome in the giant petrosal apex involving middle and posterior skull base lesions.

Methods: We collected 14 patients from 2013 Sep to 2015 Dec and analyse the mortality and morbidity of the cases. The complete surgical procedure is presented in this article including the intraoperative electrophysilogical monitoring, anatomical exposure and repair. The data was analysed to find out the relationship between the surgical procedures and mortality.

Results: The Female and Male ratio is 10/4 in our series. The 14 cases include 6 Meningiomas, 8 trigeminal schwannomas. All the patients recovered well after surgery without severe complications through the revised far lateral approach. Two cases existed the moderated symptoms of V cranial nerve and one case existed the mild symptom of VII cranial nerve.

Conclusions: Combined supra-infra tentorial approach requires the carefully anatomy in the subtemporal and presigmoid area. This approach is optimal depending on its ZERO traction and adequate exposure to the petrosal apex involing middle and posterior skull base. It supply the utmost exposure to the cavernous sinus and internal carotid artery and protection to the brain stem, nerves and blood vessles. Intraoperative electrophysilogical monitoring are necessary to judge the outcome of surgery. Less heat injury is the key during the whole surgery.

Paper ID: 160

HIJACKING THE TRANSFERRIN RECEPTOR FOR THE TARGETED TREATMENT OF BRAIN METASTASES

Joanna Macdonald [1]
Wei Duan [1] and Sarah Shigdar [1]

[1] *Deakin University*

Affecting approximately 25% of all cancer patients following primary malignancy treatment, the prognosis for patients suffering from metastatic brain tumours is very poor. Situated within a safe sanctuary provided by the blood brain barrier (BBB), treatment options for these tumours is limited, with most chemotherapeutics unable to penetrate into the brain. A promising technique to overcome this is the development of therapeutic modalities which are substrates for influx transporters present on endothelial cell membranes, in particular the transferrin receptor (TfR). Given their specificity, safety profile and stability, nucleic acid based therapeutics are ideal for this purpose.

Aims: To generate a bi-functional aptamer capable of transcytosing the BBB and deliver cytotoxic payloads to metastatic brain tumours.

Methods: The bi-functional aptamer used in this study was generated through the fusion of a 14-mer DNA aptamer against the TfR and a 19-mer DNA aptamer targeting EpCAM, a glycoprotein overexpressed in a number of solid tumours with a high incidence of metastases to the brain. Flow cytometry and confocal microscopy were employed to confirm aptamer specificity and selectivity against cells expressing the TfR or EpCAM, and a cell line expressing neither protein. Healthy mice were injected with 2 nanomoles of aptamer via tail vein injection to confirm transcytosis in a living system.

Results: The generated aptamer showed moderate affinity towards the TfR (110.32±22.04nM) and EpCAM (85.61±28.49nM), while exhibiting no binding toward the negative cell line (>1000nM). This was further supported via specific cellular internalisation. Initial in vivo work confirmed the aptamer had entered the brain.

Conclusions: These promising results demonstrate the great potential this aptamer has for the specific treatment of brain metastases. Through targeting the cancer cells specifically this transport modality has the potential to improve patient survival and mitigate neurotoxic effects.

Paper ID: 50

REPURPOSING IBUDILAST IN COMBINATION WITH TEMOZOLOMIDE FOR GLIOBLASTOMA (O)

Kerrie McDonald[1]
Wendy Ha[1], Hatice Sevim[2], Liping Chung[3], Robert Baxter[3] and Mustafa Khasraw[4]

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[2] *Recep Tayyip Erdogan University*
[3] *University of Sydney*
[4] *Royal North Shore Hospital*

Aims: Recurrence in patients with Glioblastoma (GBM) is inevitable, even in patients with O-6-Methylguanine-DNA Methyl Transferase (MGMT) methylation. We identified increased expression of the inflammatory cytokine, Macrophage Inhibitory Factor (MIF) and its receptor CD74 in patients with recurrent tumours. High levels of MIF and CD74 were associated with poor overall survival in glioblastoma patients. This study aims to determine efficacy of Ibudliast (AV411; 3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine) to block MIF expression and decrease tumour burden. Ibudilast is an anti-inflammatory drug that was developed for the treatment of bronchial asthma.

Methods: The patient derived cell lines (PDCLs) RN1 (MGMT unmethylated), BAH1 (MGMT methylated), and HW1 (MGMT methylated) were treated *in vitro* with different concentrations of ibudilast in combination with temozolomide (TMZ). Patient derived xenograft (PDX) models of GBM were developed and also treated with ibudilast in combination with TMZ. Overall survival was calculated.

Results: Regardless of MGMT status, significant synergism between ibudilast and TMZ was observed in the PDCLs. Efficacy was associated with significantly decreased expression of its targets, MIF and CD74. Downstream proteins such as Src and Akt were also significantly inhibited. The combination induced apoptosis. RN1 and HW1 tumours were established intracranially in Balb/c nude mice. Significant increases in survival times of the mice were recorded when treated with the combination.

Conclusion: Ibudilast in combination with TMZ resulted in significant blockage of MIF expression, increased apoptosis and longer survival *in vivo*. A phase I/II clinical trial for recurrent GBM patients is warranted.

Paper ID: 51

A COMBINATION OF PALBOCICLIB AND RADIOTHERAPY IMPROVES SURVIVAL IN GLIOBLASTOMA

Kerrie McDonald[1]
Swapna Joshi[1], Daniel Madani[1] and Mustafa Khasraw [2]

[1] *University of NSW*
[2] *Royal North Shore Hospital*

Aims: New treatments are urgently needed for patients diagnosed with MGMT unmethylated glioblastoma. Palbociclib (Pfizer) is a CDK4/6 inhibitor. The aim of this study was to assess efficacy of palbociclib as a monotherapy and in combination with radiotherapy on glioblastoma patient derived cell lines (PDCLs) and xenografts that were MGMT unmethylated and RB1 proficient.

Methods: A panel of 6 PDCLs were treated with different concentrations of palbociclib alone, and with radiotherapy (4Gy). We assessed the effect of treatment using clonogenic assays (the ability to form tumour colonies). We also measured expression of RB1, CDK4, CDK6, H2AX and cleaved-PARP (a measure of apoptosis). The PDCL, RN1 was intracranially injected into the brains of Nod Skid gamma mice and treated *in vivo* with palbociclib (75mg/kg; gavage) and Radiotherapy (4Gy).

Results: Palbociclib alone was effective in inhibition of tumour cell proliferation in all 6 PDCLs with concentrations ranging from 11uM to 22uM. We found significant synergy when palbociclib was administered with radiotherapy. Protein expression levels of RB1, CDK4 and CDK6 were significantly inhibited with the combination treatment and H2AX and cleaved PARP were induced. *In vivo*, significantly longer survival was observed in mice treated with the combination of palbociclib and radiotherapy. The median survival was 100.5 days (combination treatment) compared to 93 days (control); 83 days (radiotherapy only) and 92 days (Palbociclib only) (p value=0.0488).

Conclusion: The combination of palbociclib and radiotherapy significantly improves overall survival in our xenografts models. In mice, the combination is safe and crosses the blood brain barrier. A phase I/II clinical trial for Glioblastoma patients with MGMT unmethylated and RB1 proficient tumours is currently in development.

Paper ID: 144

SCREENING OF EXISTING DRUGS TO TARGET GLIOMA STEM CELLS

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Yu Dong[1], Tomohiro Kitabayashi[1], Hemragul Sabit[1], Takuya Furuta[1] and Atsushi Hirao[2]

[1] *Department of Neurosurgery, Kanazawa University*
[2] *Division of Molecular Genetics, Cancer Research Institute, Kanazawa University*

Aims: Drug repositioning is the application of known drugs and compounds to new indications. It makes us possible to jump straight to clinical studies, saving time for drug discovery, as well as the substantial cost, since agents approved for other uses already have been tested in humans, so detailed information is available on their pharmacology, formulation and potential toxicity. In glioblastoma, glioma stem cells (GSCs) are an underlying cause of tumor recurrence. Therefore, targeting GSCs for treatment is the most crucial issue. Here we tried to identify the existing drugs to target GSCs.

Methods: As first screening, drug screening Libraries (total 1,301 drugs) used for this study were: FDA-approved drug library (ENZO; CB-BML-2841J0100), ICCB known bioactives library (ENZO; CB-BML 2840J0100), kinase inhibitor library (ENZO; CB-BML-2832J0100), fatty acid library (ENZO; CB-BML-2803J0100) and phosphatase inhibitor library (ENZO; CB-BML-2834J0100). To confirm the effects of individual compounds, glioma stem cells were treated with a compound at three doses in 384-well plates, followed by analysis of cell viability with WST assay. Second screening was exclusion of drugs which have been already reported. As third screening, WST assay and neurosphere assay were performed for glioma stem cells with low concentration of candidate drugs. Subsequently, invasion and proliferation assays were performed with glioma cell lines (U87, U251, T98G, SNB19) treated by candidate drugs. Mouse glioma model made by transplantation of glioma stem cells were treated by candidate drugs.

Results: From our first, second, third screening, we selected 89, 36, 3 drugs, respectively. Then, we focused one drug and could confirm the inhibitory effect of proliferation and invasion both in vitro and in vivo.

Conclusions: We identified existing drugs which suppress glioma stem cells. We are now planning a clinical study.

Paper ID: 32

PHARMACOLOGICAL INTERVENTION IN THE PHOSPHOLIPASE A2 PATHWAY SHOWS IMPROVED POTENCY OVER TEMOZOLOMIDE IN GLIOBLASTOMA MULTIFORME CELL LINES

Phillip Nguyen[1]
Mila Sajinovic[1,2,3], Qihan Dong[4], Kieran Scott[1,2,3,5] and Paul de Souza[1,2,3,5,6]

[1] *South West Sydney Clinical School, UNSW, Liverpool*
[2] *Ingham Institute of Applied Medical Research, Liverpool*
[3] *Centre for Oncology Education and Research Translation, Liverpool*
[4] *School of Science and Health Western Sydney University, Campbelltown*
[5] *School of Medicine Western Sydney University, Campbelltown*
[6] *Liverpool Hospital, Liverpool*

Aims: Glioblastoma multiforme (GBM), a prevalent and aggressive form of brain cancer, is treated by a combination of surgery, radiotherapy and temozolomide (TMZ) chemotherapy. However, patients survive only 12-15 months, highlighting the need for better treatments. The phospholipase A_2 (PLA_2) enzymes $sPLA_2$IIA and $cPLA_2\alpha$are targets for intervention in some cancers, however, the importance of PLA_2 in GBM is largely unknown. Our aim was to determine the expression of $sPLA_2$IIA and $cPLA_2\alpha$ and the effect of pharmacological blockade of these enzymes on cell viability relative to TMZ in GBM cell lines in culture.

Methods: $sPLA_2$IIA and $cPLA_2\alpha$ expression in A172, LN229, T98G, U251 and U87MG cells was determined by ELISA and/or Western blot analysis. Cell lines were treated with increasing doses of TMZ, the selective $sPLA_2$IIA inhibitor c(2Nap)LS(2Nap)R (c2) or Wyeth-1, a selective $cPLA_2\alpha$ inhibitor, for 72 hours prior to cell viability analysis using an MTS assay.

Results: All GBM cell lines constitutively expressed $cPLA_2\alpha$ but $sPLA_2$IIA was not detected. c2 showed comparable potency to TMZ (IC_{50} 172-278μM) in 3 cell lines with improved potency in U251 (IC_{50} 88 +/-20μM) and A172 (IC_{50} 120 +/-10μM). Wyeth-1 exhibited 5-9 fold higher potency (IC_{50} 18 +/-4μM to 33 +/-4μM) over TMZ in all cell lines.

Conclusions: Both PLA_2 inhibitors showed comparable or greater potency than TMZ in all cell lines. Results are very promising and indicate that further investigation of this pathway in GBM is warranted.

Paper ID: 77

LEVETIRACETAM DOWNREGULATES O6-METHYLGUANINE DNA METHYLTRANSFERASE EXPRESSION AND SENSITIZES TEMOZOLOMIDE-RESISTANT GLIOMA CELLS

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Kazuya Aoki[1], Nozomi Hirai[1], Junya Iwama[1], Satoshi Fujita[1], Haruo Nakayama[1], Morito Hayashi[1], Keisuke Ito[1], Takatoshi Sakurai[1] and Satoshi Iwabuchi[1]

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Aims: Temozolomide (TMZ) has become a key agent in treating malignant glioma; nevertheless, its survival benefit remains dismal prognosis. Histone deacetylases are often overexpressed in cancer cells, and this leads to altered expression and activity of numerous proteins involved in carcinogenesis. Recent evidence suggests that expression of class I histone deacetylases is higher in malignant gliomas and is important in resistance to TMZ. Levetiracetam (LEV) is an antiepileptic drug that inhibits histone deacetylases, but the therapeutic effects of a combination regimen comprising LEV and TMZ are poorly understood. In this study, we found that the antitumor effects of LEV are potentiated by combining it with TMZ, especially in TMZ-resistant cell lines.

Methods: 4 glioma cell lines (U87, U251, T98, and U138) were used. We performed cytotoxicity assays using CellTiter Blue Assay.

Results: This combination significantly enhanced antitumor effects against the TMZ-resistant malignant glioma cell lines T98 and U138. This enhanced antitumor effect correlated with LEV-mediated reduction in O6-methylguanine DNA methyltransferase expression, which is important in cellular resistance to alkylating agents. In vitro, this combination enhanced apoptotic and autophagic cell death and suppressed migratory activities in the TMZ-resistant cell lines. Furthermore, an in vivo efficacy studies using an intracranial tumor model showed that combination therapy significantly increased median survival as compared with monotherapy groups.

Conclusions: Our results warrant further studies to test the efficacy of combined TMZ and LEV chemotherapy in malignant glioma.

Paper ID: 124

HISTONE DEACETYLASES INHIBITORS REGULATE MITOCHONDRIAL FUNCTION IN MALIGNANT RHABDOID TUMOUR

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David Ashley[1]

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Introduction: Deregulated cellular metabolism characterises cancer. This alteration in metabolism results from a switch from oxidative phosphorylation to glycolysis for the generation of ATP. Malignant Rhabdoid tumours (MRT) are rare, highly aggressive cancers mainly affecting children under the age of two. Previous studies have shown that restoration of the gene SMARCB1, which is genetically absent in MRT, restores histone acetylation and promotes cell cycle arrest. In addition, treatment with histone deacetylase inhibitors (HDACi) replicate the restoration of SMARCB1. This study investigated whether re-expression of SMARCB1 or treatment with HADCi affect MRT metabolism.

Methods: MRT cell line (G401), SMARCB1-inducible cell line (F22) and human embryonic kidney cell line (HEK293T) were investigated. Metabolic activity of cells with or without SMARCB1 induction or with HDACis, LBH-589, SAHA, ASH007 and ASH008, were examined using the Seahorse XF24 analyser. Wave 2.2.0 software was used to analyse the data.

Results: Metabolic analysis revealed MRT cells showed a significantly high extracellular acidification rate (ECAR) suggesting enhanced glycolytic metabolism as compared to normal HEK293T cells. Induction of SMARCB1 in F22 cells decreased glycolysis. HDACis also decreased glycolysis in MRT, but with varying potencies. LBH-589 was the most potent, reducing ECAR levels by 88%. ASH008, SAHA and ASH007 reduced ECAR by 49%, 46% and 21%, respectively.

Conclusion: Restoration of SMARCB1 expression in MRT cancer cells restores cellular metabolism to a normal, differentiated phenotype by lowering glycolysis activity. HDACi, in particularly LBH-589, also reduce glycolysis and may aid in differentiating MRT and potentially sensitising these cells to anti-cancer therapeutics.

Paper ID: 91

POST-TREATMENT INTERLEUKIN-10 LEVELS IN CEREBROSPINAL FLUID CAN PREDICT TUMOUR RECURRENCE IN DIFFUSE LARGE B-CELL LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM

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Aims: A biomarker for early diagnosis of recurrence of central nervous system (CNS) lymphoma would permit early treatment for disease attenuation and neurological deterioration. High interleukin-10 (IL-10) levels or IL-10/IL-6 ratio is an informative parameter for discriminating intraocular lymphomas from uveitis. Recently, we reported that the IL-10 level in the cerebrospinal fluid (CSF) is a potential diagnostic biomarker for CNS lymphoma (Sasagawa Y. J Neurooncol 2015). The purpose of this study was to determine whether post-treatment CSF IL-10 levels in patients with CNS lymphoma could predict tumour recurrence.

Methods: CSF IL-10 levels in 21 patients with CNS lymphoma were measured before treatment. These patients received methotrexate-based chemotherapy after pathological diagnosis. After completion of chemotherapy, CSF IL-10 levels were measured again, and were repeated following tumour recurrence.

Results: Before treatment, CSF IL-10 was detected at significant levels in all except 1 patient. In 9 of the 21 patients, the CSF levels of IL-10 were measured after completion of chemotherapy. In all 9 patients, the post-therapy CSF IL-10 level was lower (median: 2 pg/ml, range: 2-212 pg/ml) than the pre-therapy CSF IL-10 concentration (median: 28 pg/ml, range: 3-1040 pg/ml). In 6 of the 9 patients, CSF IL-10 levels were below the detection limit (2 pg/mL). Tumour recurrence occurred in 4 of 9 patients, and in these patients, the CSF IL-10 levels were elevated.

Conclusions: CSF IL-10 level may be useful not only as a diagnostic marker, but also as an indicator of the tumour state after treatment in patients with CNS lymphoma.

Paper ID: 96

INTRAOPERATIVE MAGNETIC RESONANCE SPECTROSCOPY FOR GLIOMA SURGERY

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Aims: 3-T intraoperative MRI (iMRI) detects residual tumor tissue during glioma surgery and that it helps to increase the extent of resection. However, a differential diagnosis between tumoral and nontumoral tissue at the resection border with T2-hyperintense areas in iMRI images may be difficult. The aim of this study is to examine the usefulness of intraoperative MR spectroscopy (iMRS) to detect the residual glioma tissue.

Methods: Sixteen patients with low- and high-grade gliomas underwent iMRI-assisted surgery, including pre- and intraoperative MRS measurements. Single-voxel proton MRS was performed at the resection margin in the T2-hyperintense areas of iMRI images. Peak areas under the major metabolites (N-acetyl-aspartate: NAA; choline: Cho; and creatine: Cr) resonances were estimated, and their ratios entered in the statistical analysis.

Results: Histological diagnosis of all cases were 9 glioblastomas, 3 diffuse astrocytomas, 2 oligodendrogliomas, 1 pilocytic astrocytoma, and 1 subependymal giant cell astrocytoma. Three cases were not able to detect the metabolites for bleeding and cerebrospinal fluid. The average ratio of Cho/Cr, Cho/NAA, and NAA/Cr were 1.32±0.54, 1.34±1.16, and 1.63±0.91, respectively. In 7 cases with high ratios of Cho/Cr (1.71±0.44), additional resections were performed (3 cases of GBMs and 4 cases of low-grade gliomas). Resected tissues with high ratio of Cho/Cr had residual tumor cells and high Ki-67 index. On the other hand, 6 cases with low Cho/C ratio were not performed additional resection. Finally, Gross total resections were achieved in 12 cases with no neurological complications except for one patient with hemiparesis.

Conclusions: iMRS could be used to detect residual tumor in T2-hyperintense areas around the resection cavity. iMRS may be helpful tool for an extended tumor resection.

Paper ID: 67

THE EFFICACY OF BEVACIZUMAB FOR NEWLY-DIAGNOSED MALIGNANT GLIOMA - A SINGLE INSTITUTE ONE-ARM OBSERVATIONAL STUDY

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[2] *Department of Neurosurgery, Tenri Hospital*

Aims: Bevacizumab (BEV), a monoclonal antibody against vascular endothelial growth factor, has been approved as an additional molecular targeted therapy for newly-diagnosed malignant gliomas in Japan. This study aims to examine its effectiveness for them in our institute from June 2013.

Methods: We prospectively collected the data from all patients in whom we performed removal of gliomas from June 2013 to March 2016. Fifteen patients were pathologically confirmed to have glioblastomas, two as an anaplastic oligoastrocytomas, and one as a gliomatosis cerebri. We basically apply temozolomide chemoradiotherapy and administer bi-weekly BEVs more than four weeks after the operation if an informed concent is obtained.

Results: The median follow-up period was 15.4 months (ranging 2-36 months). The median progression-free survival (PFS) was 13.8 months (ranging 2-34 months) and the median overall survival (OS) was 16.2 months (ranging 2-36 months). On the other hand, malignant glioma treated by basic temozolomide chemoradiotherapy in our institute before introduction of BEV, PFS was 8.7 months (ranging 1- 31months, 23 cases) and OS was 15.1 months (ranging 2-48 months, 20 cases).

Conclusions: We combined BEV to basic temozolomide chemoradiotherapy and obtained significant improvements in both PFS and OS in glioma patients as compared with basic temozolomide chemoradiotherapy only. Further follow-up study with more cases or RCT is necessary to prove the effectiveness of BEVs in gliomas.

Paper ID: 175

THE ONCOGENIC FUNCTION OF EPHA3 IS INDEPENDENT OF ITS TYROSINE KINASE ACTIVITY IN A CDKN2A NULL NEURAL STEM CELL MODEL OF GLIOMA

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Kate Goasdoué[1] and Andrew Boyd[1]

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Aims: Homozygous deletion of *CDKN2A* is the most common genetic alteration found in glioblastoma (GBM). It is usually detected in combination with amplification and/or mutational activation of a receptor tyrosine kinase. We have reported previously that EphA3, a receptor tyrosine kinase expressed in ~40% of GBM, is highly expressed by glioma initiating cells and has a functional role in their survival and self-renewal[1]. The aims of this study were two-fold:

(1) to investigate whether expression of EphA3 in *Cdkn2A* null murine neural stem cells is sufficient to initiate glioma formation and

(2) to investigate whether the transforming activity of EphA3 is dependent upon its tyrosine kinase activity.

Methods: Neural stem cell lines were established from *Cdkn2a* floxed mice. Bioluminescent *Cdkn2a* null neural stem cell lines were created by expression of Cre recombinase and firefly luciferase. Wild type, kinase-dead (K654R) or kinase constitutively-active (A972P) EphA3 was expressed by lentiviral transduction of these cells. Tumourigenicity was investigated by intracranial injection of transformed cells in NOD/SCID mice.

Results: Expression of EphA3 in *Cdkn2a* null murine neural stem cells was found to be sufficient to initiate high grade glioma formation in NOD/SCID mice. Both kinase-dead (K654R) and kinase constitutively-active (A972P) mutants of EphA3 initiate high grade glioma formation by *Cdkn2a* null neural stem cells.

Conclusions: Our results show that the transforming activity of EphA3 in *Cdkn2a* null neural stem cells is independent of its tyrosine kinase activity. This finding suggests that tyrosine kinase inhibitors that are being trialed as a precision medicine therapy for GBM are unlikely to abrogate the oncogenic function of EphA3 in a significant percentage of GBM.

[1]Day BW, **Stringer BW**, *et al*. (2013) EphA3 maintains tumorigenicity and is a therapeutic target in glioblastoma multiforme. *Cancer Cell* 23(2):238-248.

Paper ID: 57

5-AMINOLEVULINIC ACID-MEDIATED SONODYNAMIC THERAPY (5-ALA-SDT) USING HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) ENHANCED THE ANTITUMOR ACTIVITY BY INDUCING NECROSIS AND APOPTOSIS OF MALIGNANT GLIOMAS

Satoshi Suehiro[1]
Daisuke Yamashita[1], Masahiro Nishikawa[1], Toshimoto Seno[1], Shohei Kohno[1], Shiro Ohue[2], Takeharu Kunieda[1] and Takanori Ohnishi[1,3]

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[2] *Department of Neurosurgery, Ehime Prefectural Central Hospital*
[3] *Department of Neurosurgery, Washoukai Sadamoto Hospital*

Aims: A high invasive nature of malignant gliomas is a major cause of local tumor recurrence. To control such recurrence, novel therapies targeted towards infiltrating tumor cells are required. Here, we examined cytotoxic effects of sonodynamic therapy (SDT) combined with a sonosensitizer, 5-aminolevulinic acid (5-ALA), on malignant gliomas both in vitro and in vivo.

Methods: Using U87 and U251 glioma cells and U251$^{Oct\text{-}3/4}$ glioma stem-like cells, in vitro cytotoxicity of 5-ALA-SDT was evaluated. Cell apoptosis was analyzed by flow cytometry and TUNEL staining. Intracellular reactive oxygen species (ROS) after SDT were measured by OxySelect assay kit. In vivo effects of 5-ALA-SDT on tumor growth and survival of glioma-transplanted mice were investigated by using high intensity focused ultrasound (HIFU).

Results: 5-ALA-SDT inhibited cell growth and promoted cell morphological changes, including shrinkage, vacuolization, and swelling. Flow cytometry and TUNEL staining demonstrated that 5-ALA-SDT induced apoptotic cell death. 5-ALA-SDT generated higher amounts of ROS than the control ($p<0.05$). 5-ALA-SDT with HIFU produced a longer survival of the tumor-bearing mice compared to the control ($p<0.05$). Histological studies disclosed that 5-ALA-SDT induced necrosis and apoptosis of the tumor cells in the focused area and in the peri-focused area of the HIFU irradiation, respectively. The proliferative activity of the tumor cells in the HIFU-irradiated area was markedly decreased. Brain tissues after 5-ALA-SDT with HIFU remained normal.

Conclusions: 5-ALA-SDT was potently cytotoxic towards malignant gliomas. ROS generated by the SDT was thought to promote apoptosis of the glioma cells. 5-ALA-SDT with HIFU induced tumor necrosis in the irradiated focus area and apoptosis in the peri-focused area while the surrounding brain tissues remained normal, resulting in longer survival of the mice compared to untreated mice. These results suggest that 5-ALA-SDT with HIFU may present an effective and specific therapy for malignant gliomas, including infiltrating glioma cells.

Paper ID: 127

THE IMPACT OF BEVACIZUMAB ON MICROVESSELS IN GLIOBLASTOMA AND NORMAL BRAIN.

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[2] *Department of Pathology, Kanazawa University Hospital, Ishikawa*

Aims: Bevacizumab (BEV) for patients with malignant glioma can extend progression-free survival. However, BEV may cause severe complications, such as intratumoral hemorrhage. In present study, we examined whether BEV could affects microvessels in tumor and normal brain tissue.

Methods: A retrospective analysis was performed in 9 autopsy cases with malignant glioma who underwent tumor removal at our institution between 1998 and 2016. Pathological diagnoses were glioblastomas in 8 cases and anaplastic oligodendroglioma in 1 case. All patients were performed concomitant radiochemotherapy after tumor resection. 6 patients with recurrent tumor received BEV therapy (BEV group) and 3 patients were observed without BEV (non-BEV group). We analyzed hemosiderosis at tumor lesions and microscopic bleedings at normal lesions. Additionally, we calculated microvessel density (MVD) at both lesions and compared MVD between tumor lesions in autopsy specimens and those in primary tumors.

Results: The area of hemosiderosis that means the trace of hemorrhage tended to be larger in BEV group than in non-BEV group (8.5/mm^2 vs. 4.3/mm^2). Microscopic bleedings at normal lesions were significantly higher in BEV group than in non-BEV group (83% vs. 33%). MVD at tumor lesions was lower in BEV group than in non-BEV group (32/mm^2 vs. 65/mm^2), whereas there was no significant difference of MVD at normal lesions between BEV group and non-BEV group. In BEV group, MVD at tumor lesions was significantly lower in autopsy specimens than in primary tumors.

Conclusions: Our data suggest that BEV can suppress angiogenesis at tumor lesions. It may make microvessels fragile not only in tumor tissue but also normal brain.

Paper ID: 73

GENE THERAPY OF GLIOBLASTOMA USING A 3D-ENGNEERIED TROJAN WITH DNA NANOCOMPLEX (O)

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Mao Qing[1]

[1] *West China Hospital Of Si Chuan University*

Aims: The incomplete resection of glioblastoma always leads to poor prognosis. available treatments are ineffective for post-surgery residual cancer. Here, we show a degradable sponge containing DNA nanocomplexs, based on 3D printing technology, to eradicate post-surgery residual GBM cells.

Methods: We 3D-engineered a therapeutic device, as an oncolytic Trojan, which can match the post-surgery tumor cavity and release DNA nanocomplexs to kill the residual glioma cells. The DNA nanocomplexs was composed of pVSVMP and a degradable heparin-PEI nanogels, and could efficiently kill glioma cells after transfection.

Results: A significant number of human glioblastoma cells were apoptosis in the cancer residual model, compared with no DNA complex or no implants. Further, we demonstrate that sufficient VSVMP transfection could reduce VEGF expression and induce apoptosis genes expression in U87 cells, and finally inhibiting tumor recurrence via anti angiogenesis and promote apoptosis.

Conclusions: Our research highlight the potential of 3D conformal composites with DNA nanogels-induced inhibition of GBM cells as an novel anti residual glioma therapeutic approach.

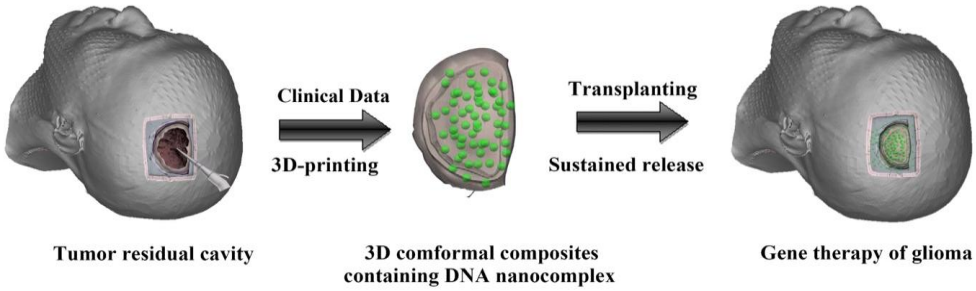
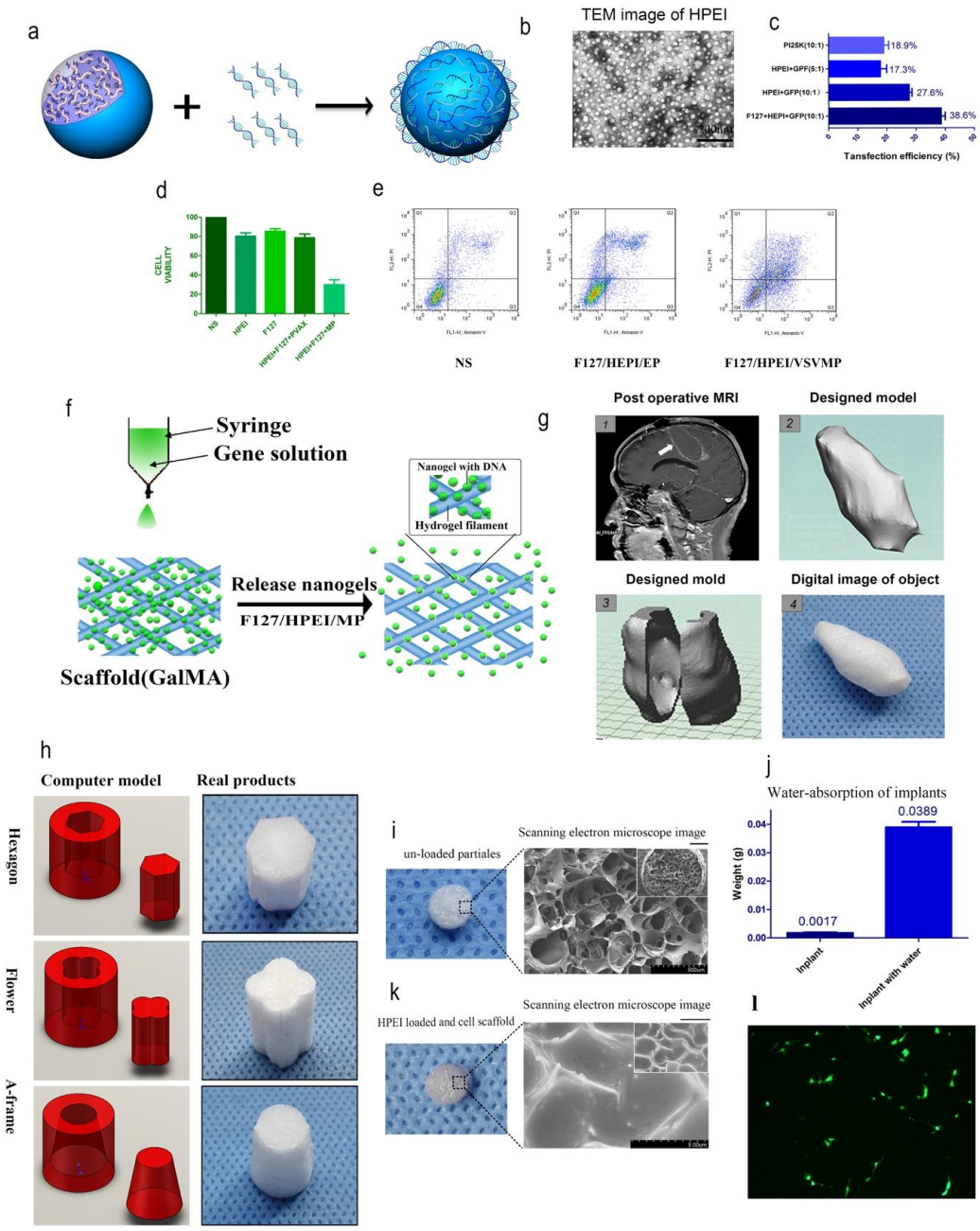


Fig 1


a
b
TEM image of HPEI
c
PI25K(10:1)
HPEI+GPF(5:1)
HPEI+GFP(10:1)
F127+HEPI+GFP(10:1)
18.9%
17.3%
27.6%
38.6%
Tansfection efficiency (%)
d
CELL VIABILITY
NS
HPEI
F127
HPEI+F127+PVAX
HPEI+F127+MP
e
NS
F127/HEPI/EP
F127/HPEI/VSVMP
f
Syringe
Gene solution
Nanogel with DNA
Hydrogel filament
Release nanogels
F127/HPEI/MP
Scaffold(GalMA)
g
Post operative MRI
Designed model
Designed mold
Digital image of object
h
Computer model
Real products
Hexagon
Flower
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k
HPEI loaded and cell scaffold
Scanning electron microscope image
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0.0017
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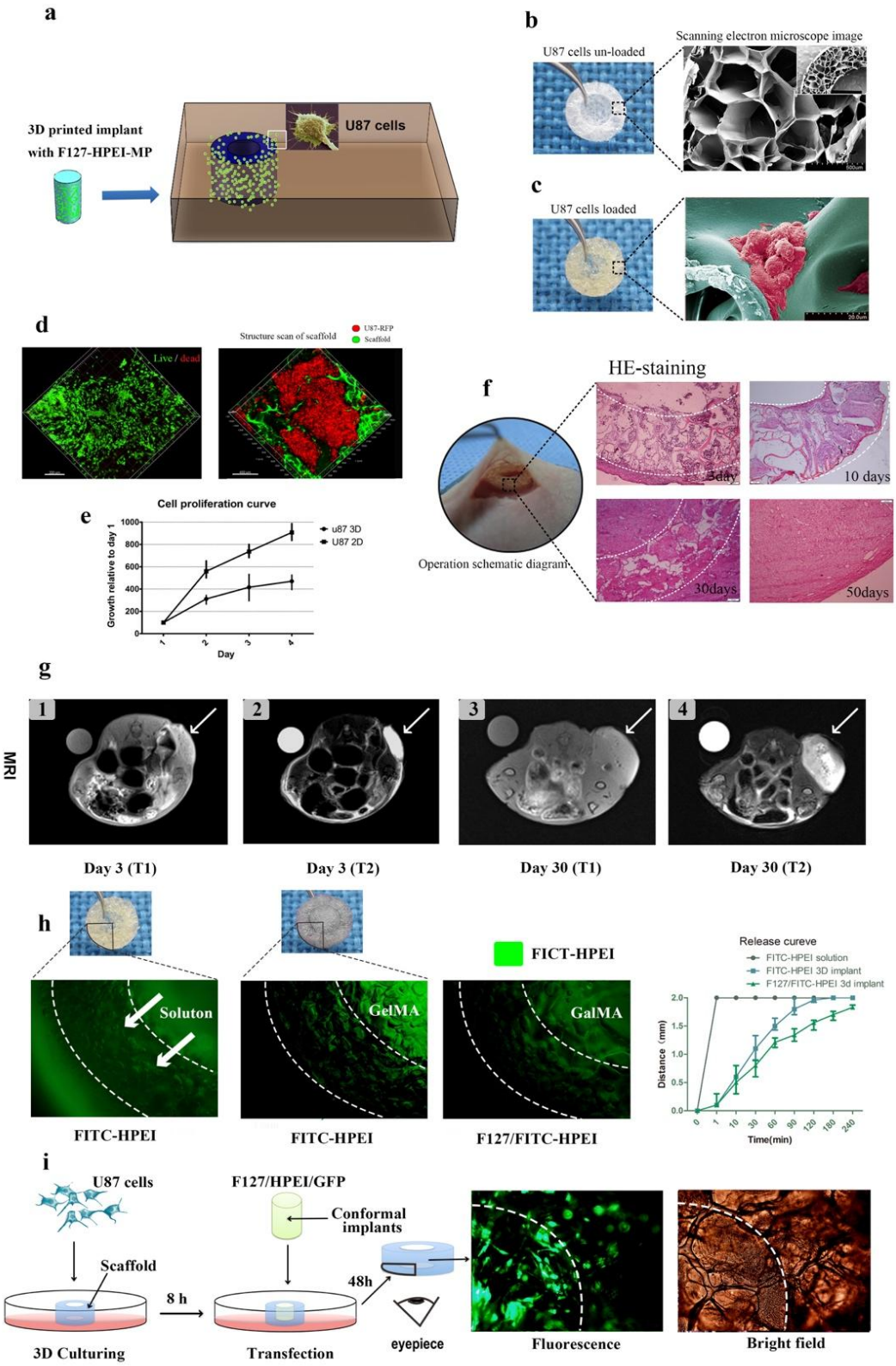
l

Fig 2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3D printed implant
with F127-HPEI-MP
U87 cells
b
U87 cells un-loaded
Scanning electron microscope image
c
U87 cells loaded
d
Live / dead
Structure scan of scaffold
U87-RFP
Scaffold
e
Cell proliferation curve
Growth relative to day 1
u87 3D
U87 2D
Day
f
HE-staining
Operation schematic diagram
3day
10 days
30days
50days
g
MRI
1
2
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4
Day 3 (T1)
Day 3 (T2)
Day 30 (T1)
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Soluton
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FICT-HPEI
GalMA
FITC-HPEI
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F127/FITC-HPEI
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FITC-HPEI 3D implant
F127/FITC-HPEI 3d implant
Distance (mm)
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i
U87 cells
Scaffold
3D Culturing
8 h
F127/HPEI/GFP
Conformal
implants
Transfection
48h
eyepiece
Fluorescence
Bright field

Fig 3

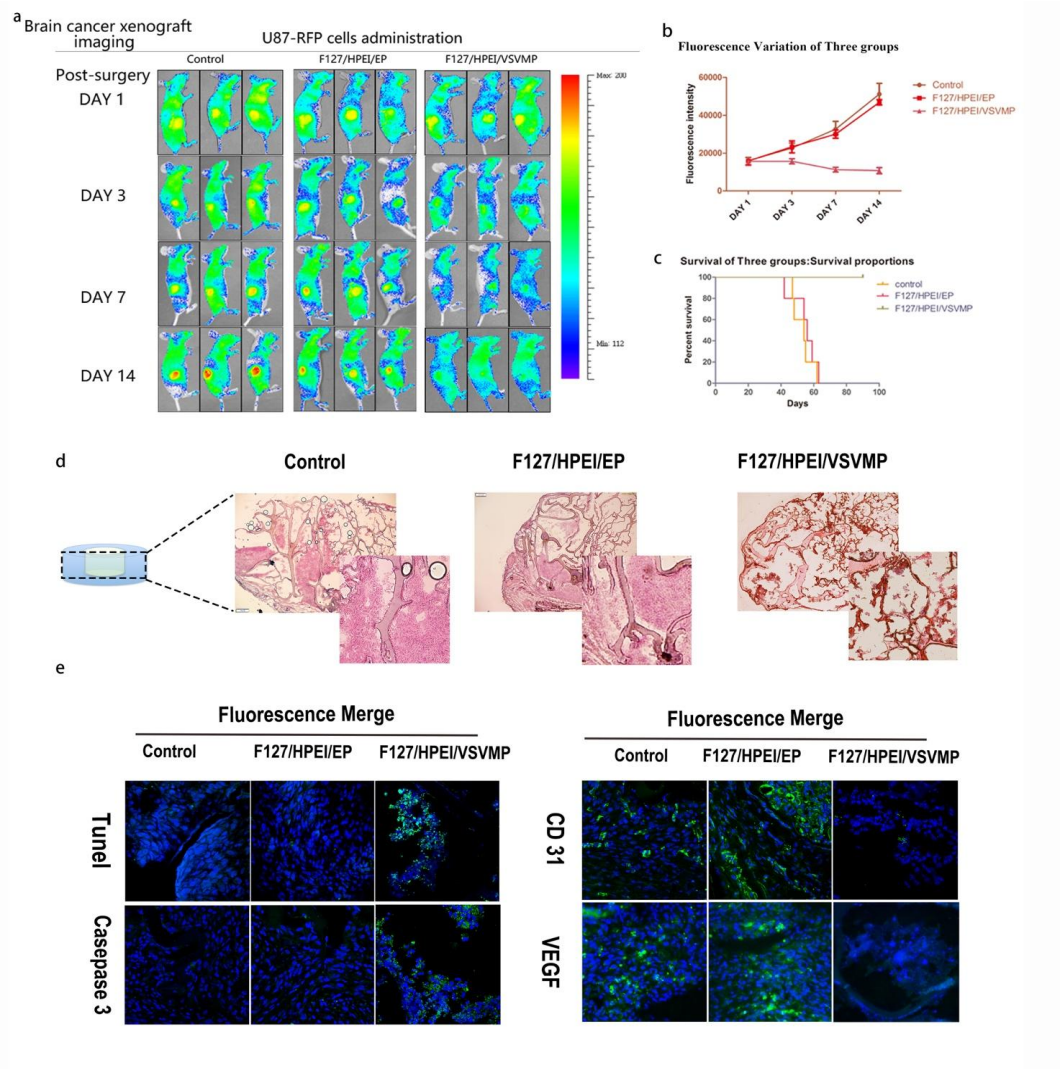
a
Brain cancer xenograft imaging
U87-RFP cells administration
Control
F127/HPEI/EP
F127/HPEI/VSVMP
Post-surgery
DAY 1
DAY 3
DAY 7
DAY 14
b
Fluorescence Variation of Three groups
Fluorescence intensity
Control
F127/HPEI/EP
F127/HPEI/VSVMP
c
Survival of Three groups:Survival proportions
Percent survival
Days
control
F127/HPEI/EP
F127/HPEI/VSVMP
d
Control
F127/HPEI/EP
F127/HPEI/VSVMP
e
Fluorescence Merge
Control
F127/HPEI/EP
F127/HPEI/VSVMP
Tunel
Casepase 3
CD 31
VEGF

Fig 4

Quality Of Life, Neurocognition, Symptom Management and Palliative Care

Paper ID: 126

REFLECTING ON SURVIVORSHIP OUTCOMES TO AID INITIAL DECISION-MAKING IN PATIENTS MANAGED FOR ANAPLASTIC GLIOMA

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Aims: Assess survivorship outcomes following intensity modulated radiation therapy(IMRT) for anaplastic glioma(AG).

Methods: Consecutive AG patients managed with IMRT from January2008 to July2015 were reviewed in regards to features associated with impact of IMRT on subsequent quality of survivorship. Patients were categorized into favourable(FAV) or non-favourable(nonFAV) molecular subtype based on presence of IDH mutation, oligodendroglial features or 1p19q. Survivorship features were recorded at baseline preIMRT, and at last follow-up/relapse. These include MRC Neurological Status, Employment status, ECOG Performance Status and CTCv4.0 Late Radiation Toxicity.

Results: 156 patients with median age 44 years were included with 124 FAV and 32 nonFAV. Median follow-up for survivors is 38 months. 66% received adjuvant chemotherapy. Progression-free survival(PFS) was improved in FAV with a 5yrPFS of 75.3% vs 26.0% for nonFAV ($p<0.001$). FAV managed with delayed RT until second or later relapse had worse ECOG ($p=0.003$) and PFS ($p=0.01$). At follow-up postIMRT 85% were ECOG0,1; and 64%MRC Neuro Status 0,1. 7pts (4%) had CTCv4.0 Grade 3 toxicity with 6 radiation necrosis events requiring surgery or Avastin; and one optic neuropathy.

Excluding retired patients, PreIMRT 89 of 133 (67%) patients were in employment of which were equally distributed between professional/clerical or retail/labourer. PostIMRT 92 patients (69%) of patients were in employment either fulltime (47%) or reduced capacity (22%). Reasons for inability to work fulltime were mostly due to physical (54%) or neurocognitive (34%) events occurring prior to IMRT. More patients returned to Employment postIMRT (7%) than ceased work (4%). In FAV patients Employment postIMRT was associated with improved PFS ($p<0.01$). Delayed use of IMRT was associated with lower Employment postIMRT ($p=0.045$)

Conclusions: FAV AG patients are young, have durable progression-free survival and good functional survival post IMRT. Delaying IMRT until second or later relapse was associated with worse PFS, performance status and impacts on subsequent employment.

Paper ID: 158

EVALUATE THE EFFECTIVENESS OF THE EDUCATIONAL BOOKLET FOR THE HIGH-GRADE GLIOMA PATIENTS IN COMBINED NEURO-ONCOLOGY CLINIC IN HONG KONG – A SINGLE CENTER EXPERIENCE.

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Danny TM Chan[2], Claire KY Lau[2], Susanna Sau Ming Fook[2] and Wai Sang Poon[2]

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[2] *Prince of Wales Hospital/CUHK*

Aims: High - grade glioma is an aggressive primary brain tumor. All glioma will attend combined neuro- oncology clinic in our Hospital. Despite detail explanation to patient and patient' s relatives in the combined clinic, patient still expressed knowledge deficit.

Methods: Since 2013, the combined clinic staffs designed an educational booklet which including the knowledge related to disease symptoms, treatment plan and patient 's sharing. The patients will attend the combined clinic and they will receive an educational booklet in their first visit and encourage them to using the booklet as their record. We would like evaluation the effectiveness of the booklet in retrospective aspect by asking five questionnaires. The first question is evaluated the information is sufficient or not. The second question is evaluated the booklet's effectiveness. The third question is asked the patient whether will apply the knowledge in their daily life. The fourth question is evaluated the booklet can improve the disease handling. The fifth question is asked for recommendation to improve their quality of life.

Results: There are total 40 booklets were distributed since mid of 2013. This retrospective study is held from December 2015 to March 2016. Fifteen patients were returned the questionnaire. Most of them (13/15) are appreciated the booklet is informative for disease management. They would apply the information in their daily life. Further, they agreed the information facilitate them in handling the symptoms. Only one patient suggested to provide information related to group activities and group support.

Conclusions: Overall, the patients agreed the booklet was helpful in handling their disease and improve their quality of life. Nevertheless, the patients have not brought the booklet during follow up. The booklet only serves as the information resource purpose.

Paper ID: 123

HEALTH-RELATED QUALITY OF LIFE OUTCOMES FROM CABARET: A RANDOMIZED PHASE 2 TRIAL OF CARBOPLATIN AND BEVACIZUMAB IN RECURRENT GLIOBLASTOMA

Kathryn Field[1,2]
Madeleine King[3], John Simes[4], David Espinoza[4], Elizabeth Barnes[4], Kate Sawkins[4], Mark Rosenthal[1,2], Lawrence Cher[5], Elizabeth Hovey[6], Helen Wheeler[7] and Anna Nowak[8,9]

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[2] *University of Melbourne, Dept of Medicine*
[3] *Psycho-oncology Co-operative Research Group (PoCoG), School of Psychology and Central Clinical School, Sydney Medical School, Un*
[4] *National Health and Medical Research Council Clinical Trials Centre, University of Sydney*
[5] *Austin Health*
[6] *Prince of Wales Hospital, Sydney*
[7] *Royal North Shore Hospital, Sydney*
[8] *Sir Charles Gairdner Hospital*
[9] *School of Medicine and Pharmacology, University of Western Australia*

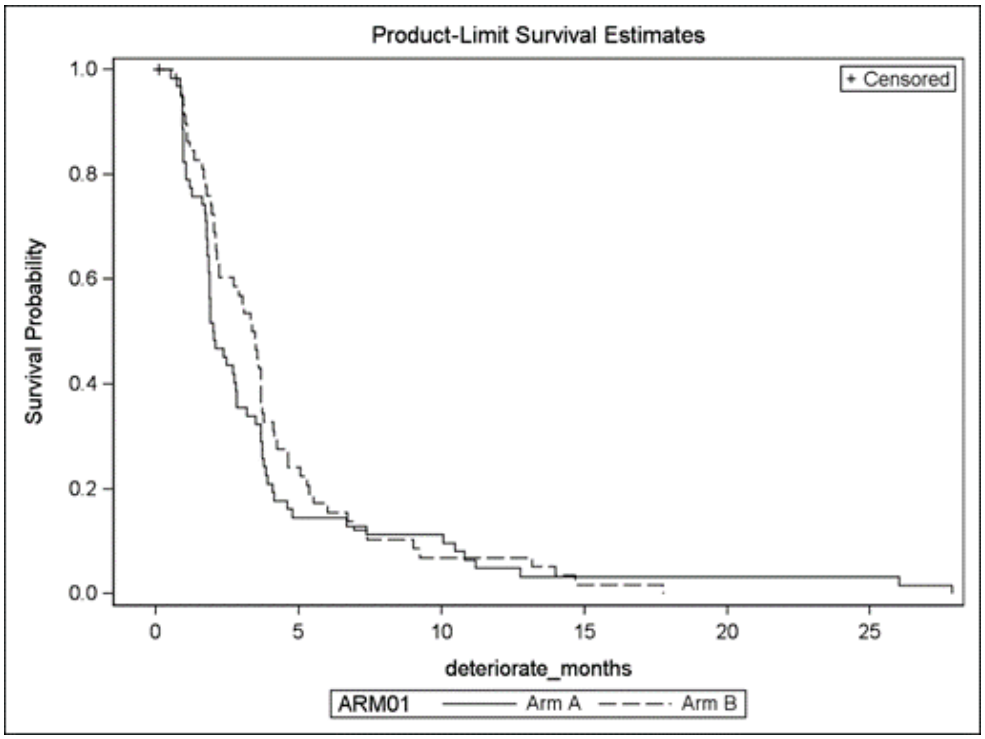
Aims: In recurrent glioblastoma (GBM) where overall prognosis is poor and no one treatment confers a clear survival advantage, health-related quality of life (HRQL) is a crucial endpoint in clinical trial outcomes. We assessed HRQL completion rates and compared HRQL outcomes between arms for patients with recurrent GBM who participated in the CABARET randomized phase 2 clinical trial.

Methods: 122 patients were randomized to receive either bevacizumab + carboplatin, or bevacizumab monotherapy. The primary endpoint, progression-free survival, was equivalent between arms, with HRQL a secondary endpoint. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Brain Cancer Module (BN20) questionnaires were utilized. We calculated changes from baseline score for each HRQL measure. Time to confirmed 10-point or more deterioration from baseline were compared for overall QoL, social function, role function, physical function, cognitive function, drowsiness, communication and motor dysfunction.

Results: At baseline, 117 of 122 patients (96%) attempted HRQL questionnaires. Completion rates were >90% except at the end of treatment visit where only 71 patients returned a HRQL form, with no difference in rates between arms. There was no evidence of differences in change scores from baseline over the treatment period between arms. Time to confirmed ≥10 point deterioration in scores from baseline was also similar between arms (Figure 1). Overall, there was more deterioration than improvement in HRQL while on study, and HRQL deterioration occurred largely prior to progression in this cohort for the domains tested.

Conclusions: Neither detrimental nor beneficial effects on HRQL were seen with the addition of carboplatin to bevacizumab in this study. Time to HRQL deterioration is a useful endpoint for neuro-oncology clinical trials that avoids bias due to attrition at the time of study completion.

Figure 1: Kaplan-Meier curve comparing deterioration in global QOL between arms



Arm A: Bevacizumab monotherapy
Arm B: Bevacizumab plus carboplatin

Paper ID: 168

DOES HEALTH RELATED QUALITY OF LIFE AND SELF-REPORTED COGNITIVE FUNCTIONING MAINTAIN AFTER GLIOMA SURGERY IN CHINESE POPULATION IN LOCAL HONG KONG HOSPITAL?

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[4] *CUHK*

Aim: Gliomas are malignant primary brain tumors and yet incurable. Palliation and the maintenance or improvement of the patient's quality of life is therefore of main importance. We would like to evaluate our glioma patients ' health - related quality of life and the cognitive function after surgery that to provide appropriate interventions in their treatment timeline.

Methods: It is a prospective study to evaluate the pre and post glioma surgery by using the European Organization for Research and Treatment of Cancer and perform the Montreal Cognitive Assessment (MOCA) and Functional Independence Measure (FIM) by the therapist.

Results: From Jan to Dec 2015, six glioma patients were recruited that four female and two male. The mean age is 47.5 year old. The mean of the global health status of pre surgery and post surgery was 59.7 and 61.1 respectively. The mean of the physical functioning of pre surgery was 81.1 while post surgery was 74.4. The mean score of cognitive functioning was 80.6 and was maintained after surgery. The pre MOCA mean score was 23.8 while post surgery is 25.3. Mean score of the FIM - motor part pre and post was 88.2 and 89.7 respectively while FIM cognitive part was maintained.

Conclusion: In our small case series, we found that patients ' reported mild worsen in the functional aspect in EORTC QLO- C 30 after surgery. However, the clinical assessment of the motor part was maintained by using FIM. In the cognitive aspect, there was no difference between EORTC QLO - C30 cognitive part and MOCA. Thus, psychological support is very important to allay the patients' stress and help them to facing the consequence treatment plan. Besides, further study should be performed according to the treatment plan timeline, which provide more information to us and then to provide appropriate interventions.

Paper ID: 136

COMMENCEMENT OF A MULTI-STATE RCT OF STRUCTURED NURSE-LED HOME BASED SUPPORT AND EDUCATION FOR CARERS OF PEOPLE WITH HIGH GRADE GLIOMA

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High grade gliomas (HGG) are invariably terminal brain tumours. They lead to a rapid decline in function with patients requiring a high level of care. Carers of patients with HGG report high levels of distress and feel inadequately prepared for their caring role.

Aims: This randomised controlled trial aims to evaluate a nurse-led education and support program to improve carer preparedness for the caring role, improve their quality of life; reduce anxiety and depression; and decrease unplanned use of health services. During this presentation we will provide results to date and describe areas where carers required assistance.

Methods: Randomised, controlled, unblinded Phase III trial comparing usual care with the intervention. The carer education program consists of 1) Telephone assessment of carer's needs; 2) Nurse-led home visit; 3) Personalised resource file individually tailored and 4) ongoing telephone support for 12 months. Endpoints are: carer preparedness, distress, anxiety and depression, quality of life, competence, supportive care needs and health economic cost-consequences of the intervention.

Results: 73 carer participants have been recruited. Problems identified during the nursing assessments with carers in the intervention group related to: caring for yourself (e.g. anxiety, carer strain/burden, respite); practical matters (e.g. occupational therapy, social work, legal advice, transport); communication; dealing with treatment; understanding physical symptoms; understanding mental and behaviour changes; fertility and sexuality; lifestyle choices and end of life care. For each of the problems identified participants were provided with appropriate support, education and referral.

Conclusions: This study will provide evidence about whether the intervention reduces carer distress, improves carer outcomes and reduces patient healthcare resource utilisation and costs. The model validated in this population has potential for adaptation for carers of people

with other aggressive cancers and progressive neurological disorders.

Paper ID: 114

SURGICAL TREATMENT OF GIANT VESTIBULAR SCHWANNOMAS: FAVORABLE FACIAL NERVE OUTCOME AND TUMOR CONTROL

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Aims: Surgical resection is considered to be the optimal treatment of giant vestibular schwannomas (GVS, maximal diameter ≥ 4cm). However, radical resection is associated with high morbidity and mortality. Philosophy of incomplete tumor resection may balance the preservation of facial nerve function and long-term tumor control. We aim to evaluate the facial nerve functional outcome and long-term tumor control rate of patients with GVS treated in our hospital and to summarize our experience on standardized surgical strategy in treating with this disease.

Methods: From September 2009 to August 2014, a total of 268 consecutive patients suffered from GVS underwent surgical treatment in West China Hospital of Sichuan University. The clinical and radiological features, extent of resection, facial nerve functional outcome and the tumor control rate were retrospectively analyzed. The surgical techniques and theraputic strategy were discussed.

Results: Gross total resection was achieved in 104 patients (38.8%) and near total resection in 164 (61.2%). All the patients achieved anatomical preservation of facial nerve. After a mean follow up of 41.2 months (range from 9 to 69 months), 232 patients (86.6%) had excellent or good facial nerve function (HB Grade I-III), 29 (10.8%) had fair function (HB Grade IV), and 2 (0.7%) had poor function (HB Grade V). During follow-up period, twenty patients suffered from tumor regrowth and the tumor control rate was 1.9% in patients with gross total resection and 11% in patients with near total resection. For patients suffered from tumor regrowth, stereotactic radiosurgery was performed and the size of residual tumors was stable.

Conclusions: Surgical philosophy of prioritizing facial nerve preservation over total tumor resection is recommended in treating with giant vestibular schwannomas, and one stage safely resection and favorable outcome can be achieved via standardized surgical strategy.

Paper ID: 180

RETURN TO WORK & THE COMPLEXITY OF CHALLENGES IN ONGOING EMPLOYMENT IN PATIENTS WITH A FAVOURABLE GRADE III ANAPLASTIC GLIOMA (IDH1 POSITIVE) TREATED AFTER 2005, AT FIVE YEAR FOLLOW UP.

Marina Kastelan [1]

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Aims: Patients who have been diagnosed with Grade III Anaplastic Oligodendroglioma 1p19q codeleted, IDH 1 positive or Anaplastic Astrocytoma IDH1 positive have a favourable outcome with survival of 85% of patients at 5 years plus, after craniotomy followed by Radiation and adjuvant Temozolomide, however, return to employment and re-socialisation for these patients can be an issue due to the neurocognitive changes and challenges which occur after treatment.

Methods: Gather numbers of patients diagnosed with a favourable Glioma (Grade III IDH positive) treated via Royal North Shore Hospital after 2005 who were alive at five years post treatment. (noting tumour location & any difference in tumour location & neuro cognitive impact).

Gather data on pre diagnosis level of education and occupation.

Work force interviews to gather data on return to work after brain tumour diagnosis, previous employment type pre diagnosis & post diagnosis.

Interviews documenting challenges in returning to work or gaining employment post treatment.

Neurocognitive assessment to assess levels of cognitive deficit.

Numbers of patients who have accessed neurocognitive retraining ie: brain training, memory retraining

Pilot Study looking at return to employment of Grade III favourable Glioma who received Radiation after 2005, still alive at 2015, who are at least five years post treatment.

Results: Unknown

Conclusions: To document the number of favourable Grade III Glioma patients post craniotomy, Radiation +/- Temozolomide who were able to return to sustained employment & the challenges of gaining employment or reemployment; & how this impacts their psychological wellbeing

Paper ID: 141

INTRAOPERATIVE ELECTRICAL MAPPING OF WORKING MEMORY AND IDENTIFICATION OF THE NEURAL NETWORK IN RIGHT FRONTAL GLIOMA PATIENTS (O)

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Aims: The working memory is one of the executive function and defined as an active short-term memory, impairment of which could affect a quality of human life. We previously reported that the superior longitudinal fascicle had a crucial role in the network of working memory, and the chronic dysfunction significantly occurred in patients with right frontal glioma after surgery (Kinoshita 2016). In this study, we investigated the neural network of working memory using intraoperative brain mapping in awake surgery of right frontal glioma, additionally with diffusion tensor and gross anatomical tractographic techniques.

Methods: Eight patients with right frontal glioma experienced awake craniotomy, and intraoperative subcortical direct electrical stimulations were performed using spatial 2-back task after tumor resection. Positive mapping areas were recorded and then overlapped in structural MRI after transformation into standardized MNI152 template. From the distribution of positive mapping sites, the most concerned white matter tract was analyzed by diffusion tensor tractography in the individual case with positive mapping and by fiber dissection of cadaveric cerebral hemisphere.

Results: Intraoperative direct electrical stimulations with spatial 2-back task reproducibly induced positive responses on the wall of resection cavity in five patients. The overlapped distribution of positive mapping sites was localized in the medial and deep region of frontal white matter around the cingulate tract. Diffusion tensor tractography individually visualized a bundle connecting between the positive mapping region and cingulum. Fiber dissection showed the white matter tract spreading to frontal regions after running parallel to the cingulate bundle from the parietal lobe.

Conclusions: The intraoperative mapping of working memory could be successfully performed in awake craniotomy. The medial pathway connecting the frontal lobe through the cingulate tract might play a role in networks of the working memory with lateral pathway of the superior longitudinal fascicle.

Paper ID: 19

THE DOMINANT TEMPORAL POLE THEORY IN LANGUAGE PROCESSING: LESSON FROM ANOMIA FOR FAMOUS PEOPLE'S NAME AFTER SURGERY IN THE DOMINANT TEMPORAL LOBE

Masanori Kurimoto[1]

[1] *Kurobe City Hospital Neurosurgery*

Aims: Recognizing people's faces and recalling famous people's name involve multiple processing stages. The aim of this study was to investigate the neuroanatomical basis for recalling famous people's name.

Methods: Seven consecutive patients underwent surgery for a brain tumor in the dominant temporal lobe. All patients were tested using a picture-naming task for famous people's faces and common objects, both pre- and postoperatively.

Results: All the patients underwent removal of tumor. Postoperatively, no patient showed worsening of speech function determined by the Western Aphasis Battery (WAB) and the Japanese Standard Language Test of Aphasia (SLTA). However, most of the patients showed highly specific anomia for famous people's name when they looked at famous person's pictures, but their semantic knowledge about these celebrities was completely preserved. The patients could explain the semantic information of these celebrities from pictures and they could point at a photo of specific person among many pictures. Postoperative common object naming was intact in most patients.

Conclusions: The dominant temporal pole does not store names or concepts themselves, so it acts as convergence zones that serve as intermediary between retrieval of semantic knowledge and retrieval of names, thereby damage of the dominant temporal pole may cause dissociation of recalling proper name and semantic knowledge This dissociation may be from the disconnection of the fibers between the dominant temporal pole, and the inferior frontooccipital fasciculus, the inferior longitudinal fasciculus, and the uncinate fasciculus. We concluded the dominant temporal pole is essential for recalling famous people's name.

Paper ID: 137

LONG-TERM PROGNOSIS OF ATYPICAL AND MALIGNANT MENINGIOMA : OUTCOME AND PROGNOSTIC FACTORS

Sun-Il Lee[1]

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Aims: Twenty one atypical and fifteen malignant meningiomas were analyzed for long time to under stand the long-term outcome and associated prognostic factors retrospectively.

Methods: Thirty three (92%) meningiomas were macroscopically complete-resected in Simpson Grade I resection and three (8%) meningiomas were resected in

Simpson Grade II. Ninety-one percent of all patients received whole brain radiotheraphy(WBRT) with nean dose of 52 Gy. We analyze the long-term survival, recurrence-free survival and prognostic significance of the grade of surgical resection and the difference between two groups.

Results: Recurrence free survival and median time to recurrence were significantly longer in atypical than malignant meningioma. But, the benefit of adjuvant radiotheraphy was not effective significantly. Also the grade of surgical resection (Simpson Grade I vs II-III) were significantly related to prognostic survival.

Conclusions: Pathological grade and the grade of surgical resection can be definite prognostic factors. However, multicenter prospective studies are necessary to clarify the management and the correct timing of radiotheraphy in such a rare disease.

Paper ID: 82

"IT'S ONLY A LOW GRADE": WORK IN PROGRESS

Dianne Legge[1]
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Background: Given the dramatic and longstanding impact Glioblastoma Multiforme has on an individual's life and family, it is not uncommon for health professionals to overlook the significance and impact of a low-grade glioma (LGG) diagnosis. Accounting for around 15% of all gliomas diagnoses in Australia, LGG has not received sufficient attention in studies investigating the challenges, impacts and supportive care needs of people with primary malignant brain tumours. There is limited understanding of the qualitatively different ways people cope with a LGG diagnosis. People with LGG's are often younger, likely to live longer, often at a time in life associated with childrearing, busy careers, and financial burdens. A significant gap in knowledge exists in understanding how people adapt to living with a LGG, how they build their resources, what the impact this diagnosis has on their relationships and life roles, and how individuals accommodate their changed situation.

Aims: To address this gap, this study will interview individuals diagnosed with LGG from 3 months to 10 years post-diagnosis.

Methods: The study will use an interpretive qualitative framework, with grounded theory methods, which will seek to understand how a LGG diagnosis impacts on a person's social interaction, relationships, work and family roles. In-depth interviews, using constant comparison strategies, will direct the purposive sampling.

Results: The expected outcome of the study will be the development of theoretical propositions drawn from generated participant data about the key study questions.

Conclusions: Such findings will direct future supportive care resources, and improve health professionals' understandings of the experiences of people diagnosed with LGG.

Paper ID: 101

POSTOPERATIVE TINNITUS AFTER VESTIBULAR SCHWANNOMA SURGERY: A NEGLECTED ENTITY

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Jayesh C Shardhara[1], Sanjay Behari[1], Awadhesh Kumar Jaiswal[1], Rabi Narayan Sahu[1], Arun Kumar Srivastava[1], Anant Mehrotra[1], Kuntal Kanti Das[1], Kamlesh S Bhaisora[1], Amit Keshri[1] and Saurin R Shah[1]

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Aims: To analyze the factors impacting the changes in tinnitus outcome after vestibular schwannoma (VS) surgery and to assess the possible etiopathogenic mechanisms of persistent tinnitus after surgery.

Methods: Total 42 consecutive patients of large/giant VS with non useful hearing operated via a retromastoid suboccipital approach were included in this study. Prospective analysis of patients included audiology, pre and postoperative THI (Tinnitus Handicap Inventory) scoring and BAER (Auditory brain stem evoked response) in postoperative persistent tinnitus.

Results: Total 22/42(52%) patients presented with non serviceable hearing loss and tinnitus preoperatively (THI score > 1). After surgery, 18 (81.8%) patients had a significantly improved THI score [THI grade reduced]. In 9 of these 18 patients, the tinnitus subsided completely [THI grade 1] while 9 had persistent tinnitus (THI grade 2). In 3(13%) patients, the THI scores remains unaltered and 1 (4.5%) patient reported worsening of the THI scores. Of the 20 patients without a preoperative tinnitus, 4(10%) patients developed tinnitus postoperatively. Thus, in 17 (40%) postoperative patients (including 4 with new onset), the tinnitus was present at 3 months follow up. Incidence of postoperative persistent tinnitus remain highest in sever SNHL (p=0.021).

Conclusions: Assessment of tinnitus is mandatory during management of VSs; as persistent, often vexatious tinnitus is common postoperatively. Most likely it is dependent on an intact cochlear nerve and cortical reorganization. Irrespective of difference in size and consistency tinnitus improved after VS surgery with cochlear nerve resection in patients with non useful hearing loss.

Paper ID: 186

COGNITIVE IMPAIRMENT PROFILE IN BRAIN TUMORS

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Aims: To obtain the prevalence and profile of cognitive impairment in brain tumor.

Methods: This study was a cross-sectional retrospective study using consecutive sampling. Data obtained from Neurobehaviour Division of Neurology Clinic and Medical Record Department of Cipto Mangunkusumo General Hospital started from January 2009 to April 2016. Subjects, aged 18 to 65 years old, were all preoperative brain tumors who undergone neurobehavioral test. Brain neoplasms were based on histopathologic findings and classified into primary and metastasis.

Results: There were 77 subjects, with primary brain tumors (58.4%) were slightly numerous than metastasis. Glioma and meningioma are two most common primary brain tumors (49% and 40% consecutively). Meanwhile, lung cancers (34.4%) and breast cancers (18.8%) are two most common origin of all metastases cases. No significant differences between males and females number, with mean age of 45.5 ± 11.7 years. Metastases were mostly found in older adults (87.5%; p=0.003) significantly, whereas primary were more likely occur in younger adults. Approximately 96% of all brain tumors had cognitive impairment, predominantly multiple domain (90.5%). Both primary and metastases are multiple domain impaired (84.1% and 100% consecutively; p=0.037). Of all cognitive domain, memory are mostly affected (79.2%), followed by executive function (74%). The difference between single and multiple domain impairment was not significantly related to number of affected lobes (p=0.11).

Conclusion: Almost all brain tumor had multiple cognitive domain impairment, majorly in memory and executive function domains. It suggested that metastases affected multiple cognitive domain. There were no significant difference whether single or multiple domain impairment related to number of affected lobes.

Keywords: cognitive impairment; metastases; primary brain tumor.

Paper ID: 89

THE CONSIDERATIONS FOR INDICATION OF OPTIMAL TREATMENTS IN ELDERLY JAPANESE PATIENTS WITH GLIOBLASTOMA MULTIFORME

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Aims: The incidence of glioblastoma multiforme (GBM), the most common malignant brain tumor in adults, has drastically increased in the elderly. Median survival in GBM patients is approximately up to 15 months; in the elderly it is less than 6 months. The standard of care for elderly GBM patients remains controversial and decisions on optimal treatments are based on relatively little evidence. The purpose of this retrospective study was to ascertain the limit of optimal treatments for elderly GBM patients by assessing the prognostic relevance of treatment-related factors.

Methods: Of 219 consecutive patients with histologically verified newly-diagnosed intracranial GBM between January 2006 and December 2014 in Kumamoto university hospital, 123 patients aged ≥ 65 years were identified and defined as the elderly patient. We assessed if treatment-related factors, i.e. extent of surgical resection and MGMT promoter methylation status were significant for overall survival (OS) by multivariate analysis.

Results: The median age was 74 (range 65-88) years old, the median KPS was 80. Gross total resection was performed in 44 (35.8%), and 100 patients (81.3%) underwent temozolomide (TMZ) based radio-chemotherapy, 9 (7.3%) did TMZ alone, 10 (8.1%) did ACNU based radio-chemotherapy, and 4 (3.3%) did radiation alone. Median OS was 350 days. Regardless of the increasing age, extent of surgical resection and MGMT promoter methylation status were the statistically significant independent prognostic factors only in the elderly GBM patients aged younger than 80 years. On the other hand neither maximum surgical resection nor MGMT methylated were associated with prolongation of survival in the very elderly GBM patients aged ≥ 80 years.

Conclusions: This study first documents that the optimal treatments should be performed for the elderly GBM patients up to their 70's while individualized geriatric assessment-based therapy is still needed for the very elderly GBM patients, e.g. aged ≥ 80 years.

Paper ID: 98

SKULL BASE BONY LESIONS: MANAGEMENT NUANCES; A RETROSPECTIVE ANALYSIS FROM A TERTIARY CARE CENTRE

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[1] *SGPGI*

Aims: to study the bony Skull base lesions and their management nuances

Methods: The histopathologically, radiologically, and surgically proven cases of skull base bony tumors or lesions involving bone were analyzed from the neurosurgery, neuropathology record of our Tertiary Care Institute from January 2009 to January 2014. All available preoperative and postoperative details were noted from their case files. The extent of excision was ascertained from operation records and postoperative magnetic resonance imaging if available.

Results: We have surgically managed 41 cases of skull base bony tumors. It includes 11 patients of anterior skull base, 13 middle skull base, and 17 posterior skull base

bony tumors. The most common bony tumor was chordoma 15 (36.6%), followed by fibrous dysplasia 5 (12.2%), chondrosarcoma (12.2%), and ewings sarcoma peripheral primitive neuroectodermaltumor (EWS pPNET) five cases (12.2%) each. There were more malignant lesions (n = 29, 70.7%) at skull base than benign (n = 12, 29.3%) lesions. The surgical approach employed depended on location of tumor and pathology. Total mortality was 8 (20%) of whom 5 patients were of histological proven EWS pPNET.

Conclusions: Bony skull base lesion consists of wide variety of lesions, and requires multispecialty management. The complex lesions required tailored approaches surgery of these lesions. With the advent of microsurgical and endoscopic techniques, and use of navigation better outcomes are being seen, but these lesions require further study for development of proper management plan.

Paper ID: 189

THE USE OF STRATEGIES TO COMPENSATE FOR COGNITIVE, BEHAVIOURAL AND EMOTIONAL CHANGES AFTER A PRIMARY BRAIN TUMOUR (O)

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Aims: Changes have been reported to cognitive, behavioural and emotional functioning among patients with primary brain tumour (PBT). It is not known though, whether individuals are utilising strategies to compensate for these changes. This study sought to measure individuals' strategy use to manage changes after the onset of a PBT and whether this changed from pre- to post-diagnosis.

Methods: Individuals (n= 38) with an average age of 52.6 years and diagnosed with a PBT were administered the Strategy Use Measure (SUM) on average 37.6 months (SD=49.0) post diagnosis. Individuals were at various stages of the treatment phase and were across the spectrum of PBT type. The SUM is a 14 item self-report measure that assesses strategy use pre and post diagnosis on a five-point Likert scale (total score range 0-56). In addition to the total score, there are three sub-scales, namely Memory and Planning (MP, 5 items), Emotion and Mood (EM, 5 items) and Cognitive Load (CL, 4 items). It has been validated on an acquired brain injury population (including PBT) and subscales have good reliability (Cronbach's alpha ranges from .82-.83).

Results: Individuals with PBT reported a significant increase in strategy use (t-tests, all $p<.001$) from pre to post diagnosis across all three sub scales of the SUM (MP, pre 9.42±4.7, post 14.71±6.0; EM, pre 5.53±4.0, post 9.82±4.0; CL, pre 3.84±3.3, post 10.32±3.6) and for total strategy use (pre 18.8±10.7, post 34.8±11.5). The highest reported increase was on the subscale that assessed the management of cognitive load and the highest individual item endorsed was managing fatigue.

Conclusions: The SUM demonstrates that clients significantly increase their strategy use in an attempt to manage the cognitive, emotional and behavioural changes post-PBT. The SUM can help measure the efficacy of interventions that seek to increase strategy use after PBT.

Rare Tumours and Other

Paper ID: 100

PRIMARY CEREBRAL RHABDOMYOSARCOMA WITH LONG-TERM PROGRESSION-FREE SURVIVAL - A CASE REPORT

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[2] *St. Luke's Medical Center*
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Aims: Primary rhabdomyosarcoma (RMS) of the brain is very rare among adults. It carries a grave prognosis with survival usually less than 12 months and exceptional beyond 24 months. We reported this case to contribute to the limited literature on primary cerebral RMS.

Methods: This is a case of a 64 year-old female who presented with a 6-month history of gradually progressive blurring of vision. MRI of the brain revealed a heterogeneously enhancing mass, 4.9x7.1x5.6 cm in AP, transverse, and craniocaudal dimensions, involving the parasagittal aspects of the bilateral parieto-occipital region (Figure 1). Histopathologic findings after image-guided biopsy of the mass were consistent with rhabdomyosarcoma (Figure 2). Gross total resection of the tumor was not deemed safe since it may cause significant morbidity due to its bilateral location. The patient received intensity-modulated radiation therapy (IMRT) with concomitant chemotherapy with temozolomide (TMZ). This was followed by adjuvant chemotherapy with TMZ and carboplatin for 6 months.

Results: Improvement in vision was noted after starting dexamethasone. Full recovery of vision was reported after completion of the 7 cycles of adjuvant therapy with TMZ and carboplatin. Currently, the patient is alive and progression-free 39 months after diagnosis. She has a normal neurologic examination and is independent in all activities of daily living. Serial cranial MRI every 4 months after completion of adjuvant chemotherapy showed no evidence of tumor recurrence (Figure 3).

Conclusions: This is the first documented case of primary cerebral RMS worldwide with the longest progression-free survival of 39 months after concurrent radiation and chemotherapy with TMZ followed by adjuvant therapy with TMZ and carboplatin without total tumor resection. Further studies should be done to elucidate the promising role of concurrent radiation and chemotherapy in the management of primary cerebral RMS.

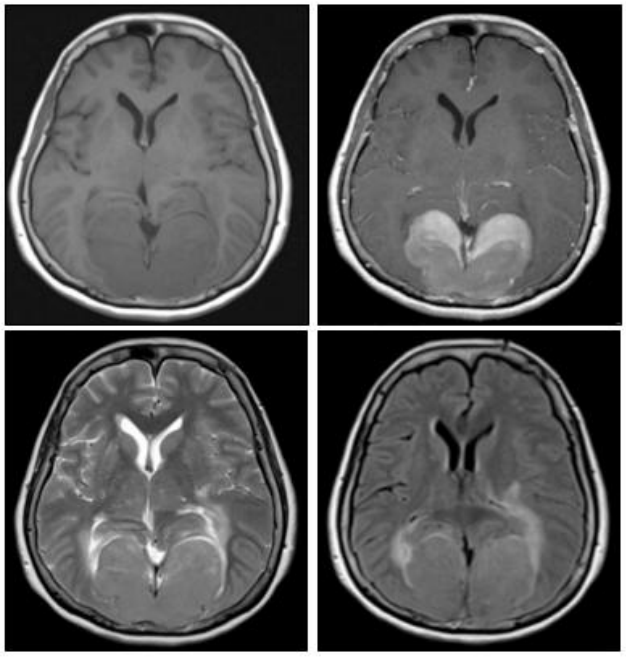

Figure 1: Cranial MRI with and without contrast.
A. Axial T1-weighted imaging shows a hypodense bilobed mass on the parieto-occipital region.
B. Axial contrast-enhanced MRI shows heterogeneous enhancement of the bilobed mass.
C. Axial T2-weighted imaging and D. FLAIR show moderate vasogenic edema surrounding the mass.

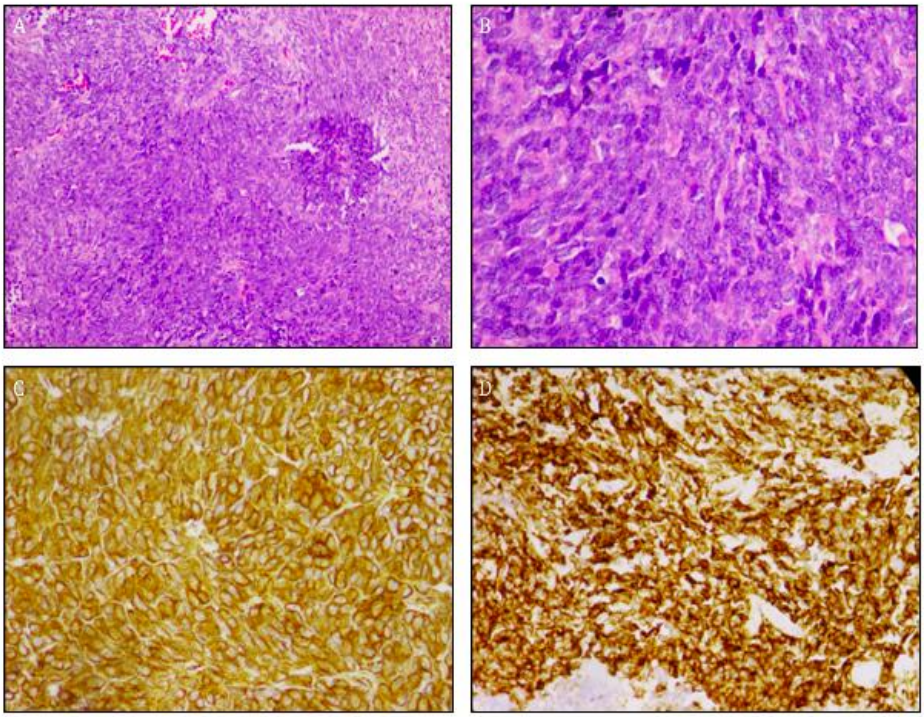

Figure 2: Histopathology and imunohistochemical stains. A. Cellular tumor with spindle cells in sheets and fascicular arrangement (H&E, 20X original magnification). B. The spindle cells have oval nuclei with fine to vesicular chromatin and inconspicuous nucleoli, and moderate amount of pale, eosinophilic cytoplasm (H&E, 40X original magnification). C. Cytoplasmic staining for vimentin in tumor cells (IHC for vimentin, 100X original magnification). D. Cytoplasmic staining for desmin in tumor cells (IHC for desmin, 100X original magnification).

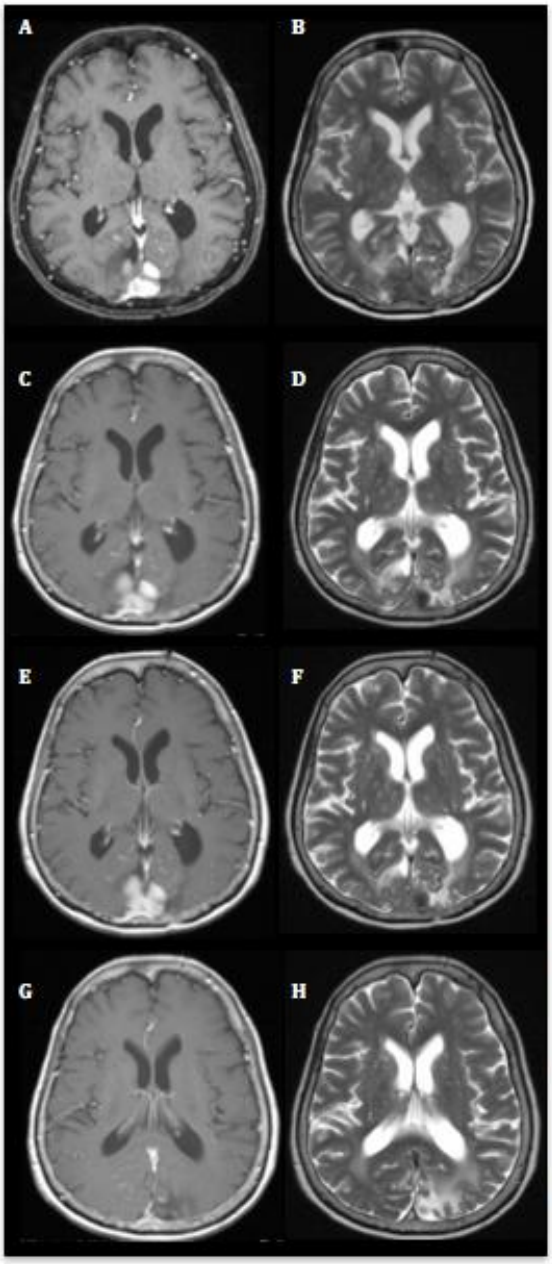

Figure 3: Serial MRI after the treatment period. A. Initial Axial T1-weighted imaging with contrast and B. T2-weighted imaging 4 months after treatment. C. Axial T1-weighted imaging with contrast and D. T2-weighted imaging after 8 months. E. Axial T1-weighted imaging with contrast and F. T2-weighted imaging after 13 months. G. Axial T1-weighted imaging with contrast and H. T2-weighted imaging after 16 months of treatment

Paper ID: 196

A CASE OF MULTIPLE SCLEROSIS MIMICKING MALIGNANT TUMOR

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Multiple sclerosis is a chronic, inflammatory demyelination of central nervous system white matter associated with axonal damage and occurred predilection in periventricular white matter, optic nerve, spinal cord, brainstem. A 50-year-old female was treated by transverse myelitis in cervical cord at 3years ago. Recently the patient discomfort right side hand weakness and leg dysesthesia with nausea, vomiting. In preoperative MRI, 28x35x39mm size irregular contour heterogenous enhancing low/high signal intensity on T1/T2 weight image mass developed in left side parietal lobe. We cannot differentiate this lesion from malignant tumors. Stereotactic tumor biopsy was undertake and the pathology revealed demyelinated inflammation lesion that is, CD68 (positive, diffuse) and GFAP (negative). After surgery, corticosteroid with interferon injection applied and the symptom was improved and discharged without a neurologic deficit.

This case report illustrates a demyelinating process mimicking malignant tumor lesions and it is of high importance to consider the diagnosis of multiple sclerosis on differential diagnosis of tumor-like lesion of the central nervous system because of treatment methods is different in each case.

Paper ID: 199

BRAINSTEM GLIOMA RESPONSIVE TO ORAL CHEMOTHERAPY TEMOZOLOMIDE (CASE REPORT)

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Introduction: Brainstem glioma are rare intracranial tumor and associated with poor prognosis. Radiotherapy is the current recommended treatment for brainstem glioma. Chemoterapy appears to be ineffective and the role of this treatment is unclear. This case report documents management of patient with brainstem glioma with good response to oral chemotherapy temozolomide. Despite limited modality of treatment, oral chemotherapy potentially offer a good prognosis for patient.

Case Report: A 14 years old patient came with acute weakness of right half body, severe headache, and vomiting. She complained a double vision for six months. MRI revealed brainstem glioma with intratumoral bleeding in pons, mesencephalon, cerebellar vermis, and thalamus with upward transtentorial herniation. She was treated with temozolomide for nine cycle and showed good response with lesion size became smaller after five cycle.

Conclusion: A patient suffered from brainstem glioma with intratumoral bleeding and upward transtentorial herniation was treated with temozolomide for nine cycles and had a good response.

Keywords: brainstem glioma tumor, oral chemotherapy, temozolomide

Paper ID: 154

COMBINING CYTOTOXIC THERAPY OR RADIATION THERAPY WITH HISTONE DEACETYLASE INHIBITOR (HDACI) TREATMENT REDUCES CELL PROLIFERATION IN RHABDOID TUMOR (RT) CELL LINES TO A GREATER DEGREE THAN TREATMENT WITH SINGLE AGENTS ALONE.

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Aims: To investigate the effect of combining cytotoxic therapy or radiation therapy with histone deacetylase inhibitors (HDACi) on cell proliferation in rhabdoid tumor (RT) cell lines.

Methods: RT cell lines (G401, SJSC and STM91-01) were treated with combinations of HDACi (LBH-589 or Romidepsin) and cytotoxic agents (Doxorubicin or Vincristine) or radiation exposure in varying temporal sequences (cytotoxic/radiation concurrent with HDACi and HDACi given as a weekly maintenance dose thereafter; cytotoxic/radiation prior to HDACi maintenance; HDACi prior to cytotoxic/radiation with no maintenance). Cell proliferation was measured by MTS assay at 7, 14 and 21 days. Reduction in cell proliferation was compared between combination groups and single agent and vehicle control groups.

Pellets were collected from cultures of treated RT cell lines and preliminary PCR arrays for expression of differentiation and cell lineage markers were performed.

Results: In the three cell lines tested the combination of cytotoxic/radiation treatment given concurrent with HDACi and with HDACi maintenance resulted in the greatest reduction in RT cell proliferation measured by MTS assay; followed by pre-treatment with radiation/cytotoxic before HDACi treatment and maintenance, when compared to single agent treatments, vehicle control and pre-treatment with HDACi before radiation/cytotoxic treatment.

Analysis of preliminary PCR arrays will follow shortly.

Conclusions: Combining cytotoxic or radiation treatment of RT cell lines with concurrent HDACi treatment and HDACi maintenance results in a greater reduction in cell proliferation measured by MTS assay than single treatments alone.

Paper ID: 203

MOLECULAR CHARECTERIZATION AND CLINICAL OUTCOME IN OLIGODENDROGLIAL AND OLIGOASTROCYTIC TUMOURS: A REPORT FROM A TERTIARY CARE CANCER CENTRE FORM INDIA.

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Rakesh Jalali[1], Sridhar Epari[1], Ayushi Sahay[1], Tejpal Gupta[1], Prakash Shetty[1] and Ali Asgar Moyiadi[1]

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Aims: To study the molecular profile and clinical outcome of Oligodendroglial and oligoastrocytic tumours

Patients and methods: Between January 2008 and sept 2015, we reviewed the charts of 238 grade II & III oligodendroglial and oligoastrocytic gliomas. At the time of analysis, 88 patients had complete details of their molecular profile and their clinical followup. We analysed the clinical and the molecular profile of these patients and correlated with clinical outcome. All the patients had standard therapy in the form of maximal safe resection followed by focal conformal RT with our without concurrent oral temozolomide (TMZ) according to standard institutional protocol. Response was evaluated clinically and radiologically with magnetic resonance imaging.

Results: The median age of the patients was 40 years (interquartile range34-48). 50 patients were males and 38 females. Near total tumor excision was performed in 35%, partial excision in 43% and decompression in 10% patients. Details were not available in rest of the patients. 1p19q co-deletion was observed in 40 pts (45%), IDH was mutated in 71 pts(81%). Wild type p53 was observed in 71pts (81%), ATRX was retained in 69% and lost in 31% pts. Median Mib-1labelling Index was 8.5% (IQR: 5-15%).64% patients received concurrent RT+TMZ and adjuvant TMZ. Mean overall survival was 85 months

(95% CI: 76 months-93 months).Estimated 5- years overall survival was 85.5%. IDH mutation was found to be significant prognostic factors for OS on univariate analysis (p=0.001).

Conclusions: Patients with oligodendroglial and oligoastrocytic tumours generally have a good prognosis with a 5 year survival of 85%.1p19q co-deletion was observed in 45% patients, although IDH mutation was seen in 81% patients. IDH mutation was found to be statistically significant prognostic factor for overall survival. An updated analysis of all the 238 patients will be presented during the conference.

Paper ID: 39

SALVAGE PCV CHEMOTHERAPY FOR RECURRENT PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS

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Background: Optimal treatment for recurrent primary central nervous system lymphomas (PCNSLs) has not been defined yet and there is no general consensus about the salvage chemotherapy after high-dose methotrexate (HD-MTX)-based chemotherapy. The purpose of the present study was to evaluate the efficacy and safety of procarbazine, lomustine, and vincristine (PCV) chemotherapy for recurrent PCNSLs.

Methods: We reviewed eight immunocompetent patients (five males/three females, mean age: 56 years) who received salvage PCV chemotherapy (procarbazine 60 mg/m2, days 8 through 21: CCNU 110 mg/m2, day 1: vincristine 2 mg, days 8 and 28) for recurrent PCNSL and two patients switched to PCV chemotherapy due to severe adverse effects of HD-MTX chemotherapy. Radiologic responses, survival, and adverse effects were analyzed.

Results: Of the eight recurrent PCNSLs, three patients (37.5%) showed radiologic complete response, one patient (12.5%) showed partial response, and four patients (50%) showed progressive disease after PCV chemotherapy. Median progression free survival (PFS) from the first administration of PCV to relapse or last follow-up was 7 months (range 5 - 32 months) and median overall survival was 8 months (range 2 - 41 months). The two patients who switched to PCV chemotherapy showed PFS of 9 and 5 months from the beginning of PCV to relapse. The common side effects were thrombocytopenia, neutropenia, and peripheral neuropathy. There were 4 grade III or IV myelo-suppression, but no fatal complications, including severe hemorrhage or infection, were observed.

Conclusion: Salvage PCV chemotherapy has a moderate anti-lymphoma activity for recurrent PCNSLs after the HD-MTX-based chemotherapy with tolerable toxicity.

Paper ID: 41

TREATMENT OUTCOME OF GAMMA KNIFE RADIOSURGERY OF VESTIBULAR SCHWANNOMAS WITH CYSTIC COMPONENT

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Objective: Many studies have shown favorable outcome of Gamma knife radiosurgery (GKRS) for vestibular schwannomas (VSs). However, there have been few studies which have shown the treatment result of cystic VSs (CVSs) for GKRS. The aim of this study was to confirm whether GKRS for CVSs continues to be safe and effective.

Methods: The study population consisted 511patients (172 males, 339 females) with VSs treated with GKRS between May 1990 and December 2013. Group 1 defined as cyst/tumor volume > 30%, group 2 was cyst/tumor volume > 50%, and group 3 was solid tumor or cyst/tumor volume ≤ 30%. To analyze factors that correlated with treatment outcomes, the following factors were assessed: tumor volume, cyst volume, tumor/cyst ratio, cyst type (single vs. multicystic), previous resection history, marginal radiation dose.

Results: The median follow up period was 52 months (range, 12-110 months). Tumor progression in group 1 was 5 (18.5%), group 2 was 1 (11.1%) and group 3 was 31 (6.4%). In group 1, 2 patients underwent delayed microsurgery at 31 and 36 months after GKRS.

Conclusions: In this study we found that GKRS for large CVS was associated with poor treatment outcome. Further study is needed to identify the mechanism of the tumor progression of CVS after GKRS

Paper ID: 62

SPINDLE CELL ONCOCYTOMA OF THE ADENOHYPOPHYSIS IN A 69-YEAR-OLD FEMALE

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Introduction: Spindle cell oncocytoma(SCO) is a very rare non-endocrine neoplasm of the pituitary adenohypophysis. Number of papers which deal with SCO is not over 20. we present a case about SCO patient who was misdiagnosed for pituitary adenoma preoperatively.

Case presentation: A 69-years-female was admitted for work up about fatigue and progressive visual loss. Bitemporal hemianopsia and pituitary insufficiency was detected. Magnetic resonance(MR) image revealed highly enhanced mass on sellar measuring 26mm X 21mm X 32mm with suprasellar extension. Cerebral angiogram revealed no definite feeder artery to the mass. She underwent trans-sphenoidal approach(TSA) and removal tumor operation. Intra-operatively, the tumor was elastic to soft and has high bleeding tendency which is differ

commonly found for pituitary adenoma. In histologic examination, spindle cell hyperplasia was seen, and it stained positive at Vimentin and S-100 protein. Final diagnosis was SCO. Her visual field was improved to bilateral quadrantanopia. Hormonal study presented sustained pituitary insufficiency. She get hormonal replacement. No postoperative adjuvant therapy was administered and her clinical course was favorable.

Discussion: SCO grows slowly and follows benign clinical course corresponding to WHO grade 1. Majority of papers confessed misdiagnosis for pituitary adenoma preoperatively. Many of them was misdiagnosed as schwannoma because of spindle morphology and the intense immunoreactivity for S-100 protein. Partial tumor resection were performed mostly due to the tumor consistency and bleedings, and secondary operation or postoperative radiation therapy were performed. In most cases, local mass controls was achieved in short duration, but tumor recurrence was noted in the longer follow-up period.

Conclusion: Because of rare incidence of diseases, SCO is not identified fully. Further investigations are need. Neurosurgeons should keep in mind for very uncommon tumors such as SCO.

Paper ID: 193

MGMT PROMOTER METHYLATION STATUS AS A PROGNOSTIC FACTOR IN THE OUTCOME OF GAMMA KNIFE RADIOSURGERY FOR RECURRENT GLIOBLASTOMA

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Aims: We conducted this study to investigate whether the methylation status of MGMT promoter influences on the outcome of gamma knife radiosurgery (GKS) for recurrent glioblastoma (GBM).

Methods: A total of 216 patients with GBM were treated with gamma knife radiosurgery (GKS) for residual tumor or local recurrence between 2004 and 2015. The methylation status of MGMT promoter by methylation-specific qRT-PCR was identified in 73 of 216 patients retrospectively. Eleven patients with GBM treated with GKS for residual tumor were excluded. Finally, a total of 62 consecutive GBM patients treated with GKS were included in this study. All patients had undergone surgical resection and CCRT followed by 6-cycle of adjuvant temozolomide. All patients were histopathologically diagnosed with GBM. The prognostic factors associated with progression and survival were examined by univariate and multivariate analyses.

Results: Of the 62 patients, 25 (40.3%) patients had methylated MGMT promoter, and 37 (59.7%) had unmethylated MGMT promoter. Median age at GKS was 57.5 years and 54 (87.1%) patients showed a KPS score of 70 or better at GKS. At first operation, GTR was achieved in 32 (51.6%) patients, STR in 25 (40.3%), biopsy alone in 5 (8.1%) patients. Median tumor volume at GKS was 6.85 Cm^3 and median marginal dose was 16 Gy. The median follow-up period after GKS was 7.5 months. Median progression-free survival in both methylated and unmethylated group after GKS were 8.9 and 4.7 months, respectively (p=0.018). Median overall survival in both methylated and unmethylated group were 14.0 and 9.0 months, respectively (p=0.021).

Conclusions: MGMT methylation is an important prognostic factor for progression and survival after GKS in recurrent GBM. Aggressive treatments such as reoperation, CTx, RTx and additional GKS at the time of progression after GKS in recurrent GBM may prolong the survival time of GBM patients.

Paper ID: 194

MULTISESSION GAMMA KNIFE RADIOSURGERY FOR ORBITAL APEX TUMORS

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Aims: This study was performed to analyze the outcome of multisession gamma knife radiosurgery (GKS) in benign tumors located at the orbital apex.

Methods: Medical records of 23 patients who underwent multisession GKS for benign orbital apex tumors were reviewed retrospectively. Three patients were diagnosed by histology, and the other 20 patients were given the diagnoses on the basis of clinical and radiological findings. Diagnoses included cavernous hemangioma (8 cases), meningioma (8 cases), and schwannoma (7 cases).

All patients were treated with 4 sessions of GKS with 12 hours of interval. Median marginal dose in each session was 5 Gy (range, 4.5-5.5 Gy) at the 50% isodose line (range, 50%-55%).

Results: Mean clinical and imaging follow-up duration after treatment were 52.1 and 34.2 months, respectively. Tumor control was achieved in 22 patients (95.7%). Significant tumor shrinkage was observed in 17 patients (73.9%), and mean tumor volume reduction rate was 53.9%. Visual function was improved in 16 patients (69.6%) and stable in 4 patients (17.4%). Deterioration of visual acuity was reported by 3 patients (13.0%). Clinical and radiological response to multisession GKS was most excellent in cavernous hemangiomas with tumor control in all patients, and the mean tumor volume reduction rate was 68.3%.

Conclusions: Multisession GKS proved to be an effective and safe management strategy for benign orbital apex tumors. Response to treatment was different according to the pathology, and multisession GKS may be considered as the initial treatment of choice for specific pathology such as cavernous hemangioma.

Paper ID: 14

SPONTANEOUS INTRACEREBRAL HEMORRHAGE SECONDARY TO ANAPLASTIC OLIGODENDROGLIOMAS: REPORT OF 2 CASES

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Aims: Hemorrhage in the context of primary or metastatic brain tumors is not infrequent over the course of the disease, ranging from 1% to 14.6%. Intracerebral hemorrhage (ICH) may be a presenting manifestation in unrecognized ODG infrequently. The authors experienced two cases of anaplastic oligodendroglioma (AO) in which the initial symptoms were spontaneous intracerebral hemorrhage. We present two cases and review the pertinent literatures.

Methods and Results: The first case is a 56-year-old woman presenting with drowsy mentality. Brain computed tomography (CT) scans revealed hemorrhagic mass at the right anterior frontal lobe area with prominent mass effect and midline shifting, sized 5.5 x 4.6 x 5 cm. She was undertaken craniotomy to remove ICH and tumor. At the operation field, grayish tumor mass was seen and severe brain edema was noted. Pathological findings showed multifocal necrosis and microcalcifications, they were consistent with AO. The second case was a 38-year-old man presenting only with headache. But his brain image showed 5.6 x 3.6 cm cystic mass at the right frontal lobe accompanying solid portion with hemorrhage. Due to this mass, midline was shifted by 1cm, and well-defined enhancement was noted in the cystic wall on post-contrast images. He underwent craniotomy and subtotal tumor removal was done. At the operation field, tumor was not well-defined and had no definite margin. Necrosis was seen with high vascularity. Pathological findings showed proliferating blood vessels and they were confirmed to be AO.

Conclusions: The authors experienced two patients with AO, who were complicated with spontaneous ICH. Hemorrhage as the initial presentation of AO may pose some diagnostic problems, especially if the tumor is small. The differential neuroradiological diagnosis of spontaneous ICH should include hemorrhage in diverse brain tumors or vascular malformations.

Paper ID: 146

ASSESSMENT OF A RARE CASE OF INTRACEREBRAL SCHWANNOMA

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A 45-year-old woman was admitted to the hospital through the emergency department. At admission the patient presented with headache, mild hypertension and hyperventilation. No neurological disturbance was detected. Imaging studies were performed. The computed tomography (CT) scan demonstrated a right frontal periventricular low density area. The magnetic resonance imaging (MRI) showed an intra-axial contrast-enhanced nodular mass with a perifocal area with high intensity in T2. The imaging studies alone were not conclusive and the differential diagnosis included high grade glioma and malignant lymphoma. In positron-emission tomography (PET), the 11C-methionine standard uptake value in the nodular contrast-enhanced part was 1.72 from the contralateral normal part . Tumor resection was performed. We used 5-aminolevulinic acid (5-ALA) and detected intraoperative fluorescence. The pathological diagnosis was intracerebral schwannoma. The patient remained with no neurological deficit and was put on observation with no visible tumor recurrence. An intracerebral schwannoma with no relation to the cranial nerves is considered to be very rare. To our knowledge, about 70 cases have been described since the first one reported by Gibson et al in 1966.

After reviewing the case retrospectively, we noted that increased myo-inositol was detected in the proton magnetic resonance spectroscopy (H-MRS). Increased myo-inositol has been reported in the literature as a clinical finding in cerebellopontine angle schwannoma or meningioma, but not seen in intracerebral schwannoma. This poses the question if there is a possibility to diagnose this lesion preoperatively and adjust the invasiveness of the surgical intervention.

Paper ID: 20

SURGERY FOR EPILEPSY IN PATIENTS WITH DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR USING ADVANCED MULTITECHNOLOGIES

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Aims: Dysembryoplastic neuroepithelial tumor (DNT) is a low-grade glioneuronal tumor causing intractable complex partial seizures. Complete resolution of seizures in a large percentage of both adult and pediatric patients is achieved with surgery. Though the primary objective of surgery is

complete seizure control without anticonvulsant therapy, the prevention of recurrent disease and the diagnosis of malignant transformation are also goals of surgical resection. The widespread surgical treatment of epilepsy due to DNT has, however, been criticized because surgery carries a nonnegligible risk of surgical sequelae including neurological, cognitive, and neuropsychological impairment. We report three cases of DNT with intractable epilepsy which were successfully treated with surgery using advanced multitechnologies with combined neuroimaging and electrophysiological examinations.

Methods: In all cases, technology beyond the routine workup was critical to success. Preoperative magnetic resonance imaging, 18F-fluorodeoxyglucose positron emission tomography (PET), 11C-methionine-PET, interictal electroencephalography, and intraoperative electrocorticography were utilized in all patients. In individual cases, however, additional procedures such as preoperative magnetoencephalography (Case 1: a 43-year-old woman), diffusion tensor fiber tractography, a neuronavigation system, and intraoperative somatosensory-evoked potential (Case 2: a 5-year-old girl), and fiber tractography and the neuronavigation-guided fence-post tube technique (Case 3: a 10-year-old girl) were instrumental.

Results: In all the cases, the objectives of total tumor resection, resection of the epileptogenic zone, and complete postoperative seizure control and the avoidance of surgical complications were achieved.

Conclusions: DNT is commonly associated with medically intractable epilepsy, and surgery is frequently utilized. As DNT may arise in any supratentorial and intracortical locations within or near the critical area of the brain, meticulous surgical strategies are necessary to avoid neurological deficits. We demonstrate in the following three cases how adjunct procedures using advanced multitechnologies with neuroimaging and electrophysiological examinations may be utilized to ensure success in DNT surgery.

Paper ID: 135

MALIGNANT TRANSFORMATION OF PURE GERMINOMAS: TWO CASES REPORT

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The prognosis of patients with germinoma is favorable; the 10 year survival rates of the patients have been reported to be approximately 8090%. On the other hand, malignant transformation of pure germinoma is very rare. Between 1975 and 2012, we experienced two patients with pure germinoma who died within less than one year after recurrence. The histopathological examinations suggested that their progressive disease may be due to malignant transformation of germinoma. The first case was a-17-year-old girl who had a tumor in the suprasellar region and underwent biopsy by transsphenoidal surgery. The diagnosis of pure germinoma was made. She underwent radio-chemotherapy and complete response was confirmed. Ten years later she revealed recurrence with dissemination and underwent biopsy and additional radiotherapy. Once the recurrent tumor disappeared, however the tumor reappeared, and she died of dissemination in brainstem 9 months later after recurrence. The second case was a-39-year-old male who had tumors in multiple regions, pineal, lateral and 3rd ventricle, and underwent biopsy. The diagnosis of pure germinoma was made. He underwent radio-chemotherapy and complete response was confirmed. Fourteen months later recurrence was observed and additional radio-chemotherapy was conducted. However he died of aggressive dissemination 8 months later after recurrence and autopsy was performed. In those two patients the serum levels of both AFP and β-HCG remained normal even after recurrence. The specimens of recurrent tumor contained no other component such as teratoma, and manifested neither AFP nor HCG staining. Interestingly the first primary tumor revealed strong positive staining for c-kit while the recurrent specimens did little staining. Thus the recurrent tumors were not due to outgrow of intrinsic component different from germinoma in the primary tumor indicating mixed tumor but due to the malignant transformation of germinoma cells themselves.

Paper ID: 115

PEDIATRIC BASAL GANGLIA GERM CELL TUMORS: CLINICAL AND RADIOLOGICAL FEATURES

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Aims: Pediatric basal ganglia germ cell tumors (GCTs) represent a rare subset of tumors with poor understandings. We aimed to summarize the clinical features and radiological findings of this disease, and demonstrate our institutional therapeutic strategy.

Methods: From January 2010 to January 2015, twelve pediatric patients suffered from basal ganglia GCTs were treated in our hospital. The clinical features, radiological findings, diagnosis, treatment and the outcome of these patients were retrospectively analyzed. Our institutional diagnostic principle and treatment strategy of this disease were discussed.

Results: GCTs accounted for 25.5% of all the pediatric basal ganglia tumors treated in our hospital. There were 9 males and 3 females with a mean age of 11.5±2.1 years. The most common symptom was progressive hemiparesis (n=9, 75%). The radiological findings showed that the lesions predominately located in caput of caudate nucleus (n=9, 75.0%), and followed by lenticular nucleus (n=3, 25.0%). The hemiatrophy was commonly observed (n=8, 66.7%). Eight patients were diagnosed as germinomas and four patients were NGGCTs. During the follow-up period, preoperative neurological dysfunctions improved in 7

patients and remained stable in 3. Two patients developed new onset of neurological dysfunctions after the treatment. Two patients suffered from tumor recurrence.

Conclusions: For basal ganglia tumors in pediatric patients, GCTs are not as rare as considered. Tumor markers should be tested as routine for the lesions located in this region. Pediatric basal ganglia GCTs are associated with distinctive clinical and radiological features including male predominant, age distribution in second decade, symptoms of progressive hemiparesis, locational feature of caput of caudate nucleus adjacent to anterior horn of lateral ventricle and ipsilateral hemiatrophy in MRI.

Tumour Microenvironment

Paper ID: 125

CLINICAL SIGNIFICANCE OF GLIOMA CELL DERIVED VESSELS (O)

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Background: Our previous study showed that vasculogenic mimicry (VM) existed in glioma and is a poor prognosis factor. However, the relationship between glioma derived vessels(GDV) and prognosis of GBM patient is unclear. This study, we analyses clinical significance of glioma cell derived vessels along with some gene alternations in GBM patients.

Methods: The clinical information and tumor tissues were collected from 64 GBM patients. The tumor samples were performed CD34-GFAP immunofluorescence (IF) staining to evaluate tumor cell derived vessels, and MGMT promoter methylation as well as *IDH1/2* mutations analysis. The tested data were accessed for Kaplan-Meier survival analysis

Results: MGMT methylation was examined in 61 of 64 patients. *IDH1/2* mutations were examined in 55 of 64 patients. Thirty-eight samples had MGMT promoter-methylateion and 7 have found *IDH1* mutation. None of 64 patients showed IDH2 mutations. Glioblastoma patients with MGMT methylation had a median survival of 13.41 months versus 9.84 months of non-methylated patients($p< 0.05$). Patients with GDV had a median survival of 9.43 months versus 14.03 months of non-GDV patients($p< 0.05$). In MGMT methylated cohort, patients with GDV had a median survival of 6.66 months versus 15.89 months for non-GDV patients($p< 0.05$). In MGMT non-methylated cohort, patients with GDV had a median survival of 9.43 months versus 11.95 months for non-GDV patients($p> 0.05$). In *IDH1* wild type cohort, patients with GDV had a median survival of 9.84 months versus 13.70 months for non-GDV patients($p< 0.05$).

Conclusion: Glioma cell derived vessels is a poor prognosis in MGMT methylated and *IDH1* wild type patients for newly diagnosed GBM patient.

Keywords: Glioblastoma (GBM); Vasculogenic mimicry (VM); Glioma derived vessel

Paper ID: 179

MALIGNANT TRANSFORMATION OF BONE MARROW MESENCHYMAL STEM CELLS VIA TERT OVER-EXPRESSION INDUCED BY GLIOMA STEM CELLS IN AN XENOGRAFT MODEL

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Objective: To observe the mutual interactions between glioma stem cells (GSCs) and bone marrow derived mesenchymal stem cells (BMSCs) in tumor micro-environment.

Methods: After irradiation of nude mice, allogeneic transplantation with $EGFP^+$ bone marrow cells was performed via caudal vein injection. Then RFP gene transfected glioma stem cell line SU3 were transplanted intracranially. After formation of xenograft tumors, high proliferative $EGFP^+$ cells were cloned. Cell surface markers, biological characteristics and relevant gene analysis of the $EGFP^+$ cells were performed. Primary culture of BMSCs from EGFP nude mice, then TERT gene was transfected into the BMSCs. Comparative studies on the biological characteristics of TERT transfected BMSCs (TERT-BMSCs) and transformed BMSCs (tBMSCs) indued by GSCs were performed.

Results: The intracranial tumor formation rate of SU3-RFP in the bone marrow reconstitution model was 100% (7/7). High proliferative $EGFP^+$ cells, with CD44, CD90, CD29 positive expression, and CD45negative expression, were proved to be derived from BMSCs. Biological analysis showed tBMSCs behaved high proliferation, aggressiveness abilities, accompanied with over-expression of TERT, and its tumorigenicity rate was 100% (5/5). Proliferation abilities, colony formation and aggressiveness abilities of TERT-BMSCs were slightly lower than those of tBMSCs, its tumorigenicity rate was 20%(2/10), which was far below than that of tBMSCs. Proliferation abilities and aggressiveness abilities of normal BMSCs were far less than tBMSCs and TERT-BMSCs, its tumorigenesis rate was 0%(0/10).

Conclusions: Malignant transformation of BMSCs with over-expression of TERT, induced by GSCs, can occur in dual-color-tracing xenograft tumor model. The mechanisms of malignant transformation of TBSCs was not only highly related with over-expression of TERT, but also other genetic abnormalities may be involved in.

Paper ID: 85

BACITRACIN, A CANDIDATE OF ANTI-INVASIVE AGENT IN MALIGNANT GLIOMA CELLS, INTERFERES THE INTEGRIN OUTSIDE-IN SIGNALING PATHWAY VIA BINDING WITH REDUCED PROTEIN DISULFIDE ISOMERASE ON THE CELL MEMBRANE

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Received 2015 Sep 23; Revised 2016 Jan 15; Accepted 2016 Jan 21.

Objective: Protein disulfide isomerase (PDI) acts as a chaperone on the cell surface, and it has been reported that PDI is associated with the tumor cell migration and invasion. The aims of this study are to investigate the anti-migration effect of bacitracin, which is an inhibitor of PDI, and the associated factor in this process.

Methods: U87-MG glioma cells were treated with bacitracin in 1.25, 2.5, 3.75, and 5.0 mM concentrations. Western blot with caspase-3 was applied to evaluate the cytotoxicity of bacitracin. Adhesion, morphology, migration assays, and organotypic brain-slice culture were performed to evaluate the effect of bacitracin to the tumor cell. Western blot, PCR, and gelatin zymography were performed to investigate the associated factors. Thirty glioma tissues were collected following immunohistochemistry and Western blot.

Results: Bacitracin showed a cytotoxicity in 3rd (p<0.05) and 4th (p<0.001) days, in 5.0 Mm concentration. The cell adhesion significantly decreased and the cells became a round shape after treated with bacitracin. The migration ability, the expression of phosphorylated focal adhesion kinase (p-FAK) and matrix metalloproteinase-2 (MMP-2) decreased in a bacitracin dose- and time-dependent manner. The U87-MG cells exhibited low-invasiveness in the 2.5 mM, compared with the untreated in organotypic brain-slice culture. PDI was expressed in the tumor margin, and significantly increased with histological glioma grades (p<0.001).

Conclusion: Bacitracin, as a functional inhibitor of PDI, decreased the phosphorylated FAK and the secreted MMP-2, which are the downstream of integrin and play a major role in cell migration and invasion, might become one of the feasible therapeutic strategies for glioblastoma.

Keywords: Bacitracin, Protein disulfide isomerase, Integrin, Glioma, Migration, Invasion

Paper ID: 138

EXOSOMAL MIRNAS DERIVED FROM GLIOMA STEM CELLS PROMOTE CELL MIGRATION AND PROLIFERATION VIA PTEN/AKT SIGNALLING PATHWAY (O)

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Aims: Glioblastomas are the most common primary brain tumours and progress rapidly. Previous studies demonstrated GSCs-derived exosomes manipulate the tumour environment in order to accommodation GSCs and promote metastasis by miRNAs but the detailed mechanism is still unclear. This study aims to identify the molecular mechanism of exosomes regulating the microenvironment and promoting metastasis.

Methods: We conducted a miRNAs expression profile from 92 glioma patients and 17 normal controls samples by Nanostring. Differential expression miRNAs were identified after quality control and normalization. Exosomes from GSCs were isolated by serial centrifuging. Wound healing assay and spheroid migration assay were performed to detect the cell migration. We employed cell viability to detect proliferation. Predicted miRNAs target genes were identified by online different target gene prediction algorithms. Western blotting was performed to detect the protein expression.

Results: Within 800 candidate miRNAs, a total of 132 upregulated and 4 downregulated miRNAs is identified by Nanostring. MiR-21/miR-29a/miR-92b/miR-383 are differential expressed in human plasma samples between gliomas and healthy controls, which also extremely highly expressed in GSC-derived exosomes. TCGA data showed these extremely upregulated miRNAs such as miR-21 are associated with glioma progressions and metastasis (p=0.021). GSCs-derived exosomes are observed to be uptaken by recipient cells in 48 hours. After uptaking, migration of glioma cells are increased significantly after GSCs-derived exosomes added (p=0.019). Cell

proliferation is observed to be improved 21.4%±15% comparing the normal controls. Different target genes predication show PTEN is the potential target genes of miR-21/miR-29a/miR-92b/miR-383, which is confirmed by western blot that PTEN expression decreased and pAKT expression increased accordingly.

Conclusions: GSC-derived exosomes are uptaken by glioma cells in order to promote cell migration and proliferation. Furthermore, the increased malignancy is induced by exosomal miRNAs such as miR-21/miR-29a/miR-92b/miR-383, by degrading PTEN expression and activation of Akt pathway.

Paper ID: 71

MTOR SIGNALING PATHWAY ACTIVATION IN PERITUMORAL TISSUES CAUSE GLIOMA ASSOCIATED SEIZURE

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Aims: Seizure activity is the most common symptom accompanying gliomas, and it was reported that nearly 80% of the glioma patients would experience seizure active at least once during the whole course of disease. The mechanism of epileptogenesis in glioma patients is poorly understood, the aims of the study was to identify the possible relationship between mTOR pathway and seizure activity in glioma patients.

Methods: we aimed to used the patch clamp recording form glioma patients to find the directly evidence of seizure focimoreover, we analyzed the mTOR pathway in the tumor and surrounded brain tissues.

Results: A total of 9 glioma patients were included in this study, consisted of 6 patients with perioperative seizure and 3 patients without. Short spontaneous paroxysmal discharges were observed in 4 of 6 peritumoral tissues of the glioma patients with perioperative seizure, yet these were absent in slices from 3 glioma patients without perioperative seizure or tumor tissues. Further more, IHC immunohistochemistry and western blot identified that the mTOR pathway was activation in the peritumoral tissues of patients with glioma associated seizure(GAS), but the patients without GAS have no mTOR pathway activation in the peritumoral tissues.

Conclusions: mTOR pathway activation in the tumor and surrounded brain tissues could cause tumor associated seizure.

Fig 1
A.Pre-operation brain MRIs from a glioma patient with tumor associated seizure and digital image of the tumor.
B.Digital image of the tumor cavity and short spontaneous paroxysmal discharges was detect in the peritumoral tissue(left panel).
C. the H&E staining of pathological samples from the patients.

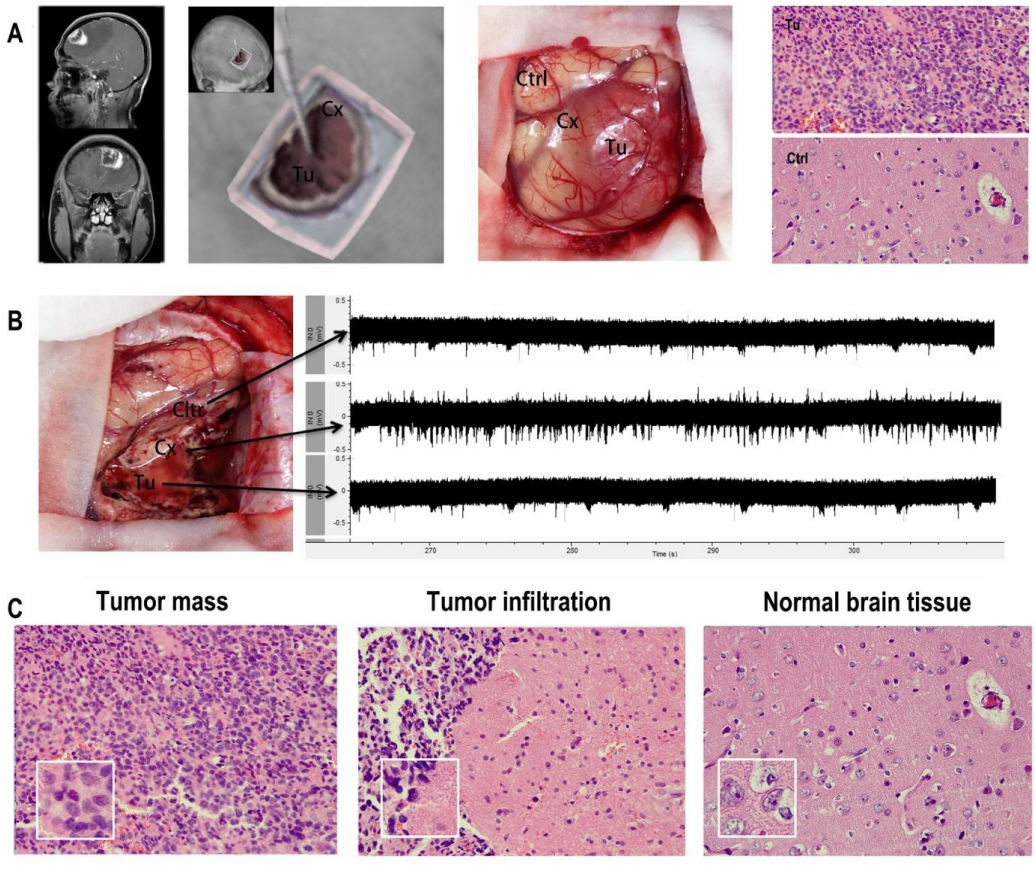

Fig 1

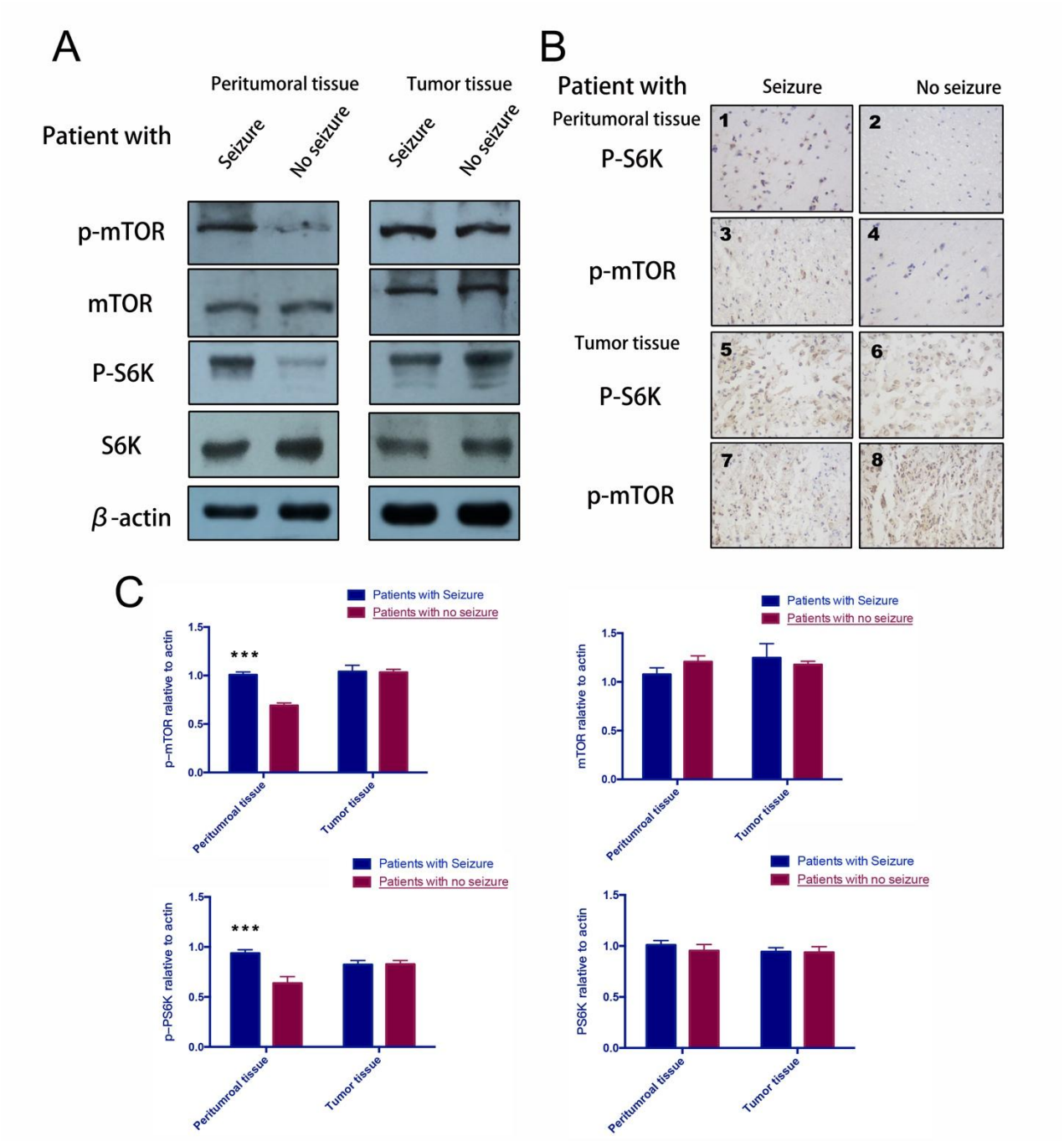

Fig 2

A. Western blot results. B. IHC immunohistochemistry.C. Western blotting results analysis.

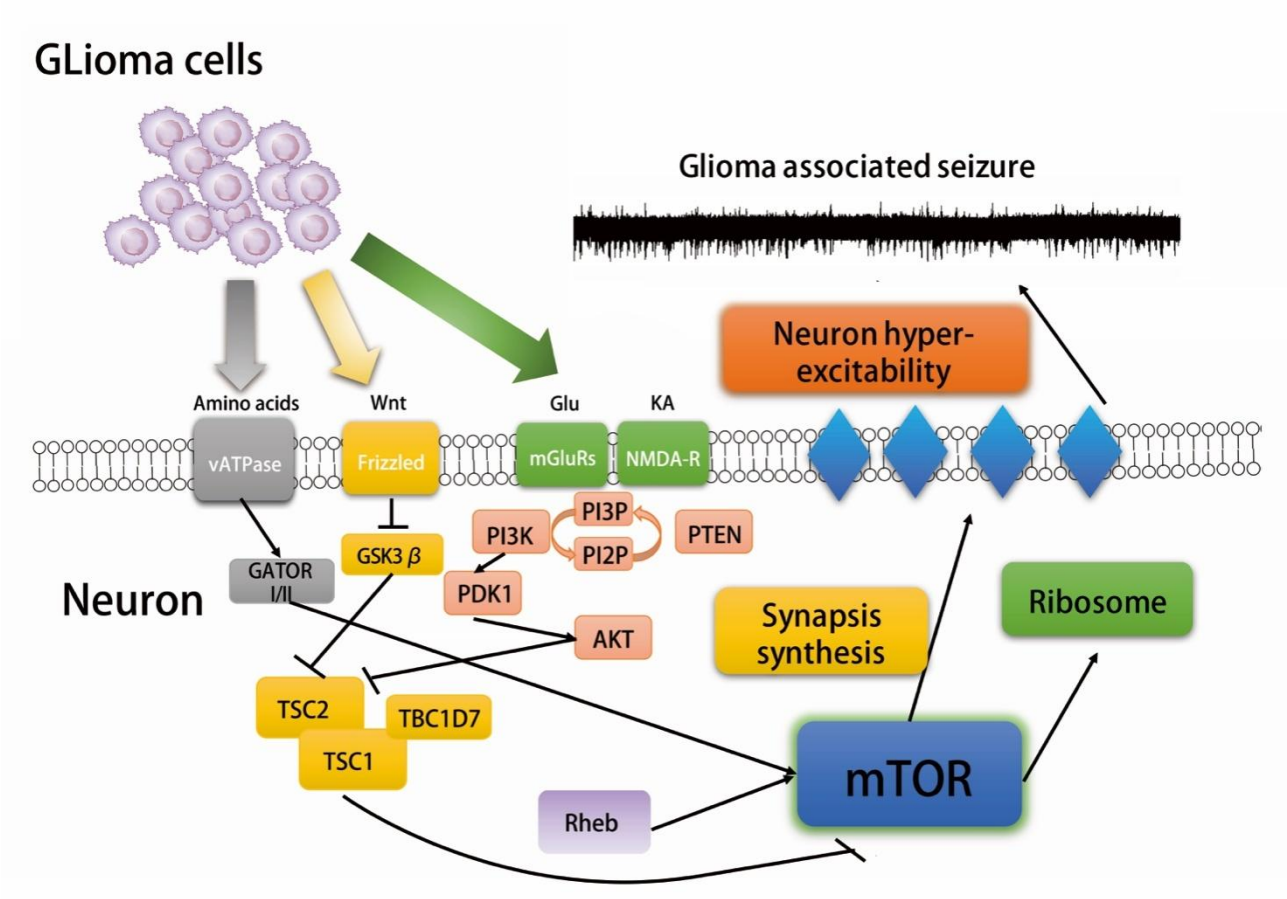

Fig 3.

Illustration of mTOR pathway signalling promotes epileptogenesis.

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