NHMRC Clinical Trials Centre

COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

The achievement of better health outcomes for patients and those affected by brain tumours through clinical trials research

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11th COGNO ANNUAL SCIENTIFIC MEETING

Targeting survival: living well with brain cancer in the era of precision treatments

Sunday 7th October – Tuesday 9th October 2018, Brisbane Convention & Exhibition Centre, Australia

CONFERENCE BOOKLET

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2018 ASM ORGANISING COMMITTEE

Dr Mark Pinkham, Convenor	Radiation Oncologist, Princess Alexandra Hospital
A/Prof Matthew Foote	Radiation Oncologist, Princess Alexandra Hospital
Dr Lucy Gately	Medical Oncologist, St Vincent's Hospital
A/Prof Lindy Jeffree	Neurosurgeon, Royal Brisbane and Women's Hospital
Dr Hamish Alexander	Neurosurgeon, Royal Brisbane and Women's Hospital
Prof Tamara Ownsworth	Clinical Neuropsychologist, Griffith University
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COOPERATIVE TRIALS **G**ROUP FOR **N**EURO-**O**NCOLOGY

The achievement of better health outcomes for patients and those affected by brain tumours through clinical trials research

Dear Colleagues

We would like to welcome you to the 11th COGNO Annual Scientific Meeting. The theme of the meeting is 'Targeting survival: living well with brain cancer in the era of precision treatments'.

We are very fortunate to host four international guest speakers, spanning a broad range of relevant disciplines:

- Prof Mark Gilbert MD
- Prof Susan Chang MD
- A/Prof Erik Sulman MD PhD
- Dr Terri Armstrong PhD ANP-BC FAAN FAANP

The meeting sessions will focus on: Glioma; Brain Metastases; Adolescent and Young Adult, Paediatric and Rare CNS Tumours; Translational Science; and Survivorship, Psychology and Supportive Care. In addition to updates from invited international and national experts, the top 18 highest-scoring abstracts have been selected to give oral presentations. I would like to thank everyone who submitted work this year, the standard was very high.

Prizes will be available for Most Outstanding Oral Presentation, Most Outstanding Poster Presentation, the Young Investigator Award and the inaugural BTAA Lynette Williams Award for the best posters related to research into supportive care for people with brain tumours. Presentations will also be made for the COGNO Neuro-Oncology Nurse/Care Coordinator Travel Grant and The MSD Hubert Stuerzl Memorial Educational Award. In addition, we are delighted to welcome the 2018 COGNO Outreach Education Preceptorship recipient, Dr Abdi Reza from Indonesia.

Our appreciation goes to all our sponsors and supporters: Cure Brain Cancer Foundation, AbbVie, Brain Tumour Alliance of Australia (BTAA) and Mark Hughes Foundation, Bristol-Myers Squibb (BMS), PharmAbcine, Genesis CancerCare Queensland, Brainlab, Boehringer Ingelheim, Regional Health Care Group Pty Ltd, and Cancer Australia.

On behalf of the Organising Committee, we hope you enjoy the ASM.

Kind regards

Dr Mark Pinkham
Convenor
COGNO ASM 2018

Prof Anna Novak
Chair
COGNO

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PROGRAM OF EVENTS

(Changes may be made to the program)

Sunday 7 October: Pre–ASM Meeting		
TIME	**MEETING**	**CHAIR**
12:45 – 1:45pm	**Brain Cancer Biobanking Australia (BCBA) clinical registry working group** (closed meeting) (P9 Room)	Anna Nowak
2:15 – 4:15pm	**Brain Cancer Biobanking Australia (BCBA) consortium meeting** (closed meeting) (P9 Room)	Anna Nowak
4:30 – 6:00pm	**Management Committee (MC) meeting** (closed meeting) (P7 Room)	Anna Nowak
6:30pm	**Convenor's Dinner** (by invitation only)	

Monday 8 October: ASM Day 1 (P10&11 Room)		
TIME	**MEETING**	**CHAIR**
8:00 – 10:00am	**COGNO Scientific Advisory Committee Meeting** (open to COGNO members only) (P9 Room)	Liz Hovey
10:00 – 10:30am	Morning Tea	
10:30 – 10:40am	**Welcome and Day 1 program overview**	Mark Pinkham
10:40 – 12:40pm	**Session 1: Opening Plenaries 1-3**	Anna Nowak and Mark Pinkham
	Plenary 1: Challenges in Testing Immunotherapies in Brain Tumor Clinical Trials: Mark Gilbert	
	Plenary 2: Developments in Radiation Therapy for Malignant Gliomas: Erik Sulman	
	Plenary 3: Patient-Centered Research in Neuro-Oncology: Improving Understanding of the Impact of CNS Tumours and Treatment: Terri Armstrong	
12:40 – 1:40pm	Lunch	
1:40 – 3:00pm	**Session 2: Brain Metastasis**	Matthew Foote
	Optimal sequencing of radiosurgery and systemic therapy for brain metastases: Mark Pinkham	
	Systemic therapies for melanoma brain metastases: Victoria Atkinson	
	Systemic therapies for lung cancer brain metastases: Chee Lee	
	Trials in Brain Metastasis: Erik Sulman	
	Paper ID O01: Developing a targeted therapeutic for brain metastases: Sarah Shigdar	
	Paper ID O02: Is volume more relevant than number of metastases? A review of patients treated with Gamma Knife in Australia between 2010 and 2017: Michael Izard	
	Paper ID O03: Proteomic analysis of breast cancer brain metastasis microenvironment in-vivo reveals a unique milieu intérieur of metabolic reprogramming: Priyakshi Kalita-de Croft	
3:00 – 3:30pm	Afternoon tea	
3:30 – 4:00pm	**Session 3: Top Scoring Abstracts**	Mark Rosenthal
	Paper ID O04: A Randomized Phase 2 trial of Veliparib (V), Radiotherapy (RT) and Temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) Glioblastoma (GBM): Feasibility and safety outcomes (The VERTU study): Mustafa Khasraw	
	Paper ID O05: Picture description versus picture naming: assessing language deficits following dominant hemisphere tumour resection: Sonia Brownsett	
	Paper ID O06: Designing targeted therapies for glioblastomas with intratumoral heterogeneity: Seçkin Akgül	
	Paper ID O07: NUTMEG: A randomised Phase II study of Nivolumab and Temozolomide (TMZ) vs TMZ alone in elderly patients with newly diagnosed	

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	Glioblastoma (GBM): Trial in progress: Mustafa Khasraw	
	Paper ID O08: Increasing antibody theranostic uptake in primary brain tumours using focussed ultrasound: Simon Puttick	
4:00 – 5:00pm	**Session 4: COGNO and Other Trials Updates**	Mark Rosenthal
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	PersoMed-I: Liz Hovey	
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Tuesday 9 October: ASM Day 2 (P10&11 Room)		
TIME	**MEETING**	**CHAIR**
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9:00 – 9:10am	**Welcome and Day 2 program overview**	Mark Pinkham
9:10 – 10:30am	**Session 5: Glioma Including Plenary 4**	Lucy Gately and Hamish Alexander
	Plenary 4: Advanced Imaging for Glioma: Susan Chang	
	Quick Update on Histone Mutated Midline Gliomas in Adults: Mark Gilbert	
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	Paper ID O09: Understanding the Tumour Suppressive Function of EphrinA5 Signalling in Adult Brain Cancer: Rochelle Dsouza	
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	Using Patient Reported Outcome Measures to Improve CNS Tumour Patient Symptom Management: Terri Armstrong	
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	Paper ID O18: Exploring cell cycle checkpoint inhibition and gemcitabine treatment for glioblastoma: Tracy Seymour	
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	"Keep the pineal gland operating and you will never grow old", Edgar Cayce: Po-ling Inglis	
	Are Adults just Big Kids? Tim Hassall	
	NCI-CONNECT: Rare adult CNS cancer project: Mark Gilbert and Terri Armstrong	
4:20 – 4:30pm	**ASM Summary and Close** – includes presentation of the Most Outstanding Oral Presentation, Most Outstanding Poster Presentation and Young Investigator Awards	

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O05 **Picture description versus picture naming: assessing language deficits following dominant hemisphere tumour resection.**
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ORAL ABSTRACTS

O01

Developing a targeted therapeutic for brain metastases

Joanna Macdonald[1], Justin Henri[1], Sarah Shigdar[1]

[1]School of Medicine, Deakin University, Geelong, Victoria, Australia

Abstract

Aims: The incidence of brain metastases following primary malignancies are increasing. Prognosis is poor due to the restrictive nature of the blood brain barrier (BBB), which prevents the majority of therapeutics entering the brain. A novel approach to overcome this is to target receptor mediated transport mechanisms present on the BBB, in particular the transferrin receptor. Given their specificity, safety profile and stability, nucleic acid based therapeutics are ideal for this purpose.

Methods: We developed an aptamer targeting the transferrin receptor to specifically cross the BBB. This was attached to an aptamer that recognises a cell surface marker on epithelial cancer cells, the epithelial cell adhesion molecule (EpCAM). The specificity was confirmed both *in vitro* and *in vivo* using an *in vitro* BBB model and an animal model of brain metastases. As further proof of principle, a common chemotherapeutic was attached to the aptamer and biodistribution was assessed *in vivo*.

Results: In vitro, the aptamer transcytosed the BBB model and targeted only EpCAM positive cells in a co-culture of EpCAM positive and negative cells. This aptamer also specifically delivered doxorubicin across the in vitro model. In vivo, we confirmed the aptamer's ability to transcytose the BBB in a healthy mouse following a single i.v. injection (40 nmol/kg)[1], and in an animal model of brain metastases. Importantly, we showed colocalisation of the drug in tumour cells in the brain.

Conclusions: These promising results demonstrate that through the fusion of two aptamer sequences, a bi-functional aptamer can be generated which has the potential to be developed for the specific treatment of EpCAM positive brain metastases.

References

[1] J Macdonald et al. Development of a Bifunctional Aptamer Targeting the Transferrin Receptor and Epithelial Cell Adhesion Molecule (EpCAM) for the Treatment of Brain Cancer Metastases. *ACS Chemical Neuroscience* **2017** 8 (4), 777-784.

O02

Is volume more relevant than number of metastases? A review of patients treated with Gamma Knife in Australia between 2010 and 2017

Michael Izard[1,2,3], Vaughan Moutrie[1], Jeffrey Rogers[4], Ken Beath[5], John Fuller[4]

[1]GenesisCare, Sydney, Australia.

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[3]Sydney Medical School, Sydney, Australia.

[4]Macquarie Neurosurgery, Sydney, Australia
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[5]Macquarie University, Sydney, Australia

Abstract

Introduction: The Gamma Knife was introduced into Australia in 2010 at Macquarie University Hosptial Sydney. Data was collected prospectively on all patients treated. This is a novel treament technique to Australia and the opportunity to assess patients response to stereotatic radiosurgery was undertaken to see if the parrarent overseas benefits translated into the Australian community

Aim: To assess the response of patients with intracranial metastases to stereotactic radiosurgery

Method: A prospetively collected cohort of 180 patients with intracranial metastases from different primaries were treated between August 2010 and July 2017. Quality of life data and survival was measured, with Cox regression for multivariate analysis

Results: At the time of assessment, 141 (78.3%) patients have died of their disease. Median survival for the group was 9.2 months, with observed differences resulting from the volume of tumor burden (11.4 months for volumes <3200mm^3 to 5.16 months for volume >9100mm^3). Overall 2-year survival was 20.7%.

Conclusions: Results from the first Gamma Knife radiosurgery center in Australia showed that the treatment is feasible and effective, consistent with the international experience. For patients with larger numbers of intracranial metastases, the total volume of the intracranial burden may be of more significance in predicting outcomes. Whilst there appeared to be a difference in survival by histologic origin, this could be related to concurrent systemic immunotherapy available for certain tumours.

O03

Proteomic analysis of breast cancer brain metastasis microenvironment in-vivo reveals a unique milieu intérieur of metabolic reprogramming

Priyakshi Kalita-de Croft[1,2], Jasmin Straube[3], Fares Al-Ejeh[1,2], Jodi Saunus[1,2], Sunil Lakhani[1,4]

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[2]QIMR Berghofer, Herston, Australia.

[3]QIMR Berghofer, Herston, Brisbane, Australia.

[4]Pathology Queensland, Herston, Brisbane, Australia

Abstract

Aims

Brain metastasis (BM) is an unfortunate clinical complication that occurs in about 15-30% of the patients with metastatic-breast cancer[1]. Extremely poor prognosis and neurological impairments of sensory and cognitive functions are salient features of BM, with survival rates varying between 4-12 months post-diagnosis [2, 3]. Therefore, there is an urgent need of unravelling novel mechanisms of BM including treatment-resistance. The tumour-microenvironment (TME) provides both the framework and mechanism for metastatic outgrowth. Despite immense negative selection-pressure tumour-cells colonise using adaptive mechanisms, including: oxidative-stress resistance, repurposing neurotransmitters and mimicking neural traits[4]. These transformations could be clinically targetable and hence we set out to identify novel adaptations in breast cancer-brain metastasis by performing proteomic analysis of the mouse brain compartment of breast cancer-brain xenografts.

Methods

MDA-MB-231 breast cancer cells were stereotactically injected into NOD/SCID mouse hosts (n=5). Mock-injected (PBS) and matching uninvolved brain (n=4) were used as controls. After three weeks, brain tissues (tumour-associated, mock and normal) were isolated using affinity-based magnetic bead separation (Miltenyi Biotec) and proteomics was performed by Mass Spectrometry (MS)-Swath at Australian Proteome Analysis Facility (APAF).

Results

Unsupervised hierarchical clustering exhibited forty-one differentially expressed proteins. We employed String and IPA analysis to further reveal Gene-Ontology (GO) terms associated with metabolic stress and extracellular vesicle transport such as extracellular exosomes and mitochondrial proteins (FDR <0.05 cut off) to be deregulated. Furthermore, they belonged to mitochondrial dysfunction, sirtuin signalling and apoptosis signalling pathways.

Conclusions

These findings suggest that tumour associated brain exhibits metabolic reprogramming, evident from deregulation of exosomal and mitochondrial pathways. This indicates that the bioenergetics demand of the microenvironment has altered the milieu intérieur of the brain. Apart from validating these findings on additional mouse brain xenografts and clinical samples, future work will focus on studying these metabolic changes for targeting and therapeutic purposes.

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2. Niikura N, Hayashi N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M et al: **Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis**. Breast Cancer Res Treat 2014, **147**(1):103-112.

3. Quigley MR, Fukui O, Chew B, Bhatia S, Karlovits S: **The shifting landscape of metastatic breast cancer to the CNS**. Neurosurg Rev 2013, **36**(3):377-382.

4. Quail DF, Joyce JA: **The Microenvironmental Landscape of Brain Tumors**. Cancer Cell 2017, **31**(3):326-341.

O04

A Randomized Phase 2 trial of Veliparib (V), Radiotherapy (RT) and Temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) Glioblastoma (GBM): Feasibility and safety outcomes (The VERTU study).

Mustafa Khasraw[1,2], Kerrie McDonald[3], Mark Rosenthal[4], Zarnie Lwin[5], David M Ashley[6], Helen Wheeler[1], Elizabeth Barnes[7], Eng-Siew Koh[8,3], Matthew C Foote[9,10], Michael Buckland[11], Lauren Fisher[7], Robyn Leonard[12], Merryn Hall[7], Sonia Yip[13], John Simes[7]

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Abstract

Background: TMZ offers minimal benefit in uMGMT GBM pts. V is synergistic with RT and TMZ in preclinical models, safe when combined with RT or TMZ clinically but the triplet (V+RT+TMZ) is poorly tolerated. VERTU examines V in pts with uMGMT GBM.

Methods: A randomised Phase 2 trial comparing experimental arm A=RT (60gy/30 fractions)+ V (200mg BID) followed by TMZ (150-200mg/m^2D 1-5) + V (40mg bid, D 1-7) every 28 days for 6 cycles vs the standard arm B= RT (60gy/30 fractions) + TMZ (75mg/m^2daily) followed by TMZ (150-200mg/m^2D 1-5) every 28 days for 6 cycles in pts with newly diagnosed uMGMT GBM. The study aims to randomize 120 pts (2:1 to arm A). Primary endpoint is 6 months Progression Free Survival (6PFS) with multiple secondary endpoints. After completion of RT in 60pts (Stage 1), feasibility and safety assessment was planned (defined as ≥70% of pts on arm A completing ≥70% of the planned treatment with ≤30% of pts having any ≥ Grade (G) 3 Adverse Events (AEs)).

Results: 60 pts were randomised in Stage 1 (Arm A=39, Arm B=21). Patient characteristics (age, gender, performance status and extent of resection) were well matched. All 39 pts in the experimental arm completed at least 80% of the planned V treatment, receiving at least 70% of the full V dose and 80% of the planned RT dose. 11 pts (28%) in arm A experienced ≥G3 AEs during concurrent treatment. Commonest severe AEs were seizures in 3pts (15%) and thrombocytopenia in 2pts (10%) in Arms A and B respectively.

Conclusions: Stage 1 of VERTU satisfied predefined feasibility and safety criteria. VERTU will continue until the target (120pts) is reached (anticipated late-2018). Efficacy endpoints will be reported after accrual completion.

(ANZCTR#ACTRN12615000407594)

O05

Picture description versus picture naming: assessing language deficits following dominant hemisphere tumour resection.

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Abstract

Background

Given the debilitating impact of aphasia on social, psychological and financial well-being, it is imperative that surgical planning for the resection of brain tumours aims to both reduce the risk of iatrogenic aphasia and to establish a detailed baseline assessment of pre-surgical language function in order to accurately report any consequences of surgery. To assess this risk, neurosurgeons typically employ confrontation naming tasks in order to map language function and evaluate the risk of iatrogenic aphasia (1, 2). We investigated the extent to which the presence of a language disorder was detected using this task, compared to tasks that demand a greater range of linguistic skills.

Methods & Procedures:

We assessed confrontation naming and picture description skills (3) in 31 right-handed patients who were about to receive, or had recently received, surgery to remove a primary tumour to the left hemisphere. Language impairment was identified using the criterion within the Comprehensive Aphasia test (3).

Results

A higher incidence of language impairment was indicated using 'picture description' compared to 'naming' tasks in both pre-surgical (36%, 7% respectively) and post-surgical patients (44%, 8% respectively). In a subgroup of patients with data for both pre- and post-surgical timepoints, 'naming' performance was consistent across both testing sessions but 'picture description' performance declined between pre and post-surgical testing points.

Conclusion

The subtle language deficits exhibited pre- and post-surgical resection of brain tumours are not adequately detected using 'confrontation naming' tasks as has become de rigueur in pre-surgical language mapping. In this study we present data that suggests that traditional naming paradigms alone are not reliable enough to demonstrate the presence, or indeed absence, of language impairments and so alternative paradigms are needed.

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O06

Designing targeted therapies for glioblastomas with intratumoral heterogeneity

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Abstract

Glioblastomas are the most common and lethal neoplasms of the central nervous system. These malignant brain tumours maintain extreme degrees of genetic and phenotypic variation, including intratumoural heterogeneity exhibited by neighbouring tumour cells. This genetic diversity allows the most adaptive clones to conserve the tumour bulk, especially after treatment. Therefore, many aggressive disease elements such as treatment resistance, recurrence, and metastasis require continuous generation and preservation of a heterogenic tumour environment.

Aims: Current project aims to recapitulate the ever-fluctuating tumour heterogeneity of glioblastoma in novel models to better understand this phenomenon, and design more effective therapeutic interventions to prolong patient survival.

Methods: **a)** Heterogenic tumour masses were deconstructed into single tumour cells, which were then expanded independently as single-cell clones. Single-nucleotide polymorphism arrays, whole-genome sequencing, and RNA sequencing were performed to determine the molecular profile of each tumour clone. **b)** Clones were optically barcoded with various fluorescent constructs. **c)** Unique responses to standards of care and various small molecule inhibitors were determined by analysing the labelled tumour cells. Specific molecular alterations are linked with resistant and sensitive phenotypes. This information will be used to design a multi-compound drug screen to uncover novel sensitivities of resistant clones.

Results: We were able to generate several single-cell tumour clones and chimeras, which displayed different pathologic behaviours, including cell morphology, growth rate, therapy resistance, and interclonal communication. We also identified precise drug sensitivities, which allowed us to target individual clones with specific inhibitors in order to maximize treatment outcome.

Conclusions: Our data suggest that reconstructed polyclonal tumours create a dynamic tumour environment with heterogenic growth rates and treatment responses contributed by distinct clones. This unique system allows us to re-enact human cases in novel models to identify the clones responsible for treatment resistance, recurrence, and metastasis.

O07

NUTMEG: A randomised Phase II study of Nivolumab and Temozolomide (TMZ) vs TMZ alone in elderly patients with newly diagnosed Glioblastoma (GBM): Trial in progress

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Abstract

BACKGROUND: An increase of mutations as we age is well documented in GBM and in cancer in general. Elderly patients with GBM may have higher mutational burden and may be more likely to respond to immunotherapies. NUTMEG is a randomised Phase II study comparing post radiation **N**ivol**U**mab and **TM**Z versus TMZ alone in **E**lderly patients with newly diagnosed **G**BM.

METHODS: 102 patients will be randomized in a 2:1 allocation to receive short course RT (40Gy/15 daily fractions) and TMZ 75mg/m2) followed by 6 cycles of adjuvant TMZ (150-200mg/m2 days (D) 1-5 q28 days) with Nivolumab (240 mg D1, 15 q28 days for cycles (C) (1-4; 480 mg D1 Q 28 days for C5-6) versus 6 cycles of adjuvant TMZ (150-200mg/m2 D1-5 q28) alone. The study is stratified for ECOG performance status, age (< 70 vs ≥ 70), MGMT methylation and extent of resection. An independent safety monitoring committee is overseeing the trial and will review safety data for the first 10 patients treated on the experimental arm (TMZ + Nivolumab). The primary endpoint is Overall Survival (OS). Secondary endpoints include: 6 month Progression Free Survival, adverse events (AEs) and immune AEs, Quality of life, neurological function (NANO Scale), and correlation of modified RANO and iRANO in the experimental arm. Translational research endpoints include correlation of clinical endpoints with mutational burden, comprehensive immune characteristics and novel MRI sequences including pH-weighted MRIs. The expected proportion of patients alive at 24 months is predicted to be 15.7%. A hazard ratio of more than 0.69 in favour of the Nivolumab + TMZ arm will be considered sufficient to warrant further investigation including converting this study into a phase III trial.

PROGRESS: At 29 June 2018, 7/18 study sites are open in Australia with 6 patients
randomized. ACTRN12617000267358.

O08

Increasing antibody theranostic uptake in primary brain tumours using focussed ultrasound

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Abstract

The theranostic treatment paradigm is gaining significant traction for treating patients with neuroendocrine tumours,[1]prostate cancer[2]and recently, meningioma[3]. The treatment is based on the delivery of a radiotherapeutic nuclide such as ^{177}Lu or ^{225}Ac conjugated to a molecule such as a peptide or antibody that binds with high affinity to a receptor overexpressed in the cancer. The development of theranostics for primary brain tumours has been significantly restricted by the challenge of delivering systemic therapies to tumour tissue protected by an intact blood-brain-barrier. Recently, it has been shown that the application of focussed ultrasound in combination with the systemic delivery of microbubbles can temporarily open the blood-brain-barrier, allowing increased uptake of intravenously delivered therapies into the brain.

Aims

In this work, we quantify the increased uptake of theranostic antibodies in high grade glioma using PET imaging and a mouse model with a fully intact blood brain barrier.

Methods

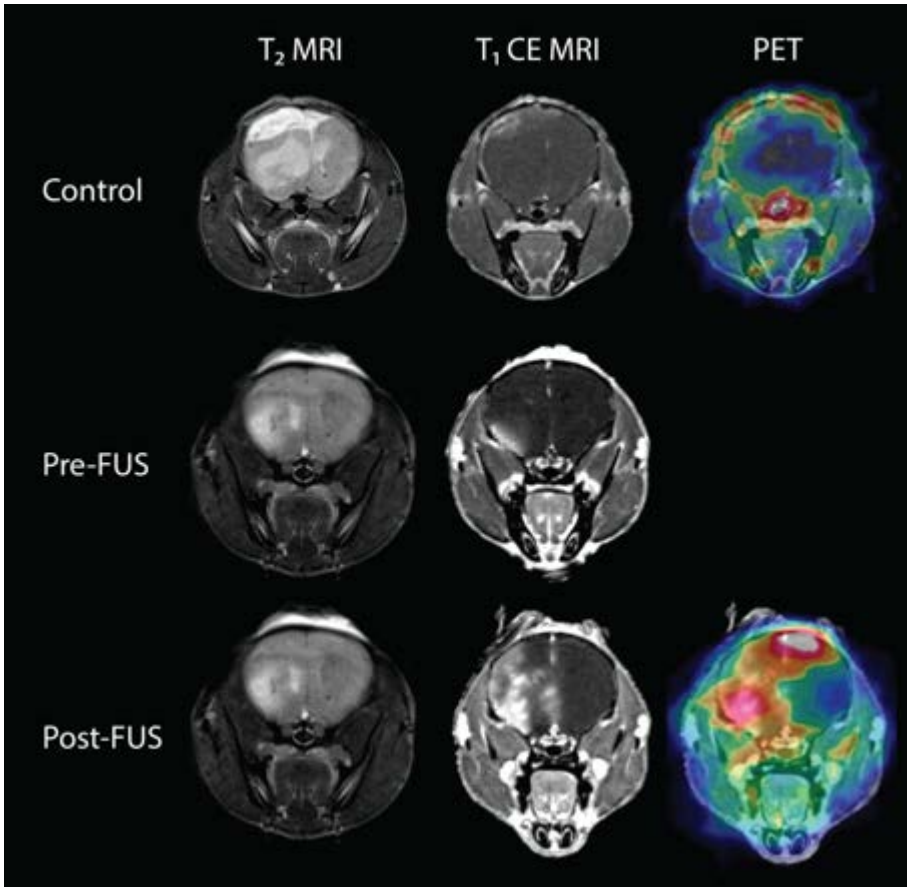
Our mouse model is generated by intracranial injection of patient derived glioma cells in NOD/SCID mice. Mice are monitored by MRI until the formation of a high grade brain tumour is evident. The integrity of the blood-brain-barrier is confirmed in each mouse by contrast enhanced MRI before application of FUS. FUS is applied using a hemispherical transducer operating at 1.1 MHz and mounted in a 3-axis stage. The positioning of the FUS is guided by the MRI image and is confined to the tumour tissue. Uptake of theranostic antibodies is measured by 89Zr PET imaging at 24 hours and 48 hours post FUS.

Results

The application of FUS in combination with microbubbles increases the uptake of theranostic antibodies in tumour tissue by 2-3 fold.

Conclusion

The use of FUS to improve the efficacy of systemic therapies in high grade glioma is extremely promising and should be explored in depth.



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O09

Understanding the Tumour Suppressive Function of EphrinA5 Signalling in Adult Brain Cancer

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Abstract

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 (TMZ) 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.

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 cellsexpress 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.

Building upon these novel findings we are further defining the growth and tumourigenic potential of EphA3 versus ephrin A5 fractions using primary GBM cell lines and primary cell line derived orthotopic mouse models. 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.

Thus, this work explores the potential of soluble ephrin A5-Fc protein to activate EphA3; and reduce GBM aggressiveness, and identify novel targets leading to an extension in GBM patient survival.

O10

Diagnostic Performance of FDG-PET/CT in the Evaluation of Glioma

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Abstract

AIM
To quantify the utility of FDG-PET/CT, alone and in combination with MRI, in identifying high-grade regions of gliomas.

METHODS
This is a retrospective review of patients who had an FDG-PET/CT performed as part of the workup of suspected glioma, or in follow-up of known glioma. FDG-PET/CT scans were reviewed and uptake coded as normal, diffusely or focally increased. Patients also had MRI with gadolinium, noting particular areas of contrast enhancement. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated for identification of high-grade histology (WHO III or IV, or metastatic disease) obtained post FDG-PET/CT.

RESULTS
Forty-nine patients had 53 FDG-PET/CT scans; 18 with suspected glioma, and 35 during follow-up of known glioma. Thirty-Three patients had 36 FDG-PET/CT and MRI scans followed by histological analysis (biopsy or debulking) within 12 months (from the time of FDG-PET/CT).
Increased FDG uptake demonstrated a sensitivity of 68% and specificity of 79%, PPV of 83% and NPV of 61% for identification of high-grade histology. When FDG-PET/CT and MRI were concordantly positive, a specificity of 91% and PPV of 93% was achieved. In five patients, FDG uptake was increased with no abnormal enhancement seen on MRI, and high grade histology was identified in 2 of these patients.

CONCLUSION
FDG-PET/CT had high specificity in identification of high-grade histology. The combination of FDG-PET/CT and MRI demonstrated marked improvement in identifying potential high-grade regions over each modality alone. Increased FDG uptake without MRI contrast enhancement rarely occurred, and predicted for subsequent identification of high grade histology in a small number of patients. Due to limited sensitivity and NPV, a negative FDG-PET/CT, alone or in combination with MRI, should not guide a decision for observation where surgery would otherwise be recommended.

O11

Sleep disturbance among adults with primary and secondary malignant brain tumours and their caregivers: a cross-sectional study

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Abstract

Emerging evidence suggests a close link between sleep disturbance (SD) and clinical outcomes and the health-related quality of life in cancer patients. Yet, understanding sleep disturbance is neglected areas in both neuro-oncology care and research.

Aims: This study aimed to determine the prevalence and predictors of sleep disturbance in brain tumour patients and caregivers, and explore any interaction between the patient-caregiver dyad's sleep.

Methods: Eighty-one adults with primary malignant (91%) or metastatic (9%) brain tumours and their adult family caregivers (n=44) completed a series of self-report questionnaires in an ambulatory neuro-oncology clinic setting in Australia. Sleep patterns and disturbance were assessed with the Pittsburgh Sleep Quality Index and the Insomnia Severity Index. Participants were grouped into high SD or low SD by the PSQI cut-off, and binary logistic regression analyses were performed to identify risk factors.

Results: Of patients, 53% reported having poor sleep quality and 49% having clinically significant insomnia. Increased fatigue severity (OR=1.7, p<0.01) and the use of anti-emetics (OR=4.3, p<0.05) were significant risk factors of SD in patients. Of caregivers, the prevalence of poor sleep quality and clinical insomnia were 55% and 14%, respectively. Anxiety was a significant risk factor of SD in caregivers (OR=1.33, p<0.01). Sleep patterns and scores of the patient-caregiver dyad were not associated. While longer weekly care hours increased the odd of caregivers being high SD (p<0.05), the level of patient's dependency on caregivers and night time care need were not associated with the dyad's sleep.

Conclusions: A substantially high prevalence of sleep disturbance and clinical insomnia was found in this sample. Demographic and clinical variables had limited influence, indicating that sleep disturbance is a more complex problem than toxicity in this sample. Understanding the underlying mechanisms of co-morbid symptoms and options for management is still warranted.

O12

Longitudinal health related quality of life in patients with benign and low-grade brain tumours

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Abstract

Aims: To assess longitudinal health-related quality of life (HRQoL), including the determinants of poor HRQoL, over 5 years in patients with acoustic neuroma (AN), meningioma (M) and low-grade glioma (LGG) and identify modifiable factors to improve HRQoL.

Methodology: Post-operative outpatients with AN, M or LGG were prospectively recruited at The Royal Melbourne Hospital and follow-up surveys were mailed out to patients. HRQoL was assessed at every clinic visit using the EORTC QLQ-C30 and BN20 validated questionnaires. The results were analysed using SPSS, looking for correlations and changes over time.

Results: 619 patients have completed the questionnaire one or more times over 5 years. 1035 completed surveys were assessed. We found HRQoL deficits ($p<0.05$) in all tumour types across multiple domains, with poor perceived cognition and impaired social function an important determinant of poor HRQoL. There were fluctuations around the mean for the global domain. There were no significant changes over a 6-month or 12-month period in any of the HRQoL domains. Patients also experienced reported fatigue as being a prominent symptom that impaired HRQoL.

Conclusion: Significant HRQoL impairments are evident in these patients, particularly related to perceived cognitive function, fatigue, social and role functioning. Longitudinally, there appear to be no major changes in HRQoL in most patients. This suggests that, contrary to popular belief, the HRQoL of patients does not improve over time and interventions need to be instigated to improve HRQoL of brain tumour patients. Further investigation with interventions aimed at improving HRQoL (e.g. managing mental health issues) are warranted.

O13

The importance of staying connected: mediating and moderating effects of social groups on psychological wellbeing after brain tumour

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Abstract

Aims: Functional impairments contribute to psychological distress after brain tumour. Changes in social groups and confidence in support potentially impact this relationship. This study aimed to investigate the influence of social groups on functional impairment and psychological wellbeing.

Methods: 70 people with primary brain tumour (46% benign; 18% low grade; 36% high grade) aged 22-75 years completed measures of cognitive and physical impairment (Functional Assessment of Cancer Therapy), social groups (Exeter Identity Transition Scale), confidence in social support (Self-Efficacy Scale), depression, anxiety and life satisfaction.

A bootstrapping method and PROCESS macro was utilized to test mediating and moderating effects of social group variables, controlling for relevant demographic and tumour characteristics.

Results: The relationship between cognitive and physical impairment and psychological distress was significantly mediated by maintenance of social groups. Indirect effects were found for depression (CI: 0.019-0.109), anxiety (CI: 0.013-0.064), and life satisfaction (CI: -0.094~-0.013). Forming new social groups had a moderating effect for life satisfaction ($p<.05$), whereby individuals perceiving more cognitive impairment who were better able to develop new social groups reported higher life satisfaction. Confidence in social support was a moderator for depression ($p<.001$), such that those perceiving more physical impairment who were more confident in their social support reported lower depression.

Conclusions: Functional impairment is related to increased psychological distress through loss of social groups. However, development of new social groups and greater confidence in support can buffer the effects of functional impairment on psychological well-being after brain tumour.

O14

What support are carers requiring over time during nurse-led support provided as part of the Care-IS study?

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Abstract

High grade gliomas (HGG) are invariably terminal brain tumours, leading 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 evaluates a nurse-led education and support program to improve carer preparedness and quality of life; reduce anxiety and depression; and decrease unplanned health service use. Data on the support provided to 10 carers following nursing assessment up to 12 months will be presented.

Methods: Randomised, controlled, unblinded Phase III trial comparing usual care with the intervention. Recruitment: WA and NSW. The carer education program consists of 1) Telephone assessment of needs; 2) Nurse-led home visit; 3) Tailored resource manual and 4) 12 months ongoing telephone support.

Results: 156 carers have been recruited to date. The most common presenting issues of the 10 participants that were reviewed were around carer strain, managing care recipients' behaviours, mobility and side effects related to chemotherapy. During their involvement in the study the nurse made an average of 5 contacts per carer to other health professionals, including the involved medical oncologist. On average, 17 recommendations were made providing educational and emotional support for carers during telephone assessments and other contacts. The most common recommendations were to the resource manual, community support services, the GP, Cancer Nurse Coordinator and a psychologist. One carer was advised to present to the emergency department with chest pains and a second carer presented to the emergency department for stress related concerns.

Conclusions: Carers were provided with a range of supports which altered as the patients' disease progressed. We hypothesise that this ongoing support will reduce care distress, increase carer preparation, improve carer outcomes and reduce patient healthcare resource utilisation and costs.

O15

The EphA3 receptor is a tumour-specific therapeutic target for adult GBM and paediatric medulloblastoma.

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Abstract

The aim of this study is to preclinically evaluate EphA3 as a drugable target in adult GBM and paediatric medulloblastoma. We previously defined EphA3 as a therapeutic target for adult GBM [1]. Our analysis of published medulloblastoma gene expression datasets [2, 3] now demonstrates that EphA3 is also expressed in a significant proportion of medulloblastoma across all subtypes. We confirmed EphA3 expression in paediatric medulloblastoma in patient-derived cell lines and xenograft models. Immunohistochemistry staining of patient tumours further showed positive EphA3 expression in medulloblastoma specimens particularly in the perivascular region, a known cancer stem cell niche. We have now developed antibody drug conjugates (ADCs) against EphA3 by conjugating our EphA3-specific monoclonal antibody IIIA4 to the highly cytotoxic tubulin inhibitor maytansine. These EphA3-ADCs are effective in vitro and, more importantly, showed significant anti-tumour activity while being well tolerated in vivo using orthotopic xenograft models. Intravital bioluminescence imaging showed that treatment with EphA3-ADCs reduced tumour burden of established brain tumours and significantly improved survival of these tumour-bearing mice. We propose that combining EphA3-ADCs with current treatment modalities has the potential to improve outcome for patients with adult GBM and paediatric medulloblastoma.

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O16

In vitro evaluation of DC vaccination combined with immune checkpoint inhibition for glioblastoma multiforme (GBM) using patient derived peripheral leucocytes

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Abstract

Aims
Dendritic cells (DC) have the potential to be used as immunotherapy for GBM due to their ability to activate antigen-specific T cells. DC vaccination for GBM has shown limited efficacy due to tumour-associated immunosuppression and the inferior migratory capacity of commonly used monocyte derived DCs (MoDCs) compared with blood DCs (BDC) [1, 2].

The aims of this research are to: describe the immune phenotype of BDCs from GBM patients (GBM) compared to healthy donors (HD), demonstrate superior function of BDCs, including immunoselected CMRF-56+ cells, compared with MoDC [3] and justify combining DC vaccination with an anti-PD-1 mAb.

Methods
The expression of immune checkpoint molecules on myeloid (CD1c+, CD141+), plasmacytoid (CD304+) BDC and T cell subsets was determined by flow cytometry. Mixed leucocyte reactions were performed using CD1c+ BDC from GBM patients to stimulate healthy donor (HD) CD3+ lymphocytes. CMV pp65 peptide pulsed HD BDC were co-cultured with CD3+ T cells to show expansion of pp65 specific T cells and their effect on GBM cell lines in combination with anti-PD-1 mAbs.

Results
BDC subsets were present in GBM in similar proportions to HD. A trend towards lower CD1c+ DC and CD4+ T cells was noted (n=10). BDC isolated from GBM and HD were functional. We observed augmentation of T cell proliferation with an anti-PD-1 mAb (nivolumab) with HD BDC but not with GBM. CMRF-56+ BDCs showed superior antigen processing and response to chemotactic signals compared with MoDC.

Conclusions
Functional BDC are present in GBM in similar proportions to HD. BDC enriched with the CMRF-56 mAb demonstrate superior immunological function. The combinatory approach has the potential to improve therapeutic efficacy by inducing antigen specific immunity (BDC vaccine) in combination with anti-PD-1.

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O17

Creating a stronger link between nanomedicine development and the clinic for the treatment of gliomas

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Abstract

Nanomedicines have been shown to have great potential for the diagnosis and treatment of a variety of cancers, but their utility towards brain cancers has been limited due to the difficulty in penetrating the blood-brain barrier (BBB). Testing of these nanomedicines requires preclinical studies, but typically rely on orthotopic glioma models which disrupt the BBB in the process and are not indicative of human glioma. Therefore, we have utilised a mouse model with endogenous glioma formation[1] where mice can be individually assessed for tumour progression and response to treatment and potentially increase the clinical efficacy of new novel nanomedicine treatments for glioblastoma.
Aim: By using clinically translatable imaging techniques in a spontaneous glioma model, can we more accurately predict the clinical viability of future nanomedicines?

Method: We used standard dynamic, pre-, and post-contrast T1 and T2 weighted MR images to assess the leakiness of the BBB and measure tumor volume, respectively. For each mouse that presented a tumour, the crossing of nanomedicines were assessed by PET. Two particles with and without antibody targeting were injected across the various stages of progression and their uptake into the tumour was measured using PET and validated with microscopy of the resected tumour.

Results: Both tumour volume and BBB leakiness were found to be equally valid but independent methods to measure the tumour progression. Smaller nanomedicines were found to cross at earlier stages of tumour progression with and without targeting, while larger particles only crossed at very late stages.

Conclusion: The work presented herein serves as a proof-of-concept that can be used to test a variety of nanomedicines of different shape, size, charge to allow the further development of BBB permeable nanomedicines in mice or larger animals and has the potential to improve the efficacy of nanomedicines or other treatments that reach the clinic.

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O18

Exploring cell cycle checkpoint inhibition and gemcitabine treatment for glioblastoma

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Abstract

Background: Glioblastoma is the most common malignant primary brain tumour. Standard therapy includes maximal surgical resection, radiotherapy and adjuvant chemotherapy with temozolomide. This is not curative as glioblastoma cells can be resistant to adjuvant treatments. Median survival is <15 months and progression-free survival is typically 7 months. These poor outcomes reflect the pressing need for more effective treatment strategies. Gemcitabine is a small, brain-penetrant, cytosine analogue that causes DNA damage, triggers the DNA damage response pathway, and has been used previously in relapsed glioblastoma. Prexasertib/LY2606368 is an inhibitor of cell cycle checkpoint 1 and 2 (CHK1/2), and has been shown to enhance DNA-damaging chemotherapy in other adult cancers.

Aim: Our study explores the hypothesis that LY2606368 inhibits gemcitabine-induced DNA damage repair, resulting in accumulated DNA damage, and enhanced death of glioblastoma cells.

Methods: In vitro drug interaction assays and western blot analyses were used to investigate the compatibility of gemcitabine and LY2606368 in glioblastoma. The immediate cellular effects and survival benefits of combination treatment were examined using orthotopic xenograft models.

Results: LY2606368 synergised and enhanced gemcitabine-induced cell death in two established glioblastoma cell lines, T98G and U87. Western blots using patient-derived GBM6 glioblastoma cells showed that LY2606368 inhibited CHK1 in these cells, and when combined with gemcitabine, phosphorylation of CDC2 was reduced, while gammaH2AX levels increased. These data suggested that LY2606368 causes a block in cell cycle arrest, leading to accumulated DNA damage. These findings were also observed in vivo. Immunohistochemistry showed LY2606368 significantly increased gemcitabine-induced gammaH2AX, and reduced tumour cell proliferation. Furthermore, combination treatment significantly extended survival in multiple orthotopic mouse models of glioblastoma.

Conclusion: This study has demonstrated the potential of therapeutically combining gemcitabine with LY2606368 and provides robust data that informs future clinical trials for relapsed glioblastoma patients.

POSTER ABSTRACTS

P01

"I'm the handbrake": a qualitative interview study of the experiences of informal carers for patients living with glioma

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Abstract

Aims: Formal and informal carers shoulder a large proportion of the burden of care for patients with glioma . Informal carers play a critical role in both survivorship and toward the end of the life course, yet what they experience, and how they contribute to social and community life, is not well understood. The aim of this study was to explore the experiences and perspectives of informal carers in supporting patients with glioma.

Methods: Qualitative semi-structured interviews were conducted with 24 informal carers of patients with low- and high-grade glioma from a quaternary hospital in South East Queensland. Interviews focused on the day-to-day aspects of caring at home in the context of a non-curable and ultimately terminal diagnosis. Interviews were conducted in partcipants' homes - particularly mapping the ways by which 'primary' carers adjusted to the diagnosis and prognosis to define their role(s) and identity. Interview data was subject to thematic analysis, driven by the framework approach, and using NVivo 11 software to support the analysis.

Results: Themes derived from the analysis include: The learning curve of keeping the patient 'Up' and not breaking the code of optimism; Carers as 'gatekeepers' of optimism, hope and realism; Carers as 'handbrakes', responsible for managing patient's capacity and expectations; and finally, Carers as responsible for managing others such as the expectations of familial and social networks, including sheilding the patient from 'brightsiding' on the part of other family members, friends or colleagues.

Conclusions: Managing optimism for the patient and other social networks is a key balancing act of the caring role. The findings of this study expose the management of hope and positivity as an additional and hitherto invisible burden of caring - particularly at the end of life. This highlights informal care as an increasingly precarious commodity in glioma survivorship.

P02

Re-irradiation in recurrent high-grade gliomas: A systematic analysis of treatment technique with respect to survival and radionecrosis outcomes

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Abstract

Introduction

Re-irradiation may be considered for select patients with recurrent high-grade gliomas. Treatment techniques include conformal radiotherapy employing conventional fractionation, hypofractionated stereotactic radiotherapy (FSRT), and single-fraction stereotactic radiosurgery (SRS). We aimed to perform a pooled statistical analysis of published studies to assess differences in survival and radionecrosis rate according to radiotherapy technique.

Methods

A population-weighted, pooled multiple regression analysis of publications from 1992 to 2018 was performed to evaluate the relationships between re-irradiation technique and median overall survival (OS) and radionecrosis (RN) outcomes.

Results

Seventy-nine published articles were analyzed, yielding a total of 3738 patients. Across all studies, initial treatment was external beam radiotherapy to a median dose of 60 Gy in 30 fractions, with or without concurrent chemotherapy. On multivariate analysis, there was a significant correlation between OS and radiotherapy technique after adjusting for age, re-irradiation biologically equivalent dose (EQD2), interval between initial and repeat radiotherapy, and treatment volume ($P < .0001$). Adjusted mean OS was 12.1 months (95% CI, 11.8–12.4) after SRS, 9.9 months (95% CI, 9.4–10.3) after FSRT, and 9.0 months (95% CI, 8.6–9.4) after conventional fractionation. There was also a significant association between radionecrosis and treatment technique after adjusting for age, re-irradiation EQD2, interval, and volume ($P < .0001$). Adjusted radionecrosis rates were 7.1% (95% CI, 6.6–7.7) after FSRT, 6.2% (95% CI, 5.6–6.6) after SRS, and 1.1% (95% CI, 0.5–1.7) after conventional fractionation.

Conclusions

The published literature suggests that OS is highest after re-irradiation using SRS, followed by FSRT and conventionally fractionated radiotherapy. Whether this represents superiority of the treatment technique or an uncontrolled selection bias is uncertain. The risk of radionecrosis was highest in FSRT followed by SRS and conventional radiotherapy however was acceptably low for all modalities overall. Re-irradiation is a feasible option in appropriately selected patients.

P03

Trends in outcomes of resected intracranial metastatic melanoma across the pre and post era of modern systemic therapies

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Abstract

Introduction:

Brain metastasis is common in melanoma and is associated with poor prognosis. In recent years, immunotherapies and targeted therapies have demonstrated promising intracranial activity. Ipilimumab was the first of many modern systemic therapies that were approved by the FDA since 2011, changing the therapeutic landscape of metastatic melanoma. This study aims to describe the outcomes of melanoma patients with resected brain metastasis at a tertiary referral centre.

Methods:

Melanoma patients with brain metastases who underwent neurosurgery at RBWH between July 2007 and October 2015 were retrospectively identified. Clinical and follow-up information were collected from medical records. Survival was analysed using Kaplan-Meier estimates.

Results:

71 patients were identified: 25 in the pre- (2007-2010) and 46 in the post- (2011-2015) ipilimumab era. Median age was 56 years. 47 patients underwent BRAF testing: 49% were BRAF mutant. Brain metastasis was the first presentation of metastatic disease in 83% of patients. 79% had ≤2 brain metastases. 35% had no extracranial disease. 62% achieved macroscopic complete resection. 60% and 37% achieved complete and partial resolution of symptoms after surgery, respectively. 7% suffered major post-operative complications. 93% were successfully discharged home post-operatively but 11% required inpatient rehabilitation prior to discharge. There was no procedure-related mortality but 1 patient died within 30 days of surgery. 20% received stereotactic radiosurgery while 66% had whole brain radiotherapy. 17% underwent repeat surgical resection for further intracranial recurrence. 63% in the post-ipilimumab group received systemic therapy compared to only 4% in the pre-ipilimumab group. Median overall survival was 6.7 months in the pre-ipilimumab group compared to 11.3 months in the post-ipilimumab group (p=0.04). Two-year overall survival rates were 16% and 37% in the pre- and post-ipilimumab groups, respectively.

Conclusion:

Favourable outcomes are seen in patients treated with surgery and modern systemic therapies, resulting in a significant proportion of long-term survivors.

P04

Pineal germinoma: A 13 year Queensland experience

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Abstract

Background

Pineal germinoma is a rare disease with high cure rates achieved following craniospinal axis radiotherapy. Studies investigating the addition of neoadjuvant chemotherapy to lower doses and smaller fields of radiotherapy suggest comparable disease control and possible reduction of adverse neurocognitive effects[1-7]. We aimed to review clinical outcomes in patients treated in Queensland during a 13 year period.

Method

Patients who commenced radiation or chemotherapy for pineal germinoma 2005-2017 were identified using the Queensland oncology online database. Demographic, diagnostic, treatment and response data were obtained from electronic case records.

Results

Nineteen patients were identified. One patient had no follow-up data available. Mean age at diagnosis was 17.6 years (range 9-46). All are still alive at a median follow-up of 4.9 years (range 0.7-11.8) since completion of primary treatment (unavailable for one patient). Fifteen patients had a histological diagnosis, in most cases tissue was obtained during management of acute hydrocephalus. Three patients were diagnosed based on characteristic radiological appearance and cerebrospinal fluid tumour marker status. All patients received radiotherapy with doses ranging from 15 to 54Gy, the majority receiving whole ventricular irradiation (11/18). 16/18 had chemotherapy prior to radiotherapy. In one patient, the chemotherapy regimen was not known and in the remaining 15, platinum based chemotherapy was used. Relapses occurred in 3 patients at 6, 14 and 29 months from diagnosis, two outside the primary radiation field and one within. All 3 were treated with high dose chemotherapy with stem cell support and radiotherapy and have had no further relapse at 2.5, 5 and 9 years after treatment.

Conclusions

Overall survival and recurrence free survival for patients with pineal germinoma in Queensland over the past 13 years are excellent. Use of reduced radiotherapy in conjunction with chemotherapy does not compromise outcome and is now standard of care at this institution.

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P05

Health related quality of life and cognition in patients with benign and low-grade brain tumours

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Abstract

Aims: To assess health-related quality of life (HRQoL in patients with surgically-treated acoustic neuroma (AN), meningioma (M) and low-grade glioma (LGG) and identify modifiable factors associated with poor HRQoL.

Methodology: Post-operative outpatients with AN, M or LGG were prospectively recruited at The Royal Melbourne Hospital. HRQoL was assessed opportunistically using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and BN-20 validated questionnaires. Objective cognition was measured with a validated, computer-based neuropsychological test battery from Cogstate. Risk of anxiety and depression was assessed using the Hospital Anxiety and Depression Scale (HADS).

Results: 619 patients completed the EORTC questionnaires and 127 completed an objective cognitive assessment. We found HRQoL deficits ($p<0.05$) in all tumour types across multiple domains, with poor perceived cognition an important determinant of poor HRQoL. Scores remained stable longitudinally. Objective cognitive testing showed no clinically significant cognitive deficit. Comparing objective and subjective cognitive scores revealed 52 patients with clinically significant perceived cognitive deficit but normal cognition on objective testing. Emotional factors, future uncertainty, communication deficit, pain and fatigue were moderately correlated with perceived cognitive deficit. Anxiety correlated with poor perceived cognition in all tumour types and depression correlated with poor perceived cognition in M and LGG. Anxiety and depression also correlated with poor scores in various other domains of HRQoL in all tumour types. Spearman's Rho > 0.5 for all correlations.

Conclusion: Significant HRQoL impairments are evident in these patients, particularly related to perceived poor cognitive function, fatigue, social and role functioning. Nearly two-thirds of patients reported poor perceived cognition but performed adequately on cognitive testing. Anxiety and depression may be targeted to improve patient-perceived cognition and other HRQoL domains. Further investigation into these relationships and interventions aimed at improving HRQoL (e.g. managing mental health issues) are warranted.

P06

Longitudinal health related quality of life in patients with benign and low-grade brain tumours

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Abstract

Aims: To assess longitudinal health-related quality of life (HRQoL), including the determinants of poor HRQoL, over 5 years in patients with acoustic neuroma (AN), meningioma (M) and low-grade glioma (LGG) and identify modifiable factors to improve HRQoL.

Methodology: Post-operative outpatients with AN, M or LGG were prospectively recruited at The Royal Melbourne Hospital and follow-up surveys were mailed out to patients. HRQoL was assessed at every clinic visit using the EORTC QLQ-C30 and BN20 validated questionnaires. The results were analysed using SPSS, looking for correlations and changes over time.

Results: 619 patients have completed the questionnaire one or more times over 5 years. 1035 completed surveys were assessed. We found HRQoL deficits ($p<0.05$) in all tumour types across multiple domains, with poor perceived cognition and impaired social function an important determinant of poor HRQoL. There were fluctuations around the mean for the global domain. There were no significant changes over a 6-month or 12-month period in any of the HRQoL domains. Patients also experienced reported fatigue as being a prominent symptom that impaired HRQoL.

Conclusion: Significant HRQoL impairments are evident in these patients, particularly related to perceived cognitive function, fatigue, social and role functioning. Longitudinally, there appear to be no major changes in HRQoL in most patients. This suggests that, contrary to popular belief, the HRQoL of patients does not improve over time and interventions need to be instigated to improve HRQoL of brain tumour patients. Further investigation with interventions aimed at improving HRQoL (e.g. managing mental health issues) are warranted.

P07

The Effect of Bevacizumab on Vestibular Schwannoma Related to Neurofibromatosis Type II

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Abstract

Aims: We describe an Australian experience of infusional bevacizumab for vestibular schwannoma (VS) in neurofibromatosis type II patients, with specific focus on 3-dimensional tumour volume and audiometry.

Methods: Data was pooled from patients with symptomatic or progressive VS over two time periods; 2009 to 2013, and 2013 to April 2018. Tumours were assessed as a total volume per patient. Bevacizumab infusions were administered every 2-4 weeks, depending on local protocol. Three-dimensional volumetric response (cm^3) was determined through serial magnetic resonance imaging, at baseline and at 3-6 month intervals, until cessation of infusions following progression or prior to surgery. Volumetric response was defined as a reduction of volume ³ 20%[1], from commencement of infusions to 6 months, and 6 months and beyond. Patients also underwent interval pure tone audiometry. A decrease in the average pure tone analyses by 10dB indicated response[2].

Results: Twenty-one VS tumours were identified in eleven patients across both periods. Median age was 26 (13 – 67yr). Average baseline tumour volume was 12.90cm^3 (range 1.45cm^3 - 37.90cm^3). Tumour volume reduction >20% was shown in 5/9 patients (55%) in the 0-6 month period (mean -9.13%), and 4/11 (36%) in the 6 month and beyond period (mean -35.04%). Of the original 5 responders, 4 had further volume reduction beyond 6 months; the remaining patient maintained response. An average decibel reduction of 10dB or more occurred in 3/7 patients (43%) from 0-6 months (average change 1.88dB, range -34 to 71dB) and 3/6 (50%) at 6 months and beyond (average change 7.05dB, range -29 to 77dB), indicating response.

Conclusion: Bevacizumab is a useful agent for reducing tumour volume and improving hearing losses due to vestibular schwannoma in neurofibromatosis type II patients. Although only a small cohort, these results are reflective of results described from the UK and US[3,4].

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P08

Comparison between currently used multi-isocentres forward planned technique and mono-isocentre inverse planning for stereotactic radiosurgery for patients with multiple brain metastases: retrospective audit.

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Abstract

Based on Yamamoto trial [1] our centre has recently introduced stereotactic radiosurgery (SRS) treatment for patients with limited volume multiple brain metastases.

At present we employ forward planning in BrainLab iPlan planning system with the use of conformal static arcs (CSAT) for multiple isocentres.

Aims: The aim of this audit is to assess whether mono-isocentric technique using inverse planning in BrainLab Elements planning system and employing multiple dynamic conformal arcs (DCAT) could be beneficial for the patients with multiple brain metastases.

Methods: The plans of the first five patients with multiple brain metastases (≥4) were exported into Elements planning system and new plans were designed. The estimated delivery time was compared with the beam-on time of delivered plans. We have also calculated and compared Inverse Paddick Conformity Index (CI) [2] and V12 Gy dose-clouds [3] for every treated lesion as well as mean brain tissue doses. CI was calculated as $\frac{PIV \times TV}{(TV \cap PIV)^2}$, where PIV is Prescription Isodose Volume and TV is Target Volume.

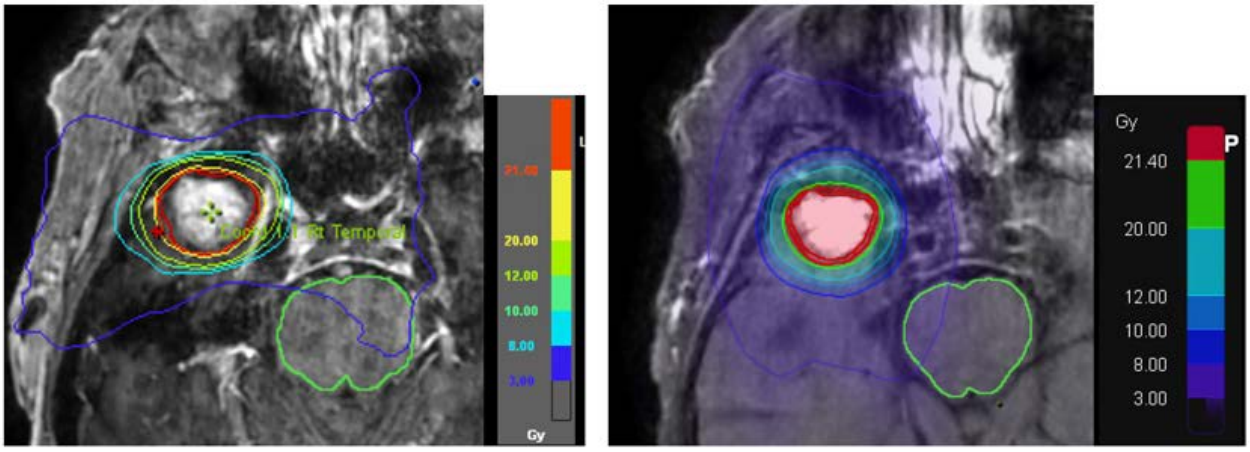
Results: Overall CIs and V12 Gy of 26 treated lesions were analysed. Mean forward planned CSAT CI was 1.7 while inversed planned DCAT CI was 1.4. Mean DCAT CI was superior for every patient (see table 1). There was no significant difference of V12 Gy dose cloud between the plans: 2.08 cc vs 2.09 cc, however the mean brain dose was slightly higher with the use of mono-isocentric technique: 1.55 Gy vs 1.85 Gy. Mean delivery time was 6.3 times longer with the use of multiple isocentres.

Representative dose distributions can be seen on picture 1. Organ at risks constrains were met in all plans.

Conclusions: Inversed planned DCAT SRS is a promising option delivering at least comparable dosimetry (provided adequate corrections to avoid rotational errors) with less discomfort for patients due to significantly shorter treatment delivery time.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CI multi-isocentres plans	1.70	1.81	2.08	1.41	1.41
CI mono-isocentres plans	1.32	1.40	1.55	1.40	1.38

Table 1: Mean Inverse Paddick Conformity Index (CI) comparison



Picture 1: representative dose distributions.
Left – forward planned multi-isocentric CSAT. Right – Inverse planned mono-isocentric DCAT

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P09

Patterns of care and outcomes of young adults diagnosed with high grade gliomas

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Abstract

Aim
There is limited information on the patterns of care, tumour molecular characteristics and outcomes of young adult patients (pts) diagnosed with high grade gliomas (HGGs).

Methods
We retrospectively assessed young adult pts (age ≤ 40 years old) with HGGs diagnosed from 2013 – 2018 treated at two major neuro-oncology centres. Clinicopathologic and treatment parameters were collected and outcomes correlated with clinical and tumour molecular characteristics.

Results
44 pts were identified with a median follow up of 34 months (range 2.8 – 69.8 months). Median age was 29 years, 68% male and 68% were employed. The most common symptoms at presentation were headache and seizures. Majority (73%) had a grade III tumour (25 (78%) anaplastic astrocytoma; 7 (22%) oligodendroglioma) and 12 (27%) pts had grade IV tumours. Of pts (34) who had IDH mutation testing, 76% had an IDH mutation. Only 2 (4%) pts had a diagnostic biopsy; 42 (96%) underwent resection; 25 (60%) had a subtotal resection (STR) and 17 (40%) had a gross total resection (GTR). Nearly all pts (93%) received radiotherapy post-surgery; 73% received concurrent temozolomide chemotherapy. 84% were treated with adjuvant temozolomide and received a median of six cycles. The overall median progression-free survival (PFS) was 45.0 months (95% CI 20.5 – 38.8) and median overall survival (OS) was not reached (NR). Pts who had a STR had numerically shorter PFS than those who underwent GTR (45.0 months vs. NR, p=0.67). Pts with glioblastoma also had a significantly shorter PFS than those with grade III gliomas (15.6 months vs. NR, p=0.019). Just over half of pts succeeded in staying employed after receiving the diagnosis.

Conclusion
Given the favourable outcome of young adult pts compared to older pts (1), strategies to reduce the socio-economic impact post diagnosis are urgently required.

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P10

Exploring the carer's experience of looking after a person diagnosed with primary brain cancer: an exploration of carers' experiences during nurse-led phone interviews for the intervention 'Care-IS'

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Abstract

Median survival for High Grade Gliomas (HGG), the most common type of primary brain tumours in adults, ranges from less than 1 year to 3 years. The diagnosis is often made after a short symptomatic period so patients and their carers need to make immediate treatment decisions and adjust their lifestyles to deal with functional, emotional or cognitive decline.

Aim: The aim of this sub-study was to understand the carers' experiences of looking after a person with brain cancer early in the disease trajectory.

Methods: A randomised controlled trial (Care-IS) is underway to assess an intervention that provides carers with additional education and support and aims to reduce distress and improve preparedness. This nurse-led education program, consists of 1) telephone assessment of needs; 2) home visit; 3) tailored resource file and 4) ongoing telephone support for 12 months. All nurse-led phone interactions with carers are tape recorded. Ten random recordings were transcribed verbatim and thematic analysis undertaken of the initial carer/nurse interaction.

Results: Six main themes emerged: taking responsibility, feeling powerless, a sense of uncertainty, experiencing and anticipating loss and needing support. Although carers embraced their role they reported a sense of powerlessness and uncertainty.

Carers expressed concerns around what the 'end' will look like and reported making sacrifices with reference to relationships, life choices and engaging in their own self-care. Carers also reported feelings of loss and isolation.

Conclusion: This study identifies areas of carer distress which may require on-going support. Carers are likely to benefit from additional psychosocial support while caring for a loved one diagnosed with brain cancer. Further analysis across time of these nurse-led consultations from the carer perspective is likely to highlight further areas where carers might benefit from additional support as the disease progresses.

P11

What support are carers requiring over time during nurse-led support provided as part of the Care-IS study?

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Abstract

High grade gliomas (HGG) are invariably terminal brain tumours, leading 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 evaluates a nurse-led education and support program to improve carer preparedness and quality of life; reduce anxiety and depression; and decrease unplanned health service use. Data on the support provided to 10 carers following nursing assessment up to 12 months will be presented.

Methods: Randomised, controlled, unblinded Phase III trial comparing usual care with the intervention. Recruitment: WA and NSW. The carer education program consists of 1) Telephone assessment of needs; 2) Nurse-led home visit; 3) Tailored resource manual and 4) 12 months ongoing telephone support.

Results: 156 carers have been recruited to date. The most common presenting issues of the 10 participants that were reviewed were around carer strain, managing care recipients' behaviours, mobility and side effects related to chemotherapy. During their involvement in the study the nurse made an average of 5 contacts per carer to other health professionals, including the involved medical oncologist. On average, 17 recommendations were made providing educational and emotional support for carers during telephone assessments and other contacts. The most common recommendations were to the resource manual, community support services, the GP, Cancer Nurse Coordinator and a psychologist.

One carer was advised to present to the emergency department with chest pains and a second carer presented to the emergency department for stress related concerns.

Conclusions: Carers were provided with a range of supports which altered as the patients' disease progressed. We hypothesise that this ongoing support will reduce care distress, increase carer preparation, improve carer outcomes and reduce patient healthcare resource utilisation and costs.

P12

'Building the Bridge': A Victorian brain cancer survivorship project.

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Abstract

Introduction

Improved survival duration is raising awareness of the magnitude of impacts and challenges confronting people with grade 2 and 3 brain cancers. Survivors can experience significant physical, cognitive and behavioural impacts from the tumour and its treatment[1-2]. Given the high probability of disease recurrence or progression, survivors are also burdened with the constant awareness of a likely premature death[1]. Currently, there is a lack of information resources and support for brain cancer survivors.

Aim

Develop a suite of tailored, accessible information resources for brain tumour survivors that support survivor self-management and provide a tool for health professionals to use in survivorship conversations.

Methods

Utilising a consensus model approach, the project will have three stages:

1a) Consumer focus groups will identify needs/priorities for resource development and preferred formats. b) Health professional interviews at three Victorian Hospitals will inform understanding of perceived gaps in survivorship information and support for this cohort.

2) Data analysis and drafting of information resources. Resource design will aim to maximise access for people with varying levels of health literacy and attentional functioning. Consumers and health professionals from stage 1 will review the resources and provide feedback.

3) Feedback reviewed and suggestions incorporated. New resources disseminated and piloted with different consumers and health professionals for acceptability and usability.

Expected Outcomes

This project will create, pilot and disseminate a suite of survivorship resources tailored to the needs and priorities of Victorian brain cancer survivors, carers and health professionals. These resources will improve the capacity of brain cancer survivors and families to self-manage post-treatment and support transition conversations between survivors and health professionals.

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P13

Implementation of Brainlab Elements Brain Metastasis software: How small a target can we hit?

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Abstract

Introduction

The Brainlab Elements V1.5 software allows for efficient radiosurgery treatment of multiple brain metastases using several arcs in one radiation treatment session. This is a development from earlier techniques where each metastasis was treated individually leading to long treatment times. In this work, we investigate how small a metastasis can be treated in Elements.

Method

All dose measurements were performed on a Varian Trilogy linear accelerator using the 6 MV SRS x-ray beam mode equipped with 2.5 mm width MLCs. Small metastases were simulated in an ART anthropomorphic head phantom using 1 mm thick CT slices with met volumes range from 0.03 to 1.9 cm^3. Pieces of the EBT3 radiochromic film were positioned within the phantom slides for measurement of doses in 2D planes. The treatment plan for the phantom was calculated in Elements with 15 Gy prescribed to each met. The head phantom was setup on the Novalis linac and ExacTrac imaging prior to each treatment field to align the phantom to within 0.5 mm/0.5°.

Results

The calculated radiation doses from Elements on the CT slice with 4 mets are shown in figure 1. The measure dose profiles in the X and Y planes through the middle of the 4 mets are shown in figure 2. The dose coverage for each met was shown to be suitable and with a spatial accuracy of 0.5 mm.

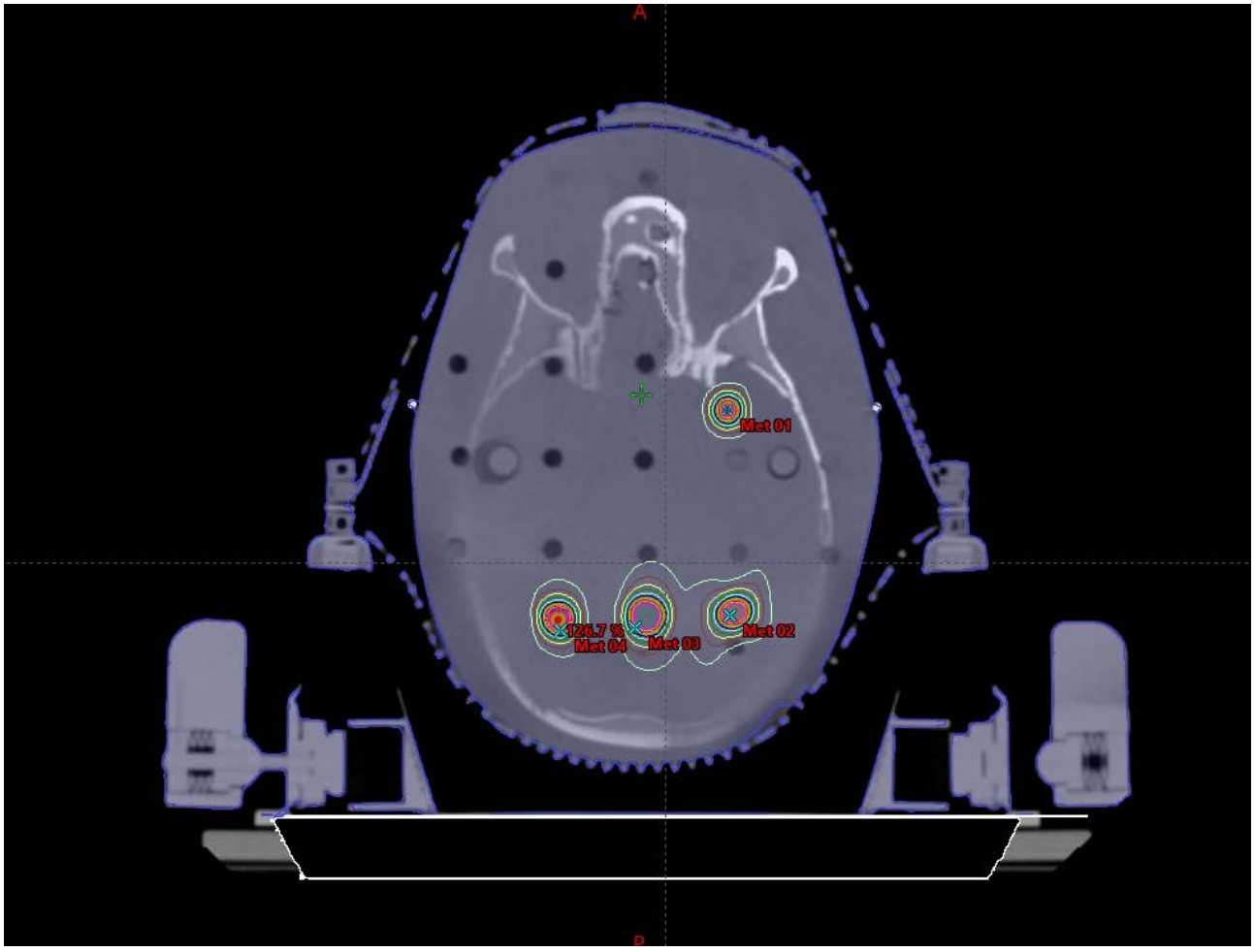

Figure 1: Anthropomorphic phantom showing 4 mets on a single plane

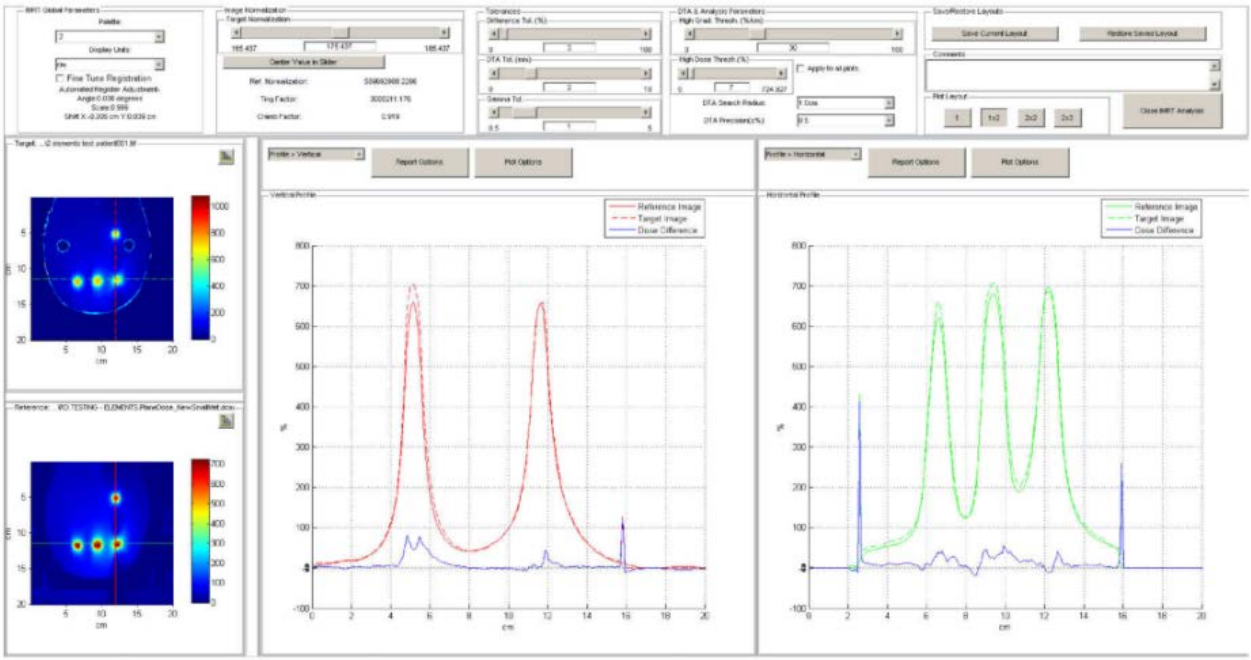

Figure 2: EBT3 film dosimetry analysis showing the position of small met targets.

Conclusion

Our work has shown that the Brainlab Elements 1.5 software can be useful in treating brain metastases with a 4 mm linear dimension to a spatial accuracy of 0.5 mm. This shows the efficacy of the Elements software for treating multiple mets in radiosurgery.

P14

Speech and language outcomes and survivorship following surgery for paediatric posterior fossa tumours

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Abstract

INTRODUCTION

The posterior fossa (PF), including the cerebellum, is the most common location for childhood brain tumours. The cerebellum plays an important role in cognition including speech and language skills. Impairments in these processes, especially language, are linked with poorer academic achievement in PF tumour survivors. However, detailed speech and language assessments are not routinely conducted pre-surgically in children with PF tumours. This pilot study investigated the rate of postsurgical cognitive deficits during the chronic recovery period in a retrospective cohort of children with PF tumour resections.

METHODS

Using retrospective behavioural data, the current pilot study investigated the prevalence of cognitive deficits in 37 children (aged 5 to 14 years) with primary PF tumours. All children had completed the Woodcock Johnson III – (Australian adaption) tests of Cognitive Abilities. Scores were standardized.

RESULTS

Overall this population presented with a range of cognitive deficits. Most prevalent was a below average score on reading fluency (52/12% scored below average/very low), calculation (57/18 % scored below average/very low), math fluency (68/20% scored below average and very low) and passage comprehension (38/14% scored below average/very low). Only on the auditory working memory subtest did the group not demonstrate any 'very low' performance, with just 10% scoring below average.

CONCLUSION

This data demonstrates a pattern of below average cognitive functioning in skills required for academic success, specifically language and numeracy skills, in over half of the group studied. In order to ascertain the extent to which these are surgically induced impairments, both pre- and post- surgical detailed assessments of these functions are indicated.

P15

Picture description versus picture naming: assessing language deficits following dominant hemisphere tumour resection.

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Abstract

Background

Given the debilitating impact of aphasia on social, psychological and financial well-being, it is imperative that surgical planning for the resection of brain tumours aims to both reduce the risk of iatrogenic aphasia and to establish a detailed baseline assessment of pre-surgical language function in order to accurately report any consequences of surgery. To assess this risk, neurosurgeons typically employ confrontation naming tasks in order to map language function and evaluate the risk of iatrogenic aphasia (1, 2). We investigated the extent to which the presence of a language disorder was detected using this task, compared to tasks that demand a greater range of linguistic skills.

Methods & Procedures:

We assessed confrontation naming and picture description skills (3) in 31 right-handed patients who were about to receive, or had recently received, surgery to remove a primary tumour to the left hemisphere. Language impairment was identified using the criterion within the Comprehensive Aphasia test (3).

Results

A higher incidence of language impairment was indicated using 'picture description' compared to 'naming' tasks in both pre-surgical (36%, 7% respectively) and post-surgical patients (44%, 8% respectively). In a subgroup of patients with data for both pre- and post-surgical timepoints, 'naming' performance was consistent across both testing sessions but 'picture description' performance declined between pre and post-surgical testing points.

Conclusion

The subtle language deficits exhibited pre- and post-surgical resection of brain tumours are not adequately detected using 'confrontation naming' tasks as has become de rigueur in pre-surgical language mapping. In this study we present data that suggests that traditional naming paradigms alone are not reliable enough to demonstrate the presence, or indeed absence, of language impairments and so alternative paradigms are needed.

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P16

Potential role of cannabidiol for seizure control in patients with glioma

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Abstract

There has been an increasing interest in medicinal cannabis in the treatment of refractory seizures in epilepsy, though the evidence for this is currently limited to paediatric patients with Dravet and Lennox-Gastaut syndrome[1,2]. Here we present a case of a 32 year old lady with recurrent glioma who had refractory seizures despite multiple anti-epileptic agents. This patient initially had a diagnosis of right frontal grade 2 oligodendroglioma in 2010 which was treated with surgical resection. She had recurrence in 2014 treated with repeat resection and adjuvant PCV chemotherapy. Disease progression appeared in 2016, treated with temozolomide with partial response, and she is currently on radiotherapy for further disease progression.

Over the last 5 years, she had progressive worsening of partial sensory and motor seizures which was managed by the neurology team with multiple antiepileptics. Up until November 2017, she had up to 20 episodes per day despite being on sodium valproate titrated up to 1.5mg BD, Zonisamide 25mg BD, and Perampanel 2mg nocte and Levetiracetam 1.5g BD. With the evidence for the potential role of cannabidiol (CBD) in the treatment of refractory epilepsy for other aetiologies, desperate attempt to control her seizures was made with the introduction of CBD in November 2017 with neurologist involvement. Within 2 weeks of commencement, her seizure frequency dramatically reduced to 0 to 1 episode per day, and she has remained seizure-free for last 4 months. She is tolerating 150mg per day of CBD with grade 1 fatigue as the only toxicity.

This case demonstrates that CBD could be an effective option in managing refractory seizures in patients with glioma. Further research required to explore CBD as an antiepileptic agent.

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P17

Baseline functional status in post-operative glioma patients prior to adjuvant radiation: relevance to participation in a supervised exercise programme

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Abstract

Introduction: Recruitment to a COGNO-endorsed prospective multicenter study of the feasibility of an exercise intervention in patients with glioma during radiotherapy delivered over six weeks (with or without concurrent or adjuvant chemotherapy) is ongoing. Patients may experience neurologic deficits or physical impairments impacting their ability to participate. The aim of this study was to describe baseline functional capacity prior to commencing radiotherapy at the Princess Alexandra Hospital, QLD and Liverpool Hospital, NSW.

Methods: Baseline assessments were performed after initial surgery in eligible patients agreeable to participate in a supervised exercise programme during treatment. Eligibility criteria included histologically-confirmed glioma, age ≥18years, performance status ECOG 0-2 and intention to receive adjuvant radiotherapy. Assessments were performed by trained physiotherapists and/or exercise physiologists including six-minute walk (6MWT), timed up-and-go (TUG) and thirty second sit-to-stand (30STS) tests. Comparison was made to normative data from healthy controls and descriptive analyses were performed using SPSS25.

Results: Baseline. To date 28 participants have undergone baseline assessment prior to exercise. Median age 50.5 years (range 28-72) and 68% were male. Mean height 175cm and weight 84.4kg with BMI 27 (indicating 'overweight'). Histologic diagnosis was WHO grade IV, III and II in 82%, 11% and 7% participants, respectively. Baseline assessments are summarised in Table 1&2 for patients ≥60 and <60 years. Performance in 6MWT was below normal healthy aged-matched norms for all ages indicating reduced exercise capacity. For patients ≥60years, slower TUG and reduced 30STS suggest balance deficits and potential increased falls risk.

Conclusion: Even in a select group of patients with glioma willing to participate in exercise during adjuvant radiotherapy, large variation in objective assessments is noted across the age spectrum. This illustrates the need for an individualised approach to exercise prescription. The relevance of comparison to age- and sex-matched controls in this population is uncertain.

Objective Measure	Mean (range)	Normative comparator
6MWT	492.6 m (330- 835)	638 m
TUG	6 seconds (7.7 -3)	8.86 seconds
30STS	15.6 (8-30)	17

Table 1. Baseline assessments in patients <60years

Objective Measure	Mean (range)	Normative comparator
6MWT	413.7 m (110-660m)	527 m
TUG	10 seconds (5.1-21.3)	8.1 seconds
30STS	14 (6-16)	17

Table 2. Baseline assessments in patients >60years

P18

EphB Receptors as Therapeutic Targets for Paediatric Medulloblastoma

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Abstract

Introduction and aims: Medulloblastoma (MB) is the most frequent malignant brain tumour to occur in children and remains the leading cause of cancer-related mortality in childhood. Current standard of care for MB patients lead to sever long-term adverse sequelae due to high-dose radiation given at an early age. Thus, better understanding the biology and genetics of the disease to help risk stratify MB patients are needed. More recently, array-based transcriptional profiling of primary MB has identified four distinct molecular subgroups: MB^{WNT}, MB^{SHH}, Group 3 and Group 4[1].

Our preliminary data shows EphB2 and EphB6 are highly expressed on a variety of MB primary cell lines.However, the functional role of these EphB receptors in MB is still unclear. The aim of this project is to investigate the expression of EphB receptors and to provide insights into the functional role of EphB receptors in tumourigenesis and progression in MB.

Methods: Despite decades of research, many aspects of the complex biology of Eph-ephrin signalling are still unknown. There is a need to better understand which signalling pathways are regulated following EphB2 and EphB6 activation upon ephrin B1 stimulation. Phospho-specific antibody array will be used to examine the downstream signalling networks following EphB2 and EphB6 activation using clustered ephrin B1-Fc.

Results: Our result shows EphB2 is elevated in all subtype tumours in comparison to normal cerebellum, especially in Group 3 and Group 4 subtypes. However, EphB6 is significantly overexpressed in MB^{WNT}, which appears to act as a favourable gene in MB. EphB receptor activation leads to reduced cell proliferation, migration and adhesion on a variety of MB cell lines.

Conclusions: EphB receptors have subgroup specific expression pattern in MB tumour samples. The receptor activation inhibits proliferation, migration and adhesion, indicating that EphB could be employed as a therapeutic target for MB.

References

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P19

Sleep disturbance among adults with primary and secondary malignant brain tumours and their caregivers: a cross-sectional study

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Abstract

Emerging evidence suggests a close link between sleep disturbance (SD) and clinical outcomes and the health-related quality of life in cancer patients. Yet, understanding sleep disturbance is neglected areas in both neuro-oncology care and research.

Aims: This study aimed to determine the prevalence and predictors of sleep disturbance in brain tumour patients and caregivers, and explore any interaction between the patient-caregiver dyad's sleep.

Methods: Eighty-one adults with primary malignant (91%) or metastatic (9%) brain tumours and their adult family caregivers (n=44) completed a series of self-report questionnaires in an ambulatory neuro-oncology clinic setting in Australia. Sleep patterns and disturbance were assessed with the Pittsburgh Sleep Quality Index and the Insomnia Severity Index. Participants were grouped into high SD or low SD by the PSQI cut-off, and binary logistic regression analyses were performed to identify risk factors.

Results: Of patients, 53% reported having poor sleep quality and 49% having clinically significant insomnia. Increased fatigue severity (OR=1.7, $p<0.01$) and the use of anti-emetics (OR=4.3, $p<0.05$) were significant risk factors of SD in patients. Of caregivers, the prevalence of poor sleep quality and clinical insomnia were 55% and 14%, respectively. Anxiety was a significant risk factor of SD in caregivers (OR=1.33, $p<0.01$). Sleep patterns and scores of the patient-caregiver dyad were not associated. While longer weekly care hours increased the odd of caregivers being high SD ($p<0.05$), the level of patient's dependency on caregivers and night time care need were not associated with the dyad's sleep.

Conclusions: A substantially high prevalence of sleep disturbance and clinical insomnia was found in this sample. Demographic and clinical variables had limited influence, indicating that sleep disturbance is a more complex problem than toxicity in this sample. Understanding the underlying mechanisms of co-morbid symptoms and options for management is still warranted.

P20

Occurrence and management of sleep disturbance in people with a brain tumour and caregivers: a survey of clinicians' views and current practice

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Abstract

Sleep disturbance(SD) is easily overlooked, and often remains untreated during primary treatment and persists in many cancer patients, including malignant brain tumours. Information about current practice and prevailing views among relevant clinicians is useful for developing an effective sleep symptom management.

Aims: This study aimed to explore perceptions of range of health professionals towards assessment and management of SD in adults with a primary malignant brain tumour or brain metastasis, and to identify facilitators and barriers for sleep-related symptom care at the clinician level.

Methods: Seventy-three interdisciplinary health professionals actively engaged in neuro-oncology care completed the anonymous survey. The survey was developed to explore clinicians' perceptions about their knowledge, skills, and confidence in managing SD, their beliefs about the importance of SD management and their role, and the accessibility of resources.

Results: Participants had a range of professions, 55% of whom were medical or radiation oncologists, with average 9.3 years of clinical experience in neuro-oncology. Clinicians perceived the prevalence of SD to be considerably high, especially in inpatient settings, during primary treatment, and after tumour progression or recurrence. However, only 20% of clinicians reported routinely (>75% of the time) asking patients about sleep. Majority (92%) reported corticosteroids as the most highly relevant risk factor of SD in this patient population, followed by psychological distress and sleeping in hospital. Providing verbal advice and prescribing medication were most frequently chosen care options for patients' SD. Clinicians found asking general symptom screening questions (regarding fatigue or steroid-related complications) helpful to identify SD. The most commonly reported barriers included a lack of time, resource, and training for managing SD.

Conclusions: Overall, clinicians perceived SD as highly prevalent in neuro-oncology and held positive views about the importance of managing sleep. Yet, there still remain practical barriers to best management that future interventions can target.

P21

Prevalence and severity of difficulty sleeping in patients with CNS cancer receiving palliative care in Australia

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Abstract

The current literature describing the incidence of sleep disturbance in the central nervous system (CNS) cancer population is very limited. Studies exploring the symptom trajectory of sleep disturbance are particularly lacking due to high attrition rates of people with malignant CNS tumours.

Aims: It aimed to establish the longitudinal trajectory of difficulty sleeping in palliative care (PC) populations with CNS cancer at different levels of care (e.g. patient, care phase and episode) and care settings (inpatient or community), and to identify clinically modifiable predictors of difficulty sleeping in palliative care.

Methods: A cohort of 2406 patients with CNS cancer who received PC in an inpatient or community setting at a Palliative Care Outcomes Collaboration (PCOC) participating centre in Australia from 2010 to 2015 were evaluated on patient-reported and clinician-rated outcomes in their routine care. Multi-level modelling was conducted to examine longitudinal changes in sleep scores, given the clustered data structure.

Results: There were 8897 PC phases constituting 3310 care episodes (54% inpatient). The patients with CNS cancer were significantly younger than the PCOC population in Australia (46% at age of <65). Reporting of mild to severe sleep disturbance ranged from 10% to 43% across care settings and phase types. Sleep scores fluctuated greatly over the course of PC, within and between individuals. However, the overall effects of change in patient's clinical status, care setting, and the length of care phase were not significant on those fluctuations. Worsening of sleep disturbance was associated with higher psychological distress (p<.0001), greater distress due to breathing problems (p<.05) and pain (p<.05), and higher KPS (p<.001).

Conclusions: This study is the first to demonstrate the prevalence, longitudinal trajectory, and predictors of sleep symptom in a thorough national-wide data with over 2000 patients solely for CNS cancer in real-world clinical settings.

P22

Glioblastoma multiforme in Queensland, 2009-2014: a snapshot.

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Abstract

Aim

The aim of this study was to assess incidence and outcomes for patients with glioblastoma multiforme(GBM) diagnosed in Queensland public and private hospitals between 2009-2014.

Methods

Patients aged ≥18years with cranial (excluding spinal) GBM were identified from a statewide registry and clinicopathologic factors were collected. The National Death Registry was used to calculate survival from diagnosis using the Kaplan Meier method. Survival predictors were modelled using multivariate Cox proportional hazards regression.

Results

There were 1174 new GBM diagnosed (average 196/year). The Australian age-standardised incidence was 4.1 per 100,000 overall, higher in males(5.0) than females(3.2). Many patients were living within city areas of South-East Queensland (SEQ) including Metro South (21%), Metro North (19%) and Gold Coast (13%). Median age at diagnosis was 64years with 5% <40 and 34% ≥70years. Most patients were without medical co-morbidities (Charlson index 0-1 in 59%).

Histological diagnosis was made in 85% overall but reduced to 40% in patients >80years. Frontal (29.1%), temporal (27.3%) and parietal (17.6%) lobes were the most frequently involved locations. Tumours involving overlapping lobes were more frequent in older patients (3.8% in 18-39years, 7.5% in 40-79years, 15% in ≥80years and mean 8% overall) and midline/central structures in younger patients (9.5% in 18-39years, 1.3% in 40-79years, 0.9% in ≥80years and mean 1.6% overall).

There were 1052 deaths during the study period. Age-standardised mortality was 3.6 per 100,000 and median survival (MS) was 9 months overall. On multivariate analysis, survival varied with age, number of medical co-morbidities and tumour location (Table 1). MS in patients <30 and ≥80years at diagnosis was 39 months and 3 months, respectively.

Conclusion

GBM affects Queenslanders of all ages. Survival is particularly poor in older patients. Many patients reside outside SEQ and consideration to optimal pathways/services for these patients is required.

Table 1: Cox proportional hazard regression analysis of GBM patients diagnosed in Queensland 2009-2014

	Hazard Ratio	95% CI	p-value
Sex			
Female	1	Reference	-
Male	1.02	[0.94-1.12]	0.597
Age Group			
18-39	1	Reference	-
40-79	2.45	[1.93-3.09]	**<0.001**
80+	8.80	[6.70-11.56]	**<0.001**
Indigenous status			
Non-indigenous	1	Reference	-
Indigenous	1.42	[0.87-2.32]	0.156
Socioeconomic status			
Disadvantaged	1	Reference	-
Medium SES	0.96	[0.86-1.08]	0.488
High SES	0.95	[0.81-1.12]	0.549
Residence			
Urban	1	Reference	-
Rural	1.03	[0.94-1.13]	0.548
Comorbidities			
0 comorbidities	1	Reference	-
1 comorbidities	1.41	[1.28-1.55]	**<0.001**
2+ comorbidities	1.89	[1.67-2.13]	**<0.001**
Anatomical location			
All glioblastoma	1	Reference	-
Brainstem	1.81	[0.90-3.64]	0.095
Central ventricle	1.12	[0.58-2.16]	0.743
Frontal lobe	0.97	[0.85-1.10]	0.616
Occipital lobe	0.98	[0.76-1.26]	0.860
Parietal lobe	0.96	[0.83-1.12]	0.629
Temporal lobe	0.91	[0.80-1.03]	0.132
Overlapping lesion	1.31	[1.06-1.62]	**0.014**

P23

The importance of staying connected: mediating and moderating effects of social groups on psychological wellbeing after brain tumour

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Abstract

Aims: Functional impairments contribute to psychological distress after brain tumour. Changes in social groups and confidence in support potentially impact this relationship. This study aimed to investigate the influence of social groups on functional impairment and psychological wellbeing.

Methods: 70 people with primary brain tumour (46% benign; 18% low grade; 36% high grade) aged 22-75 years completed measures of cognitive and physical impairment (Functional Assessment of Cancer Therapy), social groups (Exeter Identity Transition Scale), confidence in social support (Self-Efficacy Scale), depression, anxiety and life satisfaction. A bootstrapping method and PROCESS macro was utilized to test mediating and moderating effects of social group variables, controlling for relevant demographic and tumour characteristics.

Results: The relationship between cognitive and physical impairment and psychological distress was significantly mediated by maintenance of social groups. Indirect effects were found for depression (CI: 0.019-0.109), anxiety (CI: 0.013-0.064), and life satisfaction (CI: -0.094~-0.013). Forming new social groups had a moderating effect for life satisfaction ($p<.05$), whereby individuals perceiving more cognitive impairment who were better able to develop new social groups reported higher life satisfaction. Confidence in social support was a moderator for depression ($p<.001$), such that those perceiving more physical impairment who were more confident in their social support reported lower depression.

Conclusions: Functional impairment is related to increased psychological distress through loss of social groups. However, development of new social groups and greater confidence in support can buffer the effects of functional impairment on psychological well-being after brain tumour.

P24

Volumetric analysis of peri-lesional oedema after gamma knife for melanoma metastasis and its clinical correlation

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Abstract

Aims: The purpose of this study is to determine the correlation between peri-lesional oedema post gamma knife (GK) treatment in cerebral metastatic melanoma and subsequent clinical outcome. Cranial GK therapy is often limited due to the concerns regarding post treatment oedema.

We hypothesised that the greater the amount of perilesional oedema, the worse the clinical outcome.

Methods: All patients treated for melanoma metastatic lesions between October 2015 and May 2017 were included in this single centre retrospective analysis.

The pre treatment MRI was analysed and the volume of tumour and perilesional oedema respectively was calculated. After receiving gamma knife, the post treatment MRI was assessed for the same parameters. We used the ABC/2 rule for ellipsoids as it has previously been demonstrated as an accurate estimate of lesion volumes.

Morbidity and mortality were assessed using electronic records and outpatient appointments. This included unexpected surgical intervention, hospital readmission, acute cerebral haemorrhage and new seizure onset.

Results: 43 patients with 135 metastatic lesions were included in this study. Patients were followed until April 2018 (range 1- 28 months). Twenty one patients died during the study. Forty three percent of patients had a BRAF mutation. Seventy four percent of patients were on concurrent immunotherapy during their GK treatment.

Progression of oedema was seen in the majority of patients, however this was not associated with clinical deterioration. The most frequent clinical occurrence was intracranial haemorrhage and new or increased seizure frequency.

Conclusions:

Intracranial oedema post GK treatment is a common occurrence, however has no significant clinical correlation. This has implications for future treatment protocols.

P25

Stereotactic fluorescence guided resection of high grade gliomas using 5-aminolevulinic acid: case matched analysis of 46 consecutive patients in an Australian hospital

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Abstract

AIMS

The aim of this study were to evaluate effectiveness in achieving complete resection of high grade glioma (HGG) using 5-Aminolevulinic acid (5-ALA) guided surgery at an Australian hospital. Secondary outcomes included evaluation of disease progression free survival (PFS) and overall survival (OS)

METHODS

Retrospective analysis of 55 consecutive Wollongong Hospital cases in 46 patients before and after introduction of 5-ALA in July 2014. Primary outcome was evaluated by assessing the resection rate as GTR if > 98% of contrast enhancing tumour was resected on MRI post surgery. Disease progression free survival was assessed at 6 months and patients were monitored for overall survival.

RESULTS

Analysis of 55 consecutive cases using 5-ALA guided HGG resection yielded overall GTR > 98% was achieved in 58% compared to 40% in conventional white light guided HGG resection. Extent of resection (GTR > 98%) was dependent on tumor location and tumor size ($P < 0.05$). PFS at 6 months was 48% for 5-ALA guided HGG resection group and 22% for the non 5-ALA group (P<0.05). OS at 12 months was 42% and 39% for the 5-ALA guided HGG resection versus non 5-ALA groups respectively. Adverse outcomes were not significantly different for both groups.

CONCLUSION

Our series supports the growing evidence that 5-ALA guided resection of contrast enhancing HGG is safe and effective in achieving gross total resection which can improve progression free survival.

P26

Meningioma in Children: Report of 3 Cases

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Abstract

Meningioma account for only 3% of pediatric intracranial neoplasms. We report three pediatric meningioma cases which are treated between Oktober 2017 – July 2018.

Method. The study is cross-sectional. From Oktober 2017 – July 2018, we have treated three pediatric meningioma cases with surgical resection and radiotherapy.

Result. The patient's age ranges from 4-6 years. The chief complaint consists of seizure, blurred vision, and headache. The extent of resection was Gross Total Removal in one patient, and Subtotal Removal in two patients. One patient developed postoperative hydrocephalus treated with VP shunt. All patients consulted to the radiation oncology department for further treatment. Histopathological specimens confirmed one WHO grade II and two WHO grade III meningioma.

Conclusion. Pediatric meningioma is rarely found in the pediatric population. Histopathological specimens of three patients in our cases confirmed the aggressive behavior of the tumor.

P27

The Role of Gamma Knife Radiosurgery: Preliminary Assessment of Patients Indicated for Gamma Knife Radiosurgery in National Referral Hospital of the Republic of Indonesia

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Abstract

Gamma knife radiosurgery is a reliable modality for treatment of the brain tumor. Since 2014, Departement of Neurosurgery, Dr. Cipto Mangunkusumo General Hospital, which is also the national referral neurosurgical center in Indonesia, has evaluated the needs for installment of gamma knife radiosurgery unit.

Method. The study is cross sectional. From 2014 – 2018, we have obtained 3080 neurosurgery-related consultations in pediatric and adult neurosurgery cases. We selected 182 cases based on volume criteria which is suitable for gamma knife radiosurgery treatment.

Result. The patient's age ranges from 4-72 years. Lesions were divided into benign tumor, malignant tumor, and other (vascular disorders, functional disorders). Based on imaging criteria with or without tissue diagnosis, we categorized the lesions into: 21 vestibular schwannoma (11,53%), 33 pituitary tumor (18,13%), 1 craniopharyngioma (0,54%), 15 glioma (8,24%), 81 meningioma (44,50%), 3, chordoma (1,64%), 1 chondrosarcoma (0,54%), 2 metastatic brain tumor (1,09%), 2 pineal tumor (1,09 %), 23 other functional and vascular lesions (12,63%).

Conclusion. The patient population indicated for gamma knife radiosurgery treatment justified the importance of gamma knife radiosurgery as neurosurgical armamenterium in our hospital. The unit started its service in June 2018.

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