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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12th COGNO ANNUAL SCIENTIFIC MEETING

The Neuro-Oncology Picture: Now and The Future

Sunday 27th October – Tuesday 29th October 2019

International Convention Centre Sydney, Australia

CONFERENCE BOOKLET

COGNO

COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

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2019 ASM ORGANISING COMMITTEE

Dr Jonathon Parkinson, Convenor	Neurosurgeon
Dr Yael Barnett	Neuroradiologist
Dr Ben Jonker	Neurosurgeon
Ms Marina Kastelan	Neuro-Oncology Nurse Practitioner
A/Prof Mustafa Khasraw	Medical Oncologist - Until 25 Aug 2019
A/Prof Hien Le	Radiation Oncologist
A/Prof Kerrie McDonald	Scientist - Until 5 July 2019
Dr Sanjeev Gill*	Medical Oncologist - From 6 Aug 2019
A/Prof Rosemary Harrup*	Medical Oncologist - From 6 Aug 2019
Ms Jenny Chow	Executive Officer, COGNO
Ms Yi Feng	Project Officer, COGNO

*2020 ASM Co-Convenors

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Use our Conference hashtag **#COGNO19**

COMPLIMENTARY INTERNET

Complimentary wireless internet is available for all delegates in the COGNO ASM meeting rooms.

Network: ICC Sydney Public Wi-Fi
Password: No password required

Dear Colleagues

On behalf of the organising committee it is our great pleasure to welcome you to the 12th COGNO Annual Scientific Meeting.

The theme of the meeting is 'The Neuro-oncology Picture: Now and the Future'.

We are very fortunate to welcome five international guest speakers as listed below:

- Prof Colin Watts MBBS PhD FRCS(SN)
- A/Prof Helen Shih MD MS MPH
- Prof Benjamin Ellingson PhD MS
- Prof Ian Law MD PhD DMSc
- A/Prof Seema Nagpal MD

The meeting sessions will focus on: Imaging, Surgery, Skull Base Tumours, Immunotherapy and COGNO Trials Updates, Assessing Treatment Response, Basic Science, and Supportive Care.

In addition to our invited international speakers, we have representation from a broad number of disciplines across our local contributors. Also, the high quality of submitted abstracts is reflected in the oral presentations awarded.

Prizes will be available for the Most Outstanding Oral Presentation, the Most Outstanding Poster Presentation, the Young Investigator Award and the BTAA Lynette Williams Award for the best posters related to research into supportive care for people with brain tumours. Presentation will also be made for the MSD Hubert Stuerzl Memorial Educational Award. In addition, we are delighted to welcome the 2019 COGNO Outreach Education Preceptorship recipient, Ms Minjmaa Minjgee from Mongolia.

Our appreciation goes to all our sponsors and supporters: Cure Brain Cancer Foundation, The Brain Cancer Group, Bristol-Myers Squibb (BMS), Roche, Elekta, Philips, Emulate Therapeutics, Medigroup, and Cancer Australia.

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

Kind regards

Dr Jonathon Parkinson
Convenor
COGNO ASM 2019

Prof Anna Novak
Chair
COGNO

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PROGRAM OF EVENTS

(Changes may be made to the program)

Sunday 27 October: Pre–ASM Satellite Meetings		
TIME	**MEETING**	**CHAIR**
9:30am – 2:15pm	**Brain Cancer Patient Education and Support Forum** (registration via the BTAA website) (Room C3.6)	Hao-Wen Sim
10:30am – 4:15pm	**The Brain Cancer Group Scientific Meeting: Applying advanced imaging to Neuro-oncology** (registration via The Brain Cancer Group website) (Room C3.5)	
12:30 – 2:30pm	**Brain Cancer Biobanking Australia (BCBA) consortium meeting** (closed meeting) (Room C3.4)	Michael Besser
3:00 – 5:00pm	**Management Committee (MC) meeting** (closed meeting) (Room C3.4)	Anna Nowak
6:30pm	**Convenor's Dinner** (by invitation only)	

Monday 28 October: ASM Day 1 (Cockle Bay Room 1)		
TIME	**MEETING**	**CHAIR**
8:00 – 10:00am	**COGNO Scientific Advisory Committee Meeting** (open to COGNO members only) (Room C3.4 & C3.5)	Hui Gan
10:00 – 10:30am	Morning Tea	
10:30 – 10:40am	**Welcome and Day 1 program overview**	
10:40 – 12:30pm	**Session 1 – Imaging**	Yael Barnett & Jonathon Parkinson
	Recent advances in MRI for brain tumours – *Ben Ellingson*	
	Recent advances in PET Imaging for brain tumours – *Ian Law*	
	Extent of Resection – *Colin Watts*	
	Intraoperative Imaging – *Kate Drummond*	
12:30 – 1:30pm	Lunch	
1:30 – 3:00pm	**Session 2 - Surgery**	Jonathon Parkinson & Ben Jonker
	Decision making in the treatment of low grade glioma – *Raymond Cook*	
	Case based panel discussion	
	Paper ID 24: Second interim and 1st molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion – *Anna Nowak*	
3:00 – 3:30pm	Afternoon tea	
3:30 – 5:00pm	**Session 3 – Skull Base Tumours**	Ben Jonker & Hien Le
	Endoscopic Endonasal Surgery – what can we achieve? – *Richard Harvey*	
	Radiation for Skull Base Tumours – *Helen Shih*	
	Meningiomas and grading – how can we do it better? The role of DNA methylation profiling – *Joanne Sy*	
	Temozolomide for pituitary tumours – *Ann McCormack*	
5:00 – 6:00pm	**Welcome Reception and Poster Walkaround**	
~6:30/7:00 - 10:30pm	**COGNO Conference Dinner** – includes presentation of the MSD Hubert Stuerzl Memorial Educational Award, COGNO Outreach Education Preceptorship and BTAA Lynette Williams Award (L'Aqua restaurant, Terrace Room, Rooftop Level, Cockle Bay Wharf, Darling Park, Sydney)	

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Tuesday 29 October: ASM Day 2 (Cockle Bay Room 1)		
TIME	**MEETING**	**CHAIR**
8:30 – 9:00am	On arrival tea/coffee	
9:00 – 9:10am	**Welcome and Day 2 program overview**	
9:10 – 10:30am	**Session 4 – Immunotherapy and COGNO Trials Updates**	Sanjeev Gill & Hui Gan
	Immunotherapy and why has success been limited? – *Seema Nagpal*	
	Trials updates	
10:30 – 11:00am	Morning tea	
11:00 – 12:30pm	**Session 5 – Assessing Treatment Response**	Hien Le & Yael Barnett
	MRI and treatment response – *Ben Ellingson*	
	PET and treatment response – *Ian Law*	
	Pseudoprogression – how do we assess and treat – *Helen Shih*	
	Re-operation for treatment effect / progressive disease – *Colin Watts*	
	Case examples	
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1:30 – 2:45pm	**Session 6 – Basic Science**	Jonathon Parkinson & Rosemary Harrup
	Radiogenomics in glioma – *Ben Ellingson*	
	Teletrials – *Kate Burbury*	
	Paper ID 15: DeepSurvNet: Deep Survival Convolutional Network for Brain cancer Survival Rate Classification based on Histopathological Images – *Amin Zadeh Shirazi*	
	Paper ID 4: Targeted drug delivery reduces brain metastases – *Sarah Shigdar*	
2:45 – 3:15pm	Afternoon tea	
3:15 – 4:10pm	**Session 7 – Supportive Care**	Marina Kastelan & Rosemary Harrup
	Quality of Life for Glioma Patients – *Kate Drummond*	
	Palliative Care for Glioma Patients – *Anthoula Mohumadally*	
	Rehabilitation for Glioma Patients – *Andrew Cole*	
	Paper ID 26: Building the Bridge: The value of consumer co-design in brain cancer resource development – *Dianne Legge*	
4:10 – 4:20pm	**ASM Summary and Close** – includes presentation of the Most Outstanding Oral Presentation, Most Outstanding Poster Presentation and Young Investigator Awards	
4:45 – 5:30pm	**COGNO Annual General Meeting** (open to COGNO members only) (Room C3.2)	Anna Nowak

Wednesday 30 October: Post-ASM Satellite Meetings		
TIME	**MEETING**	**CHAIR**
TBA	**COGNO Consumer Advisory Panel Meeting** (closed meeting) (Novotel Sydney Darling Square, Cockle Bay Room)	Desma Spyridopoulos
	OzMRS Symposium (UTS Science Building, Lecture Theater CB04.03.310, registration via OzMRS symposium website)	

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ORAL ABSTRACTS

24

Second interim and 1st molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion

Anna Nowak[1], Helen Wheeler[2], Mark Rosenthal[3], Michael Back[4,2], Rosalind Jeffree[5,6], John Simes[7], Sanjeev Gill[8], Katharine Drummond[3], Gail Ryan[3], Anthony Dowling[9], Rosemary Harrup[10], Lawrence Cher[11], Robyn Leonard[4], Thierry Gorlia[12], Vassilis Golfinopoulos[12], Johann Kros[13], Sara Erridge[14], Michael Vogelbaum[15], Brigitta Baumert[16], Martin van den Bent[13]

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[2]Royal North Shore Hospital, Sydney, Australia.

[3]University of Melbourne, Melbourne, Australia.

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[5]Kenneth G. Jamieson Department of Neurosurgery, Royal Brisbane and Women's Hospital, Herston, Australia.

[6]University of Queensland, Brisbane, Australia.

[7]NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia.

[8]Monash University, Melbourne, Australia.

[9]St Vincents Hospital, M, Australia.

[10]The Royal Hobart Hospital, Hobart, Australia.

[11]The Austin Hospital, Melbourne, Australia.

[12]European Organisation for Research and Treatment of Cancer, Brussels, Belgium.

[13]Erasmus Medical Centre, Rotterdam, Netherlands.

[14]The University of Edinburgh, Edinburgh, United Kingdom.

[15]Moffit Cancer Centre, Tampa, USA.

[16]University Maastricht, Maastricht, Netherlands

Abstract

Background. The first CATNON interim analysis showed benefit from adjuvant (adj) temozolomide (TMZ) on overall survival (OS) but remained inconclusive about concurrent (conc) TMZ. A second interim analysis was planned after 356 events.

Methods. CATNON randomized 751 adults with newly diagnosed non-codeleted anaplastic glioma in a 2x2 factorial design to either 59.4 Gy radiotherapy alone; radiotherapy with concTMZ; radiotherapy and 12 cycles adjTMZ or radiotherapy with both concTMZ and adjTMZ. *MGMT* promoter methylation (*MGMT*meth) status was re-assessed and Isocitrate dehydrogenase 1 and 2 (IDH) mutation (mt) status was assessed.

Results. With median follow-up 56 months and 356 events, the hazard ratio (HR) for OS adjusted for stratification factors after concTMZ was 0.968 (99.1% CI 0.73, 1.28). 5-year OS was 50.2% with and 52.7% without concTMZ (95% CI [44.4, 55.7] and [46.9, 58.1]). 335 (70%) of 480 assessed cases had IDHmt. Median OS was 19 mo in IDHwt and 116 mo in IDHmt.

Table: HR for OS after concTMZ (known IDH status).

	n	Events	HR [95% CI]	interaction test
IDH				
wt	145	120	1.27 [0.89, 1.82] p = 0.19	
mt	335	92	0.67 [0.44, 1.03] p = 0.06	p = 0.016

IDHmt predicted benefit from adjTMZ (IDHmt HR: 0.41, 95% CI 0.27, 0.64; IDHwt: HR 1.05, 95% CI 0.73, 1.52; interaction test p = 0.001).

In IDHmt patients receiving adjTMZ, HR for OS after concTMZ was 0.71 (95% CI 0.35, 1.42, p=0.32). *MGMT*meth was found in 288/410 assessed cases (70%), interaction test for concTMZ (p = 0.092) and adjTMZ (p = 0.166) did not reach statistical significance.

Conclusions. In the entire cohort, concTMZ did not increase OS. However, in IDHmt tumours a trend towards benefit of concTMZ is present. AdjTMZ increased OS in IDHmt but not IDHwt tumors. Further analyses and follow-up will allow full efficacy assessment in molecular subgroups.

15

DeepSurvNet: Deep Survival Convolutional Network for Brain cancer Survival Rate Classification based on Histopathological Images

Amin Zadeh Shirazi[1], Eric Fornacieri[2], Narjes Sadat Bagherian[3], Lisa Ebert[1], Barbara Koszyca[4], Guillermo Gomez[1]

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[2]Dept. of Mathematics of Computation, University of California, Los Angeles, USA.

[3]Dept. of Ophthalmology, Mashhad University of Medical Sciences, Mashhad, Iran, Islamic Republic of.

[4]SA Pathology, Royal Adelaide Hospital, Adelaide, Australia

Abstract

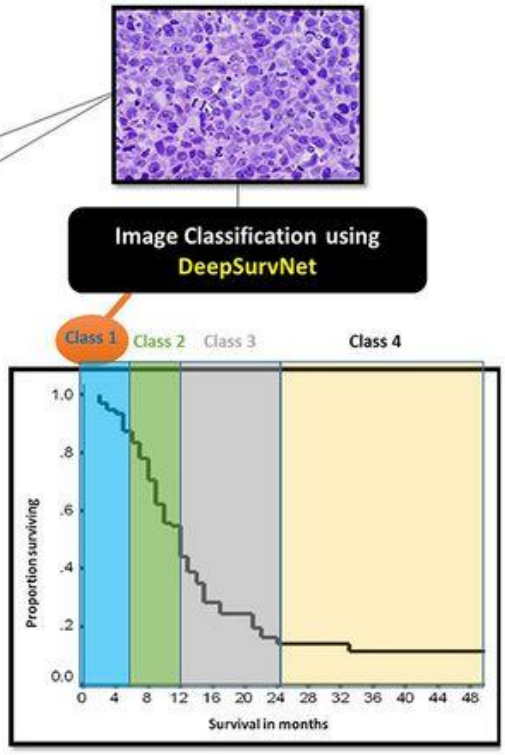
AIMS: Use Artificial Intelligence methods to analyze histopathological whole slide images of hematoxylin and eosin (H&E) stained biopsies. Slide images contain valuable information with relation to brain cancer disease and its clinical outcomes, but still there are no highly accurate automated methods to correlate histolopathological images with brain cancer patients' survival. This can help in scheduling patients therapeutic treatment and allocate time for preclinical studies to guide personalized treatments.

METHODS: We developed a new classifier namely DeepSurvNet powered by deep convolutional neural networks to accurately classify in 4 classes brain cancer patients' survival rate based on histopathological images (Class I: 0-6 months, Class II: 6-12 months, Class III: 12-24 months and Class IV: >24 months survival after diagnosis, Figure 1). After training and testing of DeepSurvNet model on a public brain cancer dataset, The Cancer Genome Atlas, we have generalized it using independent testing on unseen samples collected in local hospitals in Adelaide.

RESULTS: Using DeepSurvNet we obtained precisions of 0.99 and 0.8 in the testing phases on the mentioned datasets, respectively, which shows DeepSurvNet is a reliable tool for brain cancer patients' survival rate classification based on histopathological images. Moreover, analysis of the frequency of mutations in patient-samples with different survival rates revealed differences in terms of frequency and type of genes associated to each class, supporting the idea of a different genetic fingerprint associated to patient survival.

CONCLUSION: We conclude DeepSurvNet constitutes a new artificial intelligence tool to assess the survival rate in brain cancer.

Primary Diagnosis	Patient ID	Dead_Time (Month)
Glioblastoma	TCGA-12-0657	0
Glioblastoma	TCGA-19-2624	0
Glioblastoma	TCGA-41-4097	0
Oligodendroglioma, anaplastic	TCGA-HT-7616	0
Glioblastoma	TCGA-06-0201	0
Glioblastoma	TCGA-06-0213	1
Glioblastoma	TCGA-02-0439	1
Glioblastoma	TCGA-19-0962	1
Glioblastoma	TCGA-08-0392	1
Glioblastoma	TCGA-06-0219	1
Mixed glioma	TCGA-E1-A7YU	1
Glioblastoma	TCGA-41-2571	1
Glioblastoma	TCGA-06-0750	1
Glioblastoma	TCGA-14-1455	1
Glioblastoma	TCGA-14-1794	1
Glioblastoma	TCGA-41-3392	1
Glioblastoma	TCGA-19-2621	1
Glioblastoma	TCGA-14-1396	1
Glioblastoma	TCGA-14-1453	1
Oligodendroglioma, NOS	TCGA-DU-6400	1
Glioblastoma	TCGA-08-0352	1
Glioblastoma	TCGA-14-0813	1
Glioblastoma	TCGA-06-6391	1
Glioblastoma	TCGA-28-1755	2
Glioblastoma	TCGA-81-5910	2
Glioblastoma	TCGA-08-0345	2



4

Targeted drug delivery reduces brain metastases

Joanna Macdonald[1], Delphine Denoyer[2,3], Ingrid Burvenich[2,3], Normand Pouliot[2,3,4], Sarah Shigdar[1]

[1]Deakin University, Geelong, Australia.

[2]ONJCRI, Melbourne, Australia.

[3]La Trobe University, Melbourne, Australia.

[4]The University of Melbourne, Melbourne, Australia

Abstract

Prognosis for patients diagnosed with brain metastases is poor, with survival time measured merely in months. This can largely be attributed to the limited treatment options capable of reaching the tumour as a result of the highly restrictive blood-brain barrier. While methods of overcoming this barrier have been developed and employed with current treatment options, the majority are highly invasive and non-specific treatments, leading to severe neurotoxic side effects. A novel approach to address these issues is the development of therapeutics targeting receptor mediated transport mechanisms on the BBB endothelial cell membranes. We have developed aptamers as targeted delivery agents that can also cross the blood brain barrier. Aptamers are smaller than antibodies, and thus can more

effectively deliver drugs into the tumour. We have combined two aptamers for the targeted delivery of chemotherapeutics to brain metastases which can cross the blood brain barrier and specifically target cancer cells. Using this approach, we intercalated doxorubicin into the bifunctional aptamer targeting the transferrin receptor on the blood brain barrier and epithelial cell adhesion molecule (EpCAM) on the metastatic cells. The ability of the aptamer-doxorubicin to transcytose the blood brain barrier and selectively deliver the drug to EpCAM-positive tumour cells was evaluated in an in vitro model and confirmed in vivo. We show that co-localised aptamer and doxorubicin fluorescent signals are clearly detectable within the brain lesions 75 minutes post administration. Additionally, following a short treatment schedule, brain metastases were shown to decrease following bifunctional-aptamer-doxorubicin treatment, as compared to control or free drug. As well, metastases decreased in bone and ovaries following treatment. Collectively, the results from this study demonstrate that through intercalation of a cytotoxic drug into the bifunctional aptamer, a therapeutic delivery vehicle can be developed for the specific targeting of epithelial cell adhesion molecule-positive brain and systemic metastases.

26

Building the Bridge: The value of consumer co-design in brain cancer resource development

Dianne Legge[1], Steffi Renehan[1], Emma Daly[2], Louise Saliba[3], Paula Howell[4]

[1]Olivia Newton-John Cancer Wellness & Research Centre, Austin Health, Melbourne, Australia.

[2]Cabrini Health, Melbourne, Australia.

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Abstract

Background

Improved survival has raised awareness of the impacts and challenges confronting people with grade 2/3 brain cancers. To assist people re-engage with a productive and purposeful life, the *Building the Bridge Project* partnered with Victorian consumers, health professionals and lead cancer agencies to create a resource focused on what happens after treatment. How to access timely and appropriate help, and how to get back to fundamental life roles was the project target. Project partners were Austin, Cabrini and Monash Health and NEMICS.

Aim

Develop a tailored, accessible information resource for brain cancer survivors that supports self-management and provides a tool for health professionals to use in survivorship conversations.

Methods

Experience-based co-design placed survivor experiences central to the project. During stage one, focus groups with 27 consumers and carers defined high prevalence issues experienced when returning to life post-treatment. Consultation with neuro-oncology professionals and project partners refined themes and explored information accessibility. Further consumer consultation scoped resource format. Stage two developed resource content consistent with themes identified in the data. Further consumer feedback was incorporated prior to design. Final stage tested and evaluated the resource with consumers not previously engaged in co-design.

Results

Building the Bridge to Life with Brain Cancer is a 130-page hard copy, spiral bound resource embedded with patient stories, tips, strategies, checklists and targeted resources to facilitate re-engage in everyday life. Accessible language and non-medicalised content is presented in small chunks for ease of reading. Evaluation found high levels of acceptability, relevance and usefulness.

Conclusion

Consumer co-design placed the voice of the person with brain cancer at the centre of resource development. This was an important and powerful approach, yielding a relevant and accessible resource aimed at improving people's capacity to self-manage their condition, access appropriate supports and re-engage in community life.

POSTER ABSTRACTS

1

A case of pituitary carcinoma successfully treated with immune checkpoint inhibitor therapy

Lydia S. Lamb[1,2], Ann I. McCormack[1,2,3], David M. Thomas[2,3], Hao-Wen Sim[3,4,5]

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[2]Garvan Institute of Medical Research, Sydney, Australia.

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[4]Kinghorn Cancer Centre, Sydney, Australia.

[5]Central Clinical School, University of Sydney, Sydney, Australia

Abstract

Background

Pituitary carcinomas are rare aggressive tumours, defined by the presence of craniospinal or systemic metastases, and are associated with mortality rates up to 66% at 12 months. There is a paucity of effective treatment options. Immune checkpoint inhibitors have proven clinical utility across multiple malignancies, although their role in pituitary carcinoma is unknown. Here we describe a case of pituitary carcinoma responsive to immune checkpoint inhibitor therapy.

Case report

A 72yo female with progressive non-functioning pituitary carcinoma and dural metastases underwent a series of treatments including transsphenoidal resection (2014, 2015, 2016 and 2018), radiotherapy (2017 and 2018) and temozolomide (2018). Despite these treatments, there was inexorable disease progression. Extrapolating from an isolated case report of immune response in a ACTH-secreting hypermutated pituitary carcinoma, our patient received immunotherapy with ipilimumab 3mg/kg and nivolumab 1mg/kg on a three-weekly basis. Ipilimumab was discontinued after two cycles due to autoimmune nephritis, and maintenance nivolumab 3mg/kg on a two-weekly basis continues. There was marked clinical and radiological response of the primary pituitary carcinoma and all metastatic lesions, which is still durable at 7 months. The tumour was mismatch repair-proficient, PD-L1 <1%, had average mutational burden (6.8 Mut/Mb) and harboured no actionable variants based on genomic profiling and Molecular Tumour Board review.

Conclusion

Immune checkpoint inhibitor therapy may present a novel treatment option for pituitary carcinoma, which is not limited to hypermutated tumours. This may be worth pursuing in the prospective clinical trial setting.

2

Radionecrosis in Patients Receiving Stereotactic Radiosurgery for Brain Metastases

Philippa Ell[1], Yael Barnett[2], Peter Earls[3], Louise Emmett[4], Michael Rodriguez[3], Cecelia Gzell[5]

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Abstract

Aim: To examine factors contributing to radiation necrosis (RTN) in patients receiving stereotactic radiosurgery (SRS) for brain metastases

Methods: Single institution series of 51 consecutive patients with intracranial metastases undergoing SRS. Follow-up imaging was on standard protocol of MRI 6 weeks post-treatment then 3 monthly thereafter.

Results: Median age at diagnosis 59 years (range 24-86) with median survival of 19.4 months (range 0.9-53.4). Demographics include 56.9% female, 43.1% male, and 9.8% (n=5) had brain metastases at the time of initial diagnosis. Histopathology included: lung 37.3%, breast 17.6%, melanoma 11%, colorectal 5.5%, and other malignancy 25.5% (adenoid cystic, sarcoma, prostate, transitional cell, and renal cell). Craniotomy was performed in 80% (N=41) of patients prior to SRS for at least one intracranial lesion. De novo SRS was delivered to 82 metastases (85%) and cavity SRS was delivered in 65 cases (44%)

Rate of RTN was 20% (n=10). Diagnosis was based on histopathology in 6 patients, MRI and FET-PET in 1 patient, and MRI alone in 3 patients. Patients with RTN had the following features: 50% (N=5) had concurrent systemic therapy (doublet therapies including Herceptin and pertuzumab, dabrafenib and trametinib, or androgen deprivation therapy). One patient with RTN also had whole brain radiotherapy to a dose of 30Gy/10# with a boost of 6Gy/3# to the tumour bed 11 months prior to SRS. Of the patients with RTN 60% (N=6) were asymptomatic and 40%

(N=4) were symptomatic. Decompression surgery was needed in 4 patients for symptomatic relief.

Median survival of patients with RTN was 37.5 months (range 9-53) compared to 10.4 months (range 0.9-53.4) in patients without necrosis (P=0.0391).

Conclusion: RTN occurred in 20% of included patients in this series. The presence of necrosis may be prognostic for improved median survival. Further analyses are planned to investigate other contributing factors.

3

The "ART" of symptoms: Symptomax, a novel physician-assisted mobile application with artificial intelligence for symptom tracking, as a front-end for applied radiation therapeutics (ART)

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Abstract

Aims: Symptomax is a novel, physician-assisted, mobile application that incorporates human interface guidelines for brain tumour affected patients (BTAP). It is a first of its kind frontend for applied radiation therapeutics (ART).

Introduction: BTAP is a unique subset of chronic cancer affected individuals as they suffer from a higher incidence of recall bias and forgetfulness after definitive therapy. Besides, missed medications leading to emergent admissions and morbidity, it increases the burden on resource-constrained healthcare systems.

Methods: Symptomax is available for Android and iOS platforms with HIPAA compliance for personal health information. Patients sign up for a central database that allows tracking symptoms in real-time, formulating treatment plans, automating reminders for medications and comprehensive lab investigations. It also has a hosted interactive community to assist in a smooth progression from "hospital to home care paradigm" that allays anxieties of caregivers related to treatment effects. Gamification mechanisms will ensure continuous user engagement.

Integrated machine learning algorithms will initially gather insights from symptoms; subsequently from radiological images, radiation planning datasets and genetic sequencing in a planned phased rollout.

Symptomax is designed to be financially self-sustaining. Other researchers can access anonymised datasets. It can also be integrated with hospital and pharmaceutical companies' resource planning systems as it would provide predictive analytics with a mechanism for appointments and pharmacy refills.

Conclusions: Symptomax addresses an unmet need to quantify symptoms in real-time, identify patterns and provide quality of life studies.

5

Soft substrates mechanically matched to brain tissue reveal brain tumour reveal resistance to kinase inhibitors

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Abstract

AIMS: Seminal studies in the tissue engineering field have revealed that culturing stem cells on matrices which match the softness of brain induced the cells to differentiate into neuronal lineages, independently of any other external factors. While a role for biomechanical forces has begun to be addressed in a number of solid cancer types, to date there has been limited consideration of this parameter in brain cancer. We hypothesized that mechanosensing may alter the biology and response of glioblastoma (GBM) brain cancers to anti-cancer treatments.

METHODS: This was tested using combinations of kinome screening and materials engineered to recapitulate the brain's soft features, together with primary patient-derived glioblastoma (GBM) cells cultured in defined media to maintain *in vivo* characteristics.

RESULTS: Kinome screening identified a number of mechanosensitive kinases, including EGFR, a major drug target in GBM. We demonstrate that GBM patient lines are significantly resistant to EGFR inhibitors when cultured on soft surfaces mimicking the brain's biomechanical features. Activation of MAPK signalling downstream of EGFR is significantly suppressed on soft substrates. Our studies suggest that the brain's biomechanical milieu is indeed an important determinant of GBM biology and response to anti-cancer treatments.

CONCLUSIONS: Our work suggests that assessment of the mechanopharmacology of putative treatments for GBM should be considered as part of the preclinical assessments in the progression of novel treatments to clinical trial.

6

START: A single-arm, phase IIa trial of the activity of seviteronel in patients with androgen receptor (AR)-positive central nervous system (CNS) tumours

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Abstract

Background: Systemic treatments for CNS tumours such as glioblastoma (GBM) are limited. AR is an established therapeutic target in prostate cancer, and recent data support a role in AR-positive non-prostate cancers[1]. The AR gene was found to be amplified in 27% and 38% of GBMs in men and women, respectively[2]. Furthermore, AR gene transcription levels are elevated in GBMs compared to other tumour types (see figure 1)[3]. Thus the AR is a novel target for treatment of GBM. Seviteronel is a novel dual-selective CYP17 lyase inhibitor and direct AR inhibitor that penetrates the blood-brain barrier. Preclinical data revealed that seviteronel can inhibit the growth of AR-positive GBM cell lines at achievable in vivo concentrations[3]. This suggests that seviteronel may be an effective treatment option for AR-positive CNS tumours.

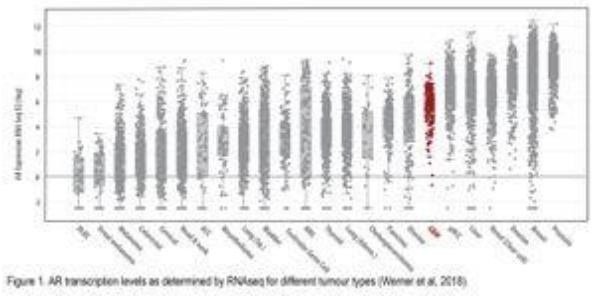

Figure 1. AR transcription levels as determined by RNAseq for different tumour types (Werner et al, 2018)

Methods: START is a single-arm phase IIa trial to investigate the activity of seviteronel in any CNS tumour subtype selected by AR positivity, confirmed by immunohistochemistry (AR>0%). Other key eligibility criteria: failure or intolerance of all standard anticancer therapy. Primary endpoint: overall response rate (ORR). Secondary endpoints: overall and progression-free survival; safety; health-related quality of life.

Seviteronel will be administered 450 mg po daily in combination with dexamethasone 0.5 mg po daily (and GnRH analogue depot injection every 3 months for men and pre-menopausal women), until failure or intolerance. 16 patients will be enrolled over 48 months (A'Hern single-stage design, 10% significance level, 75% power, to detect ORR ≥30% while rejecting ORR ≤10%).

START is open at The Kinghorn Cancer Centre, St Vincent's Hospital Sydney. Optionally, pre-screening for AR immunohistochemistry can be performed prior to referral, and this will be confirmed centrally. Collaborations are sought for future confirmatory studies. AR-positive rate on pre-screening: currently 9 of 24 patients. First patient accrued: November 21, 2018. ClinicalTrials.gov NCT number: NCT03600467.

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7

Developing a National Paediatric and Adult Brain Cancer Registry: A Clinical Feasibility Study

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Abstract

BACKGROUND AND PURPOSE:

Brain cancer is a significant cause of death and disability but the nuanced landscape of brain cancer incidence, treatment patterns and outcomes is not well understood across Australia.

A Brain Cancer Clinical Registry would:
- collect, collate and report clinical quality metrics
- provide feedback to clinicians
- assist researchers with clinical information
- facilitate clinical trials
- inform the community and government about brain cancer incidence and outcomes.

This study was carried out to identify the possible scope and mechanisms for development of an Australian National Paediatric and Adult Brain Cancer Clinical Registry.

METHODS:

Data was collated from a literature review, clinician consultations, review of existing information systems at different institutions across Australia, and case studies of local and international clinical registries. This data was used to develop a Brain Cancer Clinical Registry Framework and publish a Feasibility Study Report (1)

RESULTS:

This scoping study identified that pathways for the treatment of brain cancer are complex, iterative and involve multiple providers and locations. Administrative, diagnostic, treatment and outcomes data are scattered (and duplicated) across a range of paper and electronic systems. Based on this information different repository models were developed.

CONCLUSIONS:

Three potential repository models were identified for consideration:
1. A single national repository, or
2. A two tier repository with state registries feeding into a national registry
3. A two tier repository with local hospital or HHS data collections feeding into a national registry.

BCBA is now developing a preliminary set of clinical quality indicators to inform stage one – the quality of care component – of the registry and inviting pilot sites to implement data collection. This is a timely initiative, coinciding with the publication in May of the "Draft National Clinical Quality Registry Strategy" by the Australian Government Department of Health (2).

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8

Management and visual outcomes in optic nerve sheath meningioma - a multicentre study and pooled data analysis

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Abstract

Aims: Optic Nerve Sheath Meningiomas (ONSMs) are benign neoplasms accounting for 2% of orbital tumours. Radiotherapy has shown favourable outcomes compared with surgery or observation, however the optimal modality of radiotherapy remains unknown.

Methods: We performed a retrospective analysis of visual outcomes and side effects in ONSM patients treated with radiotherapy at three centres in Sydney, Australia, between 2000 and 2016 (n = 15). Pooled data analysis of available

studies was performed, allowing comparison between different radiotherapy modalities.

Results: In our cohort, a significant majority experienced improved visual field outcomes (10/13 >3 dB mean deviation improvement, p = 0.046), and stable or improved visual acuity (1/13 ^{3}2 Snellen lines decline, p = 0.0017) and colour vision (0/6 ^{3}1 Ishihara plate decline, p = 0.015) after fractionated stereotactic radiotherapy (either VMAT or IMRT, mean follow up = 46.5 months). 2/15 patients had complete documented neuro-ophthalmological review pre- and post-treatment. Pooled data analysis with strict inclusion criteria revealed poorer visual acuity in 3D-CRT compared to fractionated stereotactic radiotherapy (fSRT, see Fig 1). When all published studies were included, stereotactic radiosurgery (SRS) was equivalent to fractionated methods (3D-CRT, FSRT, IMRT) in visual outcomes. Rates of long-term side effects were lowest with SRS, and 3D-CRT had significantly higher rates of lacrimal dysfunction and cataract (see Fig 2). IMRT was more likely to improve visual outcomes, while FSRT and SRS were more likely to stabilise visual outcomes.

Conclusion: Our results favour fSRT, IMRT or VMAT over 3D-CRT in offering superior visual outcomes post-treatment. SRS appears to be a viable treatment option for ONSM patients despite higher radiation doses. Where preserving or improving vision is the goal of treatment, we advocate for thorough neuro-ophthalmological assessment pre- and post-treatment.

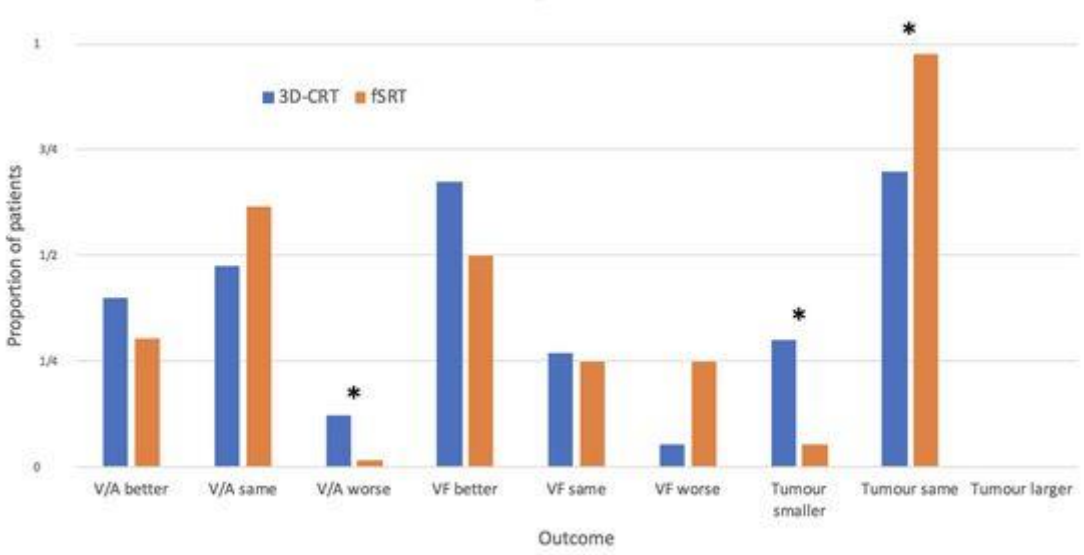

Figure 1 - Outcomes comparing 3D-CRT and fSRT. * = significant difference

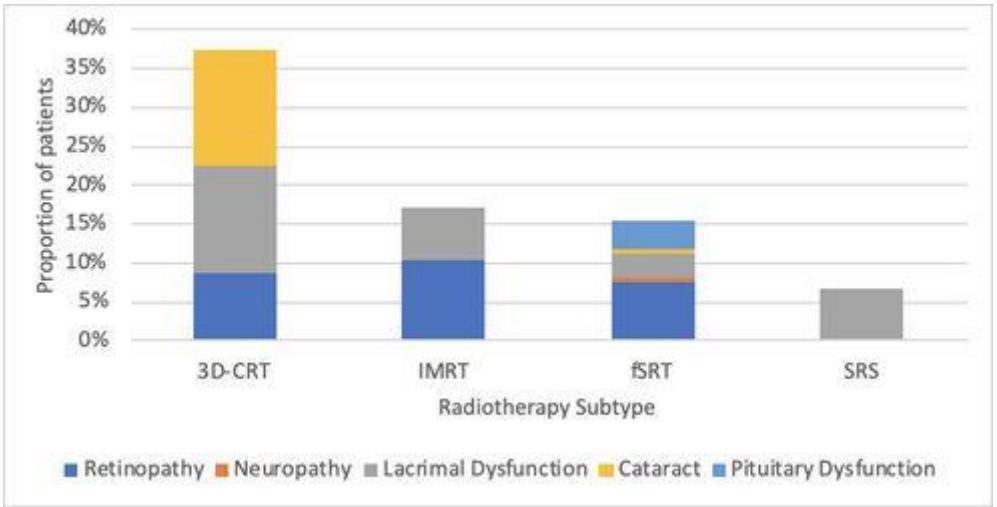

Figure 2 - Side-effect rates between radiotherapy subtypes

9

Innovative 'omics approaches reveal the exciting promise of extracellular vesicle profiling as a blood test for monitoring glioma patients

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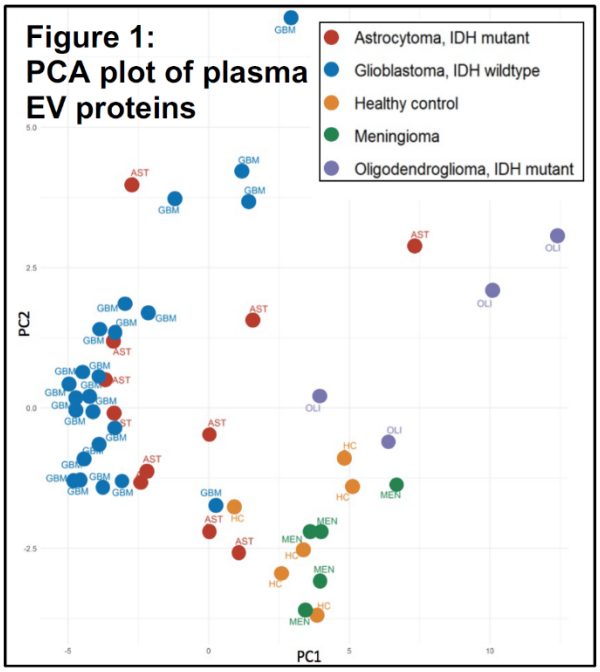
Abstract

Introduction: There is a real need for biomarkers that can indicate glioma disease burden and inform clinical management, particularly in the recurrent glioblastoma setting where treatment-associated changes can confound tumour surveillance methods. The last decade has seen a rapid rise in extracellular vesicle (EV) research, describing integral roles in cancer biology [1-2] and identifying EVs as promising biomarker reservoirs for monitoring and stratifying patients [3-6]. EVs (30-1000 nm membranous particles) can cross the blood-brain-barrier into the periphery where they are stable and readily-accessible. As such, non-invasive sampling of tumour-derived molecules cargoed in EVs hold enormous potential for revolutionising how glioma tumours are assessed *in situ*.

Methods: We show that molecular profiling of EVs captured from patient blood is a promising approach to assess tumours in real-time. With access to modern instrumentation, we have developed innovative approaches to profile the miRNA, proteomic and metabolomic signatures within blood-EVs that can distinguish glioma subtypes from healthy and non-glioma controls and indicate tumour burden. This includes our innovative EV proteome profiling platform using state-of-the-art 'SWATH' mass spectrometry, powered by the development of a custom, glioma EV spectral library detailing reference sequences for 8662 protein species.

Results: In a pilot study, absolute quantitation of 4909 plasma-EV proteins (q-value<0.05) was achieved, which is the most comprehensive EV proteomic coverage to date. Of these measured EV-associated proteins, 463 changed significantly across glioma and non-glioma cohorts (*adjust.*p<0.05; n=49). Principal component analysis showed excellent discrimination between the patient groups studied **(Figure 1)**, highlighting the promise of this approach as an accurate, sensitive tumour monitoring method.

Conclusions: Objective blood-based measurements of glioma tumour activity will support the implementation of next-generation, patient-centred therapies and are ideal surrogate endpoints for recurrent progression that would allow clinical trial protocols to be more dynamic and adapt to the individual patient and their cancer.



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10

Disruption of the Blood-Brain Barrier using MR-guided Focused Ultrasound Increases Antibody Delivery to Non-Enhancing High Grade Glioma

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Abstract

High grade glioma (HGG) remains one of the most aggressive types of brain cancers with a very poor median survival time of 14 months following current standard of care. A major challenge in improving prognosis is the inability of current therapeutic strategies to address a clinically significant burden of infiltrating tumour cells that extend beyond the margins of the primary tumour mass and cannot be surgically excised nor efficiently targeted by chemotherapy or radiation therapy. Therapeutic intervention for this population of cells is significantly hampered by the presence of an intact blood brain barrier (BBB).

Aims: In our work, we perform a pre-clinical trial investigating the efficiency of MR-guided Focused Ultrasound (MRgFUS) to temporarily open the BBB and achieve delivery of a targeted antibody in infiltrating tumour regions.

Method: In our study, we use structural MRI, dynamic-contrast enhancement (DCE) MRI and histology to fully characterise the MR enhancing properties of a patient derived orthotopic mouse model of HGG, and develop a robust and reproducible model of non-enhancing HGG. Using this model, we evaluate for the first time the efficacy of MRgFUS to increase the concentration of a ^{89}Zr radiolabelled antibody in non-enhancing HGG tissue by use of PET/CT imaging techniques.

Results: Our results show that using MRgFUS leads to a significant increase in both BBB opening and antibody uptake in the non-enhancing HGG tissue, and that antibody uptake is linearly correlated with the extent of BBB opening induced by MRgFUS in the non-enhancing tumour (**Figure 1**).

Conclusions: Overall, our study demonstrates that the use of MRgFUS would lead to an increased efficacy of current and emerging chemotherapies and opens up the possibility of using MRgFUS in combination with systemic therapies that have previously proved ineffective in HGG due to poor BBB penetration.

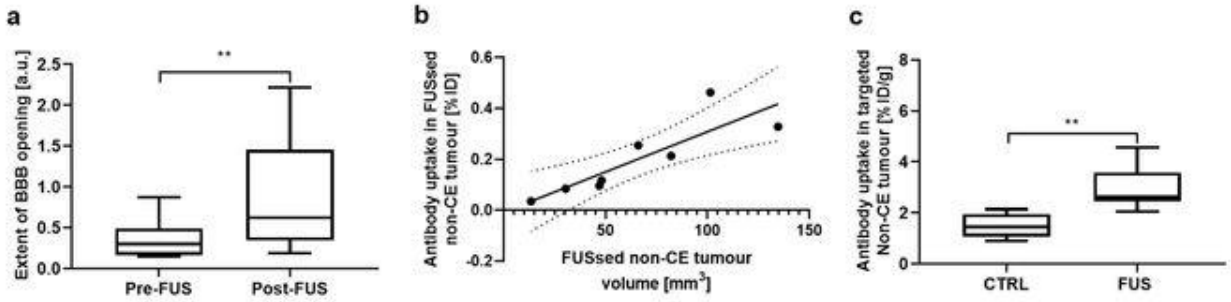

Figure 1. *Plots of quantitative analysis of FUS-induced degree of BBB opening and values of antibody tumour uptake in non-enhancing HGG.* **a)** The plots shows a comparison of the extent of FUS-induced BBB opening in the FUS group between pre- and post-FUS treatment. The FUS treatment significantly increased extent of BBB opening in the tumour in all of the mice (p=0.0078, Wilcoxon test). **b)** The plot shows a direct linear correlation between the total percentage of antibody tumour uptake in the FUSsed non-CE tumour and the total volume of the FUSsed non-CE tumour of the FUS group mice. The statistically significant linear correlation (Pearson r coefficient 0.8621, p=0.0059) between the two parameters implies that antibody tumour uptake can be proportionally increased by increasing the volume of tumour targeted with FUS. **c)** The plot shows a comparison of the mean value of antibody uptake in the targeted non-CE tumour between the CTRL group and the FUS group. The significantly higher values of the mean antibody tumour uptake (p=0.0013, Mann-Whitney t-test) in the targeted non-CE tumour of the FUS mice compared with the control mice demonstrates the ability of the FUS treatment to enhance antibody delivery in otherwise inaccessible regions of the tumour.

11

Targeting EphA3 with radioimmunotherapy or antibody-drug conjugates is an effective therapy for GBM

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Abstract

Despite aggressive therapy, prognosis for glioblastoma (GBM) remains poor and novel therapeutic targets for drug development are urgently needed. We recently characterised the receptor tyrosine kinase EphA3 as a functional tumour-specific therapeutic target in glioblastoma (GBM), where it is most highly expressed on glioma stem cells (GSCs) and has a functional role in maintaining self-renewal and tumourigenesis. Recent findings by others have further demonstrated the importance of EphA3 in GBM and shown that receptor levels are significantly elevated in recurrent disease. To therapeutically target EphA3-positive tumour tissue we developed EphA3 antibody drug conjugate (ADC) and radioimmunotherapy approaches. *In vitro* testing confirmed the effectiveness of EphA3 ADCs conjugated to either auristatin-E (MMAE) or maytansine (USAN) to halt GBM cell growth and induce apoptosis. *In vivo* brain uptake studies, using PET imaging, show EphA3 antibodies are effectively delivered across the blood brain barrier and accumulate specifically at the tumour site with no observed normal brain reactivity. Both EphA3 ADC and radioimmunotherapy approaches effectively targeted orthopically engrafted GBM tumours. A robust anti-tumour response with no toxicity was observed leading to a significant increase in overall survival. These findings reveal the effectiveness of EphA3 pay loaded targeting strategies to induce a tumour-specific anti-tumour response in GBM.

12

Multiparametric serial magnetic resonance imaging assessment of gross tumour volume and hippocampal changes over the course of adjuvant brain cancer radiotherapy

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Abstract

Aims: Understanding the significance of anatomical and functional imaging changes during brain cancer radiation therapy (RT) is key to developing personalized adaptive radiotherapy (ART) approaches. This project aims to determine imaging predictors of brain tumour response. Anatomical and functional changes in gross tumour volume (GTV), tumour subvolumes and hippocampi (organ at risk affecting neurocognition) were assessed using multiparametric MRI during CNS RT.

Methods: This prospective pilot study involved 34 patients with glioma (high grade=18, low grade=5) and secondary brain cancer (n=11). Patients underwent imaging at RT planning (baseline-BL), mid-treatment (if receiving ≥25 daily fractions-FU1), at the end of RT (FU2) and four weeks post RT (FU3). The 3T Siemens Skyra MRI acquisition protocol included anatomical T1 and T2, diffusion weighted imaging (DWI), dynamic contrast enhancement (DCE), susceptibility weighted imaging (SWI) arterial spin labelling (ASL), and apparent diffusion coefficient (ADC) maps. GTV and hippocampi were manually contoured on the anatomical imaging at each time-point. Tumour subvolumes including enhancing tumour, necrotic area and oedema were also segmented using manual and automated techniques. Analysis was undertaken using Pyradiomics v2.2.0 to extract first order statistics for the segmented volumes.

Results: Over time, a reduction in GTV was demonstrated with mean BL volume 4.3 $x10^4 mm^3$ compared to FU3 3.5 $x10^4 mm^3$ (Figure 1). Similarly, hippocampal volumes decreased with mean BL volume of 2.34 $x10^3 mm^3$ and FU3 of 1.95 $x10^3 mm^3$. An increase in ADC was seen throughout the study time-points for the GTV. Patients with high grade glioma experiencing local recurrence, had a larger enhancing tumour subvolume with lower ADC values compared to those without documented local recurrence (Figure 2).

Conclusion: Linking functional information to tumour subvolumes may guide where to target radiation dose during ART process. The results of this pilot study will form the basis for a larger trial focusing on glioblastoma with multi-institution recruitment.

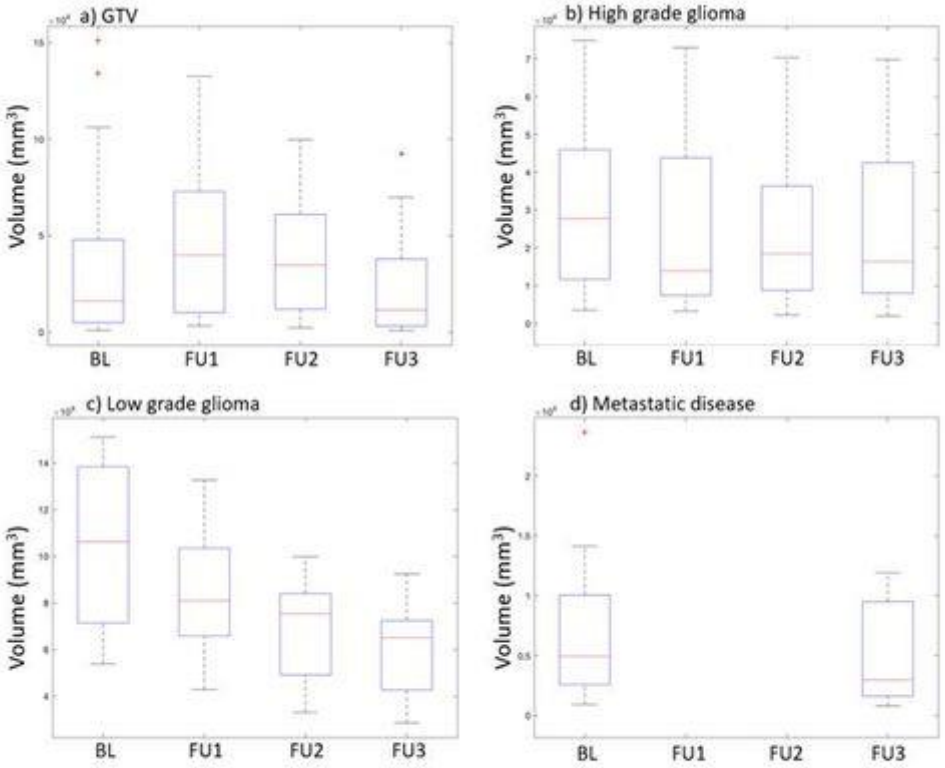

Figure 1. Tumour volume changes during study time-points. a) GTV, b) high grade glioma, c) low grade glioma, d) metastatic disease.

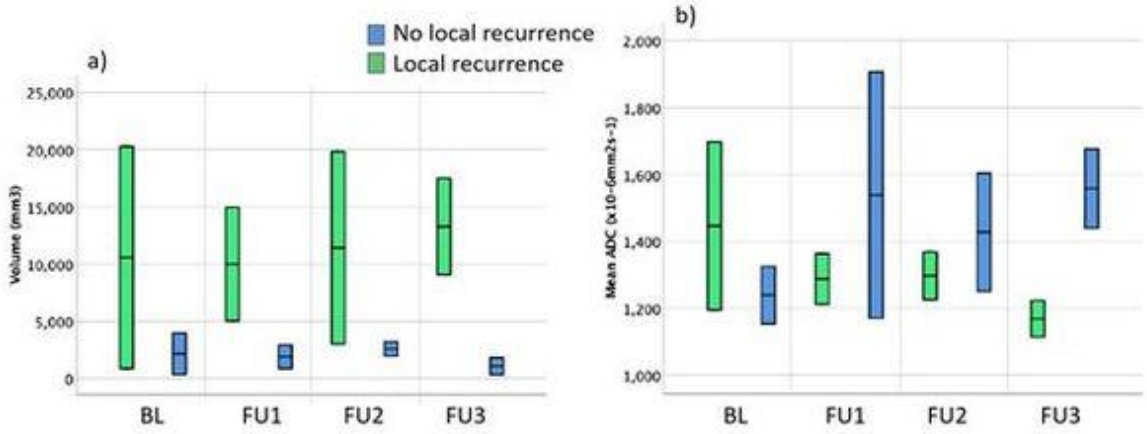

Figure 2. Enhancing tumour a) volume change b) ADC value change during study time-points for high grade gliomas.

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DYRK1A and Rb cooperatively control the proliferation-dormancy switch and therapy resistance in glioblastoma

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Abstract

Glioblastoma, the most common and aggressive brain tumour, is propagated by stem-like cancer cells refractory to chemotherapy. We have identified that the incomplete killing of glioblastoma stem cells by chemotherapy is not caused by drug-resistant cells but rather by a fraction of cells that is able to resonate between proliferative drug-sensitive and dormant drug-tolerant states. Upon removal of the chemotherapeutic agents, dormant glioblastoma stem cells resumed proliferation.

To understand the molecular mechanisms that control the proliferation-dormancy plasticity, we performed proteomic and phosphoproteomic analysis as well as a panel of orthogonal mechanistic studies. We discovered that dual-specificity tyrosine-phosphorylation regulated kinase 1A (DYRK1A) and retinoblastoma (Rb) protein cooperate to control the proliferation-dormancy plasticity of glioblastoma stem cells. Intriguingly, the proliferation-suppressive DYRK1A and Rb signalling was detrimental to the efficacy of chemotherapy. Glioblastoma stem cells expressing Rb and DYRK1A were significantly more tolerant to cytotoxic drugs and transitioned to drug-tolerant dormant state. Inhibition of DYRK1A disrupted the proliferation-dormancy switch in Rb-deficient glioblastoma stem cells, rendering them sensitive to chemotherapy.

Our findings reveal for the first time that glioblastoma stem cells use tumour-suppressors Rb and DYRK1A to derange the effectiveness of chemotherapy. Our results also demonstrate that a wake-up strategy for Rb-deficient dormant glioblastoma stem cells using DYRK1A inhibitors might be of therapeutic value in combination with chemotherapy.

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Australia and New Zealand Children's Haematology / Oncology Group (ANZCHOG): a novel pathway for enrolment of adolescent / young adult (AYA) patients with central nervous system (CNS) malignancies

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Abstract

Tumours of the CNS are among the most common in AYA and often carry high morbidity / mortality. Furthermore, outcomes for AYA have failed to improve at the rate of younger patients, in part due to lower enrolment on clinical trials. ANZCHOG, the national cooperative trials group for childhood cancer, together with COGNO, has recently formed an AYA sub-committee, aimed at improving clinical trial enrolment for this under-represented population.

ANZCHOG has 3 currently open diagnostic studies –

1./2. **AIM BRAIN / MNP2.0**, both utilizing whole genome methylation analyses to increase diagnostic accuracy of CNS tumours and develop an accredited Australasian service (< 21 yo) and

3. **PRISM**, identifying molecularly driven therapeutic targets and personalised treatment for high-risk cancers (< 21 yo) -

and 8 open / soon to be opened therapeutic studies

1. **BIOMEDE**, an exploration of therapies for DIPG (< 25 yo)
2. **INFORM2,** a phase I/II study of the anti-PD1 nivolumab and the HDAC inhibitor entinostat in refractory malignancies (< 21 yo)
3. **LOGGIC,** a phase III trial comparing standard chemotherapy to the MEK inhibitor trametinib for LGG (<21 yo)
4. **OZM-075**, a pilot study of nivolumab in hypermutant cancers (<25 yo)
5. **NORTH,** a phase II study of the HDAC inhibitor panobinostat in ATRT(< 40 yo)
6. **PARC**, a phase II study of pegylated arginase in relapsed cancers (< 24 yo)
7. **SJ-ELiOT**, a phase I evaluation of the CHK1/2 inhibitor prexasertib in recurrent medulloblastoma (< 25 yo) and
8. **TiNT**, a phase II study of trametinib in NF-1 associated plexiform neurofibromas or optic pathway LGG (< 25 yo) – for patients older than 18 years of age with a CNS malignancy.

Further AYA studies, in collaboration with the Pacific Pediatric Neuro-Oncology Consortium (PNOC) and the Collaborative Network for Neuro-Oncology Clinical Trials (CONNECT), are expected in the near future.

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Redo craniotomy or Bevacizumab for symptomatic steroid refractory true or pseudoprogression following IMRT for Glioblastoma

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Abstract

Aim: There is minimal evidence to support decision-making for symptomatic steroid-refractory pseudoprogression or true progression occurring after IMRT for glioblastoma (GBM). This study assessed the survival outcome of patients managed with redo craniotomy (RedoSx) or Bevacizumab (BEV) for steroid-refractory mass effect after IMRT for GBM.

Materials and Methods: Patients with GBM managed between 2007 and 2017 with the EORTC-NCIC Protocol were entered into a prospective database. Patients with symptomatic steroid-refractory mass effect within 6 months of IMRT managed with either RedoSx or BEV were identified for analysis. For the primary endpoint of median overall survival (OS) post intervention, outcome was analysed in regards to potential prognostic factors, and differences between groups assessed by log-rank analyses.

Results: Of 348 patients managed with the EORTC-NCIC Protocol, 59 required an intervention within 6 months of IMRT completion for either true or pseudoprogression (38 with RedoSx and 21 with BEV). Subsequently 14 of the 38 patients managed with RedoSx required salvage with BEV. Median OS post intervention was 8 months (95%CI: 6.1-9.9) for the total group; and 6 months (95%CI: 3.0-9.0) for RedoSx and 9 months (95%CI: 7.6-10.4) for BEV (p=0.19).Age, time from IMRT, and ECOG performance status were not associated with OS. In the RedoSx patients, subsequent BEV salvage was associated with improved OS (8 vs 4 months, p=0.02). Immunohistochemical features such as Ki67% reduction correlated with survival however the presence of residual glioma cells did not.

Conclusion: At time of symptomatic steroid-refractory true or pseudoprogression following IMRT for GBM, BEV was equivalent to RedoSx in terms of OS. Use of BEV after RedoSx was associated with improved survival over RedoSx alone.

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Reflecting on survivorship outcomes to aid initial decision-making in patients managed for IDH-mutated Anaplastic Glioma

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Abstract

Aims: Patients with anaplastic glioma (AG) harbouring an isocitrate dehydrogenase (IDH) mutation have potential durable survival following intensity modulated radiation therapy (IMRT) and chemotherapy. Understanding long-term functioning, and the factors that impact on later effects is important for decision-making. This study aims were to document the functional status of patients in the 3-5 years after therapy for an IDH mutated anaplastic astrocytoma and the factors that impact on worse outcome.

Methods: Consecutive AG patients managed with IMRT were reviewed regarding six Survivorship Domains including ECOG Performance Status (ECOG); Medical Research Council Neurological Status (MRC); Late Toxicity; Co-morbidity; Functional Status (Employment/Driving); and Psychosocial Events. Assessments were performed at baseline pre-RT, month+6, and Years +1, +3 and +5 post-RT. Primary endpoints were ECOG at Year+3 and Employment at Year+3.

Results: 146 patients were included, with 5.1 years median follow-up. The 6-yearOS was 78.7% (95%CI:71.1-87.0). Baseline ECOG was 0 -1 in 82.2% but improved at Y+1(95.7%) and Yr+3(97.2%). Employment at Yr+3 and Yr+5 was 70.1% and 76.5% respectively; compared with 61.6% baseline. On multivariate analysis, worse ECOG at Yr+3 was related to multiple craniotomies prior to RT (p<0.001), worse ECOG preRT (p<0.001), worse MRC Score preRT (p=0.003), presence of prior relapse (p=0.001), and anaplastic astrocytoma subtype (p=0.002). Absent or impaired Employment at Yr+3 related to older age (p=0.002), multiple craniotomies prior to RT (p=0.005), worse ECOG preRT (p<0.001) and worse MRC Score preRT (p<0.001).

Conclusion: AG with IDH mutation have potential for prolonged survival. Functional status is good in patients who are progression free at three to five years following IMRT with greater than 95% of patients having high performance status and greater than 75% in employment.

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Identifying barriers to completion of adjuvant therapy in patients with newly diagnosed glioblastoma multiforme: an exploratory study

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Abstract

Hypothesis/Purpose: This study aims to identify the key factors that are influencing one third of medically eligible newly diagnosed glioblastoma (GBM) patients diagnosed at St. Michael's Hospital to choose to decline or withdraw from the recommended regimen of chemoradiation, the Stupp protocol. We hypothesize that there are underlying factors that influence a GBM patient's decision to decline or withdraw from the Stupp protocol, other than those related to the disease itself, and that these factors fall within Kim et al.'s Conceptual Framework for Individual and Family End-of-Life Decision Making[1].

Methods: In this mixed methods study, data will be collected from two sources: medical chart review and semi-structured interviews. During the chart review of newly diagnosed GBM patients (n=150), factors that are common amongst patients who have not completed treatment will be analyzed in order to identify profiles of those at risk of decline or withdrawal from care. Next, semi-structured interviews will be conducted with three groups: newly diagnosed GBM patients who have declined or withdrawn from treatment (n=20), caregivers (n=20), and healthcare providers (n=10). Data collected from the interviews will be analyzed to identify common themes or factors related to the decision to decline or discontinue treatment and the decision-making process.

Results: Data collection is underway and we anticipate that analysis will be completed by October.

Conclusion: The results of this study may be used to inform practitioners by identifying barriers to completion of chemoradiation which in turn, may lead to the identification of patient profiles at risk of withdrawing from care. Identifying these risk factors may help in the development of tailored resources that can be used to better support GBM patients in the treatment and decision-making process. The findings from the analysis will also offer supporting or non-supporting evidence to Kim et al.'s framework.

References

1. Kim, K., Heinze, K., Xu, J., Kurtz, M., Park, H., Foradori, M., & Nolan, M. T. (2018). Theories of Health Care Decision Making at the End of Life: A Meta-Ethnography. Western Journal of Nursing Research, 40(12), 1861–1884. https://doi.org/10.1177/0193945917723010

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K27M histone mutated diffuse midline Gliomas in older patients

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Abstract

Background

Histone mutations in the K27M gene were first described in 2014 and were incorporated into the WHO 2016 CNS tumour classification in 2016. They are associated with Diffuse Midline Gliomas (DMG) and usually occur in children. Median survival for these patients is only 9 months. There is limited treatment and outcome data for those older patients who present in late adolescence or as adults. Biopsy samples are small, limiting extensive genomic testing. Histological appearance can greatly vary. Here we describe 8 patients with K27M DMG from our adult Glioma data base and correlate outcome with clinical, radiological and histopathological features and treatment.

Methods

Our Glioma database (2009-2018) was used to identify patients. Selection criteria included those who presented with a midline Glioma, had undergone biopsy and had tissue available for immunohistochemistry (IHC). The Sigma-Aldrich Clone RM192 antibody was used for to determine the presence of a K27 mutation. Clinical, radiological, treatment and outcome data was then correlated.

Results

Eight patients who fitted our selection criteria are reported. The median age at diagnosis was 23 (range 17-47), 2/8 were female. Four presented with acute hydrocephalus.
Four lesions were supra-tentorial, 3 in the brainstem and 1 in the cervical cord. Three were non-enhancing and 5 had patchy gadolinium enhancement. Histology revealed 4 glioblastoma, 3 anaplastic astrocytoma and 1 diffuse low grade glioma. Four were treated with concurrent chemo-radiotherapy followed by adjuvant temozolomide, and four with radiotherapy alone. The median PFS 12.5 months (4-17months) and OS 20.5 months (4-44 months).

Conclusion

This case series documents the clinical features of 8 older patients with K27M mutated DMG. Ongoing studies are needed to characterize the molecular differences and clinical course of these tumours in older patients to determine if they differ from the paediatric population and identify better therapeutic options.

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Next generation sequencing impacts the classification and management of gliomas

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Abstract

Introduction

The 2016 WHO Classification of Central Nervous System Tumours heralded a shift towards an integrated diagnosis for gliomas, which incorporates both histological features and molecular data. Next generation sequencing (NGS) is an efficient and cost-effective method which enables parallel analysis of multiple genetic alterations in a single platform. Our institution obtained NATA accreditation for an NGS custom glioma panel in November 2018. Here we compare the initial histological and the final integrated diagnoses in the first 4 months of utilising NGS in our diagnostic workup of primary brain tumours.

Method and results

We use a custom glioma gene panel that uses multiplex PCR with ion semiconductor sequencing (AmpliSeq, Ion Torrent S5) to assess a panel of key gene mutations and copy number variations. The NATA-accredited genes include *TERT*, *H3F3A*, *BRAF V600E*, *IDH1/IDH2*, *EGFR* amplification, and chromosome 1p/19q co-deletion. Of the 74 tumours that were analysed, 15 cases (20%) had an altered diagnosis defined by a change in tumour classification or grade. Fourteen cases (19%) had their diagnosis refined through the identification of a mutation not detected by routine immunohistochemistry, and 27 tumour diagnoses (36%) were confirmed by NGS. Of the remaining 18, 15 did not yield any significant findings on NGS, 2 had no histological details provided and one did not have sufficient DNA for analysis.

Conclusion

This early analysis has highlighted the utility of NGS in refining glioma classification, since some tumours are now defined by their molecular signature rather than by histology alone. Furthermore, the NGS platform is adaptable and has the potential to expand as new molecular prognostic markers and therapeutic targets are identified.

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Clinical trials in Glioblastoma: learning from previous experiences towards optimal development of trial design

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Abstract

AIMS: We postulate inefficiencies in the Phase 2/3 transition contribute to majority of GBM phase 3 trials (P3T's) being negative.

METHODS: Studies between 2005-2019 inclusive were identified though MEDLINE(R) using keywords and MeSH terms, and manual bibliography searches. Clinical, statistical and sponsor characteristics were extracted independently by two reviewers (AB&AG). For each P3T, phase 2 trial (P2T) data was "optimally matched" where the same drug was used in similar schedule and GBM population; "partially matched" where dis-similar schedule and/or treatment setting; and "lacking" in all other circumstances. Data were compared by Pearson Correlation, t-test or chi-square as appropriate.

RESULTS: 20 relevant P3T's and 17 P2T's were identified. The median progression free survival (mPFS) and median overall survival (mOS) in P3T's were 7.7 and 20.1 mths respectively for first line studies; 2.2 and 7.3 mths respectively for recurrent studies. These were 10.0 and 16.1 for 1st line P2T's, and 3.6 and 8.3 mths respectively for recurrent studies. 55% of P3T had optimally matched P2T, with high P3T/P2T concordance for mPFS (r^2= 0.90, p< 0.01) and mOS (r^2= 0.87, p< 0.01). The remaining P3T had only 'partially matched' (15%) or lacked P2T data (30%). Partially matched P3Ts/P2Ts (25%) lacked concordance for both mPFS (r^2= 0.46, p=0.528) and mOS (r^2= 0.09, p=0.624). 84.2% of P3T (16/19) did not meet the pre-defined statistical endpoint for benefit. All first-line P2T with mPFS< 14 months and/or OS< 22 months had negative P3T. All recurrent P2T with mPFS< 6 months and mOS< 12 months had negative P3T. Impact of sponsors and molecular subtypes will be presented.

CONCLUSIONS: Selection bias, lack of optimally matched P2T/P3T and underpowered P3Ts contributed to the large number of negative trials and need to be considered in any future trial design.

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Mapping of B7-H3 immune checkpoint expression to diagnostic morphological features in glioblastoma using deep convolutional neural networks

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Abstract

Background and Aims:

Glioblastoma multiforme (GBM) is a common and fatal primary brain tumour. Immune checkpoint targeting has emerged as a promising new treatment approach in a number of traditionally untreatable cancers. Consequently, there is significant interest in the expression of immune checkpoint molecules in GBM. Accordingly, we set out to study B7-H3 (CD276), which discriminates endothelial cells of malignant tissue from normal endothelial cells, in glioblastoma using tissue sections of glioblastoma biopsies and deep convolutional neural networks (DCNNs) to analyse CD276 expression *in situ*.

Methods:

Biopsies of 37 cases of GBM, provided by the AGOG tissue bank, were stained for H&E and immunohistochemically labelled using a monoclonal anti-CD276 antibody. All histological slides were examined by a neuropathologist and then scanned using a slide scanner. Two DCNNs were designed using Keras with TensorFlow as the backend to detect palisading necrosis, microvascular proliferation, geographic necrosis, normal blood vessels, normal brain tissue and cellular tumour areas as well as expression of CD276. The tissue distribution of CD276 in relation to the diagnostic morphological features was then visualized using heat maps representing the DCNNs' predicted classes with different colours.

Results:

The trained DCNNs reliably identified the diagnostic morphological features they had been trained to recognize and allowed us to correlate the occurrence of each feature with the tissue expression of CD276. Notably, the close association between CD276 and microvascular proliferation in GBM samples was faithfully visualized by the heat maps, permitting qualitative as well as quantitative morphological analysis of an entire histological section within one minute, speeding up analysis by several orders of magnitude.

Conclusion:

Our study demonstrates the versatility of DCNNs for the mapping of immunohistochemical markers. This may greatly facilitate tissue analysis for molecules that show a complex tissue distribution and opens up a new avenue for research in neuropathology.

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Modern Brain Cancer Biobanking: It's not just about preserving tumour tissue

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Abstract

Historically cancer biobanks have focused on preserving surgically resected tumour tissue, either as formalin-fixed, paraffin-embedded or cryopreserved specimens and stored for future research. In the current era of translational and precision medicine however more and more researchers require fresh biospecimens for generating cell lines, 3D organoid models and xenograft studies. Providing researchers with freshly resected tumour tissue requires good communication and close cooperation between the neurosurgeons, theatre staff, biobank coordinator and the

researchers involved to facilitate the collection and transport of specimens in a timely manner.

The South Australian Neurological Tumour Bank has been collecting neurological tumour specimens since 2015. However, the majority of the research groups we currently support primarily require fresh biospecimens for their projects. In addition to the challenges of coordinating prompt transfer of specimens from the theatre to the laboratory, in vitro culturing of tumours generally necessitates collecting larger quantities of starting material than many other experimental endpoints. As the majority of the tumour is commonly debulked using surgical aspiration, we now collect the aspirate and provide this fresh to researchers. Aspirated tumour material can be used for generating cell lines with a success rate comparable to solid tumour tissue.

Research in the era of translational and precision medicine has a greater demand for biospecimens linked with patient clinical data. As a result modern biobanking has seen a shift in focus from primarily sample driven to data driven strategies. We are in the process of developing a comprehensive database that will align with the Brain Cancer Biobanking Australia (BCBA) minimum dataset and will be situated behind the SA Health firewall enabling neurosurgeons, clinicians and trainees to view and contribute to clinical data entry.

Modern cancer biobanks need to adapt to the changing needs of researchers to get the most research value from the specimens they collect.

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Building the Bridge: The value of consumer co-design in brain cancer resource development

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Abstract

Background

Improved survival has raised awareness of the impacts and challenges confronting people with grade 2/3 brain cancers. To assist people re-engage with a productive and purposeful life, the *Building the Bridge Project* partnered with Victorian consumers, health professionals and lead cancer agencies to create a resource focused on what happens after treatment. How to access timely and appropriate help, and how to get back to fundamental life roles was the project target. Project partners were Austin, Cabrini and Monash Health and NEMICS.

Aim

Develop a tailored, accessible information resource for brain cancer survivors that supports self-management and provides a tool for health professionals to use in survivorship conversations.

Methods

Experience-based co-design placed survivor experiences central to the project. During stage one, focus groups with 27 consumers and carers defined high prevalence issues experienced when returning to life post-treatment. Consultation with neuro-oncology professionals and project partners refined themes and explored information accessibility. Further consumer consultation scoped resource format. Stage two developed resource content consistent with themes identified in the data. Further consumer feedback was incorporated prior to design. Final stage tested and evaluated the resource with consumers not previously engaged in co-design.

Results

Building the Bridge to Life with Brain Cancer is a 130-page hard copy, spiral bound resource embedded with patient stories, tips, strategies, checklists and targeted resources to facilitate re-engage in everyday life. Accessible language and non-medicalised content is presented in small chunks for ease of reading. Evaluation found high levels of acceptability, relevance and usefulness.

Conclusion

Consumer co-design placed the voice of the person with brain cancer at the centre of resource development. This was an important and powerful approach, yielding a relevant and accessible resource aimed at improving people's capacity to self-manage their condition, access appropriate supports and re-engage in community life.

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Estimation of BRAF V600E mutations using Immunohistochemistry(IHC) in new diagnosis and recurrent malignant glioma patients managed at the Canberra Hospital

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Abstract

Introduction

Gliomas have demonstrated a range of behaviours with high grade gliomas, especially Glioblastoma Multiforme and IDH1/2 wild type tumours have known to be aggressive. Surgery, radiotherapy and Temozolamide seems to be the cornerstone of the therapy. Hence there is a need for target approach similar to other solid tumours.

VE – BASKET study was an open labelled, non-randomised, multi-cohort study of BRAF v600 mutant non melanoma cancers. These patients were treated with Vemurafenib 960 mg twice a day continuously until disease progression, withdrawal or intolerable adverse effects. In this study 24 patients were treated out of which 11 were high grade gliomas. The ORR was 25% and median PFS as 5.5 months. In the high-grade glioma group, 1 patient had a partial response and 2 of the patients had stable disease for >12 months.

Objective

a. BRAF V600E mutation is a driver of mutation in malignant glioma patients.

b. BRAF V600E mutated patient have better progression free survival and overall survival when treated with targeted approach with BRAF inhibitors.

Methods

- We identified 20 patients with diagnoses of high grade gliomas diagnosed and managed at the Canberra Hospital in late 2017.
- BRAF V600E IHC was conducted for the 20 identified patients at the ACT pathology using the commercial BRAF immunohistochemistry V600E mutation-specific antibody (VE1) available.

Results

- All 20 patients were negative for the BRAF V600E mutation.

Conclusions.

- The Incidence of BRAF V600E mutation in high grade gliomas is low.
- Thus, immunohistochemistry is good as a screening tool but the mutations can be missed and needs confirmation with PCR.
- We aim to confirm the results using the The Qiagen Thera screen BRAF PCR kit is used to detect 5 somatic mutations in the BRAF gene using real time PCR (V660E, Ec, D, K and R).

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Challenges in regional neurosurgery – analysis of distance and time in the surgical management of brain metastases in North Queensland

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Abstract

Aims:

The Townsville Hospital (TTH) has North Queensland's only neurosurgery unit, providing neurosurgical oncology care for a geographically regional and remote population of 695,000. It is unclear if there are significant barriers to accessing neurosurgical oncology services related to distance, specifically for surgery for brain metastases.

Methods:

We performed a five year retrospective review of all patients who underwent neurosurgery for brain metastases at TTH between 2014 to 2019. Distances between patients' home hospital location and Townsville were calculated. Statistical analysis of demographic, time to review and surgery, and distance travelled to TTH was performed with SPSS.

Results:

120 patients underwent neurosurgery for brain metastases, with local referrals accounting for 48 and 72 from other regional and remote hospitals. 49 (40.8%) were female and 71 (59.2%) were male, and the mean age was 61 years. Patients travelled between 88 to 902 km with a mean distance of 440 km. The mean time from referral to review was 3.6 days (1.63 for Townsville, and 4.94 for patients from regional and remote hospitals, P=0.0002). The mean time to surgery was 11 days with no statistically significant difference between Townsville locals and patients from other regional and remote hospitals (P = 0.308). The most common resected brain metastases diagnoses were melanoma and non-small cell lung cancer with 31 cases (25.83%) each.

Conclusions:

In the surgical management of brain metastases at a regional center, referral from other regional and remote hospitals was associated with a statistically significant increase in time to review compared with referrals from Townsville, however this difference did not greatly alter surgical management as there was no significant difference in time to surgery despite the mean distance of 440 km.

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Postoperative hypofractionated stereotactic radiotherapy for intracranial metastases: relationship between dose and local control

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Abstract

Introduction

Hypofractionated stereotactic radiotherapy (HFSRT) to the cavity after resection for brain metastases improves local control. We aimed to assess the relationship between prescribed dose and local control in an institutional cohort of patients receiving HFSRT after surgery.

Methods

A retrospective review of consecutive patients receiving HFSRT to the surgical cavity between January 2012 and December 2018 was performed. Treatment was delivered using an appropriately-adapted linear accelerator with ExacTrac™ on board imaging and Hexapod couch corrections. The primary outcome was defined as time to radiological or histological confirmation of local recurrence following completion of radiotherapy. Dose-fractionation regimens were converted to biologically equivalent doses assuming $\alpha/\beta=10$ ($EQD2_{[10]}$). Multivariate Cox proportional hazards modelling was performed to determine hazard ratios (HR) with respective 95% confidence intervals (CI). The Log-rank test was used to determine p values taking statistical significance $p<0.05$.

Results

There were 134 patients and 144 cavities identified. The most common primary histologies were melanoma (n=49) and lung (n=32). 116 patients (87%) underwent a gross total resection. Median treatment volume (PTV) was 28ml (range 2.4-149.2). The most common dose-fractionations were 24Gy in 3 fractions ($EQD2_{[10]}$ 38.4Gy, n=80), 27.5Gy in 5# ($EQD2_{[10]}$ 37.125Gy, n=27) and 30Gy in 5# ($EQD2_{[10]}$ 40Gy, n=11). Median dose was $EQD2_{[10]}$ 38.4Gy (range 22.3-59.7). 12 (9%) patients demonstrated local recurrence at median interval 215 days (range 4-594). 7 (5%) patients experienced grade 3 or higher toxicity attributed to HFSRT. There were no significant associations for histology, age, residual volume, PTV or target location with local failure. In multivariate analysis, $EQD2_{[10]}$ was associated with local failure such that increased equivalent doses improved local control [HR=0.79 and 95% CI 0.65-0.96, p=0.0192].

Conclusion

Local control after HFSRT to the surgical cavity improves with increasing dose. Rates of grade 3 toxicity were low overall.

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Understanding the Function of Ephrin A5 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.

The EphA3 receptor is frequently elevated in GBM, particularly in the mesenchymal subtype and is most highly expressed in tumour-initiating cells[1]. Our data in GBM tissue shows that tumour cells expressing the high-affinity EphA3 ligand, ephrin A5; are distinct from EphA3 expressing cells. The ephrin A5 positive cells express the known glial differentiation marker GFAP, are less proliferative and less stem cell-like. EphA3 is expressed in the vimentin positive, highly proliferative, mesenchymal cells in GBM. Ephrin A5 over-expression in primary cell lines led to a more differentiated phenotype *in-vitro*. Ephrin A5 over expression orthotopic mouse models showed a moderate reduction of GBM aggressiveness and downregulation of stem cell markers.

More recently, we have also shown that EphA3 antibody drug conjugates (ADCs) doubled survival in vivo whilst inducing minimal toxicity in GBM orthotopic animal models[2]. However, following EphA3-ADC therapy, tumours invariably recurred despite efficient targeting and reduction of EphA3 receptor levels in recurrent tumours. A significant reduction in EphA3 mRNA tumour levels was seen in the treatment group, while ephrin A5 levels were maintained. This indicates that the recurrence may be in part due to the ephrin A5 expression and targeting this could lead to further improvement in survival.

In summary whilst better understanding the biology of ephrin A5 expression, we will also validate antibody-based approaches to perform dual targeting of EphA3 and ephrin A5, leading to an extension GBM patient survival.

References

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