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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14th COGNO ANNUAL SCIENTIFIC MEETING

Reconnecting Neuro-Oncology

Sunday 16th October – Tuesday 18th October 2022

Hilton Brisbane, Queensland, Australia

CONFERENCE BOOKLET

COGNO

COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

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2022 ASM ORGANISING COMMITTEE

- Dr Hamish Alexander, Co-Convenor (Neurosurgeon & Spinal Surgeon, Briz Brain & Spine)
- A/Prof Ben Chua, Co-Convenor (Consultant Radiation Oncologist, GenesisCare Rockhampton & Brisbane)
- Prof Bryan Day (Group Leader, Sid Faithfull Brain Cancer Laboratory, QIMR Berghofer & Co-Director of the Children's Brain Cancer Centre)
- A/Prof Georgia Halkett (Senior Research Fellow, Curtin School of Nursing, Faculty of Health Sciences, Curtin University)
- A/Prof Zarnie Lwin (Senior Staff Specialist, Medical Oncology, Cancer Care Services, Royal Brisbane & Women's Hospital & University of Queensland)
- Dr Wayne Ng (Staff Specialist Neurosurgeon, Gold Coast University Hospital, Gold Coast Private Hospital & Spine Centre)
- A/Prof Mark Pinkham (Radiation Oncologist, Icon Cancer Centre North Lakes & Greenslopes Private Hospital & Adjunct Professor, Queensland University of Technology)
- Dr Jim Whittle (Medical Oncologist specialising in Neuro-oncology, Peter MacCallum Cancer Centre & Laboratory Head, The Brain Cancer Centre)
- Ms Jenny Chow (Executive Officer, COGNO)
- Ms Danielle Massey (Project Officer, COGNO)

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Co-Convenors' Welcome

Dear Colleagues

It is our pleasure to welcome you to the COGNO Annual Scientific Meeting for 2022 "*Reconnecting Neuro-Oncology*" in Brisbane, Queensland, Australia from Sunday 16th - Tuesday 18th October 2022. The vibrant city of Brisbane, Meanjin, is on Yuggera Country, the traditional lands of the Turrbal and Jagera peoples.

We are delighted to be meeting face-to-face once more and for the opportunity to meaningfully reconnect and refocus on the significance of COGNO in Australasia today.

Our exciting program featuring acclaimed international and local speakers runs over three days. Presentations cover a wide range of neuro-oncology topics such as translational science, novel therapies and supportive care. New sessions have been scheduled to delve deeper into spinal oncology, medicinal cannabis and also a special education workshop for trainees.

In keeping with the theme of reconnection we are also looking forward to updates from international and local neuro-oncology organisations as well reconnecting socially at the conference dinner to be held at GOMA overlooking the Brisbane river and central city.

Gurumba Bigi! We look forward to seeing you all.

Dr Hamish Alexander and A/Prof Ben Chua
Co-Convenors
COGNO ASM 2022

The COGNO Scientific Program has been developed independent of sponsor involvement.

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ORAL ABSTRACTS

15

Determining research priorities for adult primary brain tumours in Australia and New Zealand: A Delphi study

Georgia Halkett[1], Lauren Breen[1], Melissa Berg[1], Rebecca Samspon[1], Hao-Wen Sim[2,3,4,5], Hui Gan[6,7,8], Benjamin Kong[2,9], Anna Nowak[10,11], Bryan Day[12], Rosemary Harrup[13], Melissa James[14,15], Frank Saran[16], Brett Mcfarlane[17], Chris Tse[18,19], Eng-Siew Koh[3,20,21]

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Abstract

The aims of this project were to 1) determine, for adult primary brain tumour research in Australia and New Zealand, the most important research priorities, barriers and enablers and 2) identify where COGNO should focus its future leadership, involvement and advocacy in relation to these identified priorities and enablers.

Methods: COGNO members and consumers from Australia and New Zealand were invited to participate in a modified Delphi study conducted in two phases from June to December 2021. Phase 1 consisted of an online open-ended survey (Total=91; consumers=42, health professionals=29, researchers=20) and then focus groups (Total=29; consumers=7, health professionals=13, researchers=9) to identify 60 research priorities, 26 barriers and 32 enablers. Phase 2 consisted of two online surveys to 1) refine the list to 37 research priorities which had consensus (>75% 2-point agreement) and had high mean importance ratings (Total=116; consumers=63, health professionals=33, researchers=20) and 2) determine the most important priorities (selected then ranked), barriers and enablers (selected), including those which COGNO could lead/advocate (Total=90; consumers=48, health professionals=25, researchers=17).

Results: The top ten ranked research priorities for the overall group and each sub-group are shown in Figure 1 and the 5 priorities selected for COGNO are indicated. Variations were found between groups, with health professionals prioritising molecular targets and researchers (predominantly psycho-oncology researchers) prioritising collection of patient reported outcomes in clinical trials. The top ten barriers to conducting brain tumour research were in the categories of: funding and resources (n=5), trial availability, accessibility and awareness (n=2), collaboration (n=2) and process (n=1). The top ten research enablers related to funding and resources (n=5), collaboration (n=3) and workforce (n=2).

Conclusions: Participants identified many priorities across the following areas: tumour biology, pre-clinical research, clinical and translational research and supportive care. These findings will be used by COGNO to inform future research strategy.

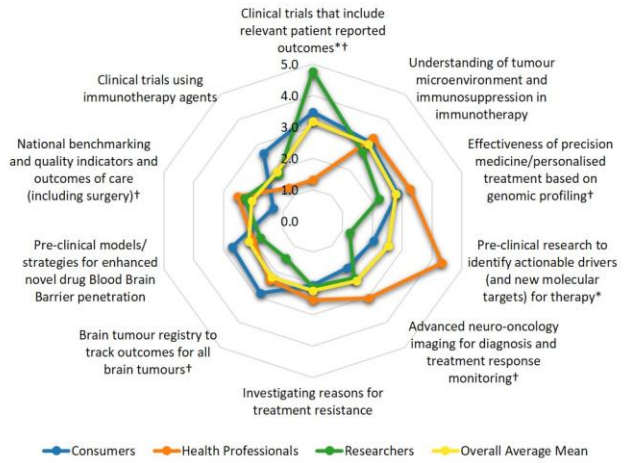

Figure 1 Adjusted mean rankings for top ten ranked research priorities by group and overall average mean (higher mean equals higher priority). Priorities are shown from highest to lowest overall mean (from top in clockwise direction). Means were adjusted by setting zero values for participants who did not select the priority. To adjust for group sizes in the mean rank of the overall group, sub-group means were averaged. † Indicates a priority which was a top five selected research priority opted for COGNO to lead or advocate. Priorities with notation (*0.01 ≤ p < 0.05) have significant inter-group differences.

Theme

Other

18

BIOBRAIN: Utilising patient-derived organoids for a personalised medicine strategy in glioblastoma

Lucy Gately[1], Andrew Gogos[2], Peter Gibbs[1,3], Oliver Sieber[1]

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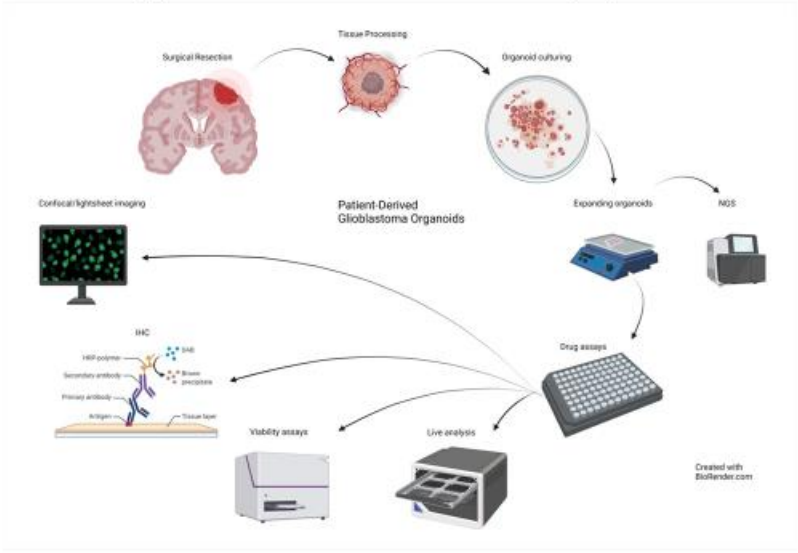
Abstract

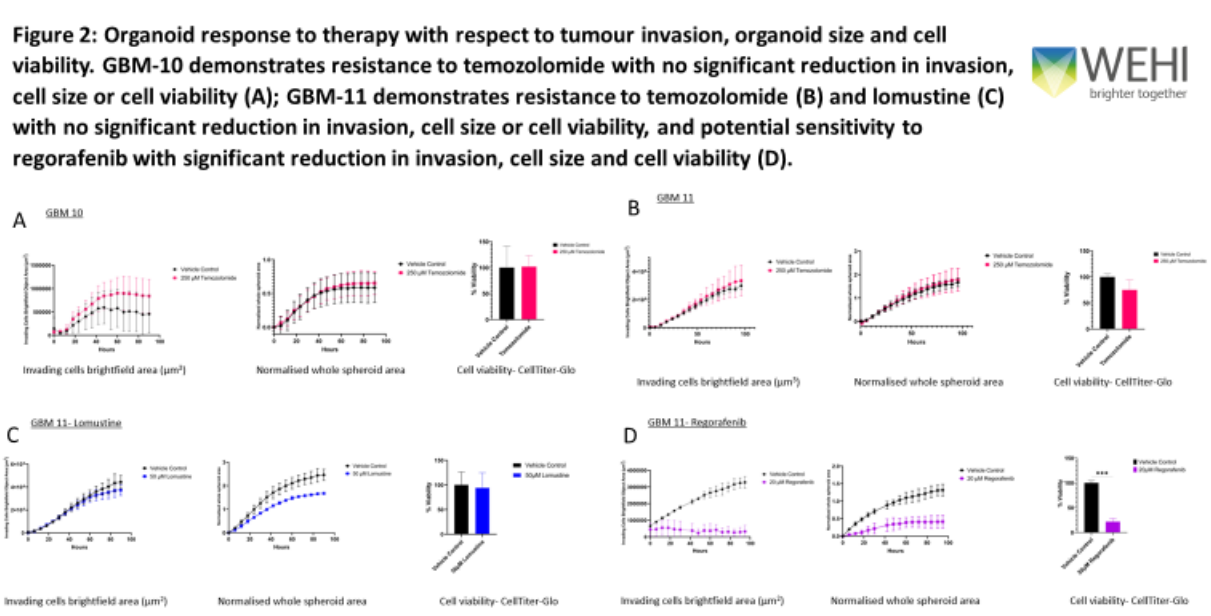
Background: Patient-derived tumour organoids are miniature 3D versions of an individuals' tumour grown in culture. They overcome some challenges of traditional models, maintaining heterogeneity, molecular characteristics, and relevant cellular/stromal interactions, and can be established within weeks. BIOBRAIN, established in 2021, facilitates collection of biospecimens with matched clinical data contained in the BRAIN registry. Here we describe our initial experience.

Methods: Fresh tissue was collected from St Vincent's Hospital Melbourne with established consent, collection and transport procedures. Organoids were established using locally refined techniques based on the Jacob method followed by a standard pipeline including histology, omics and multi-dimensional drug assays using known active agents(Figure 1). Clinical data was extracted from BRAIN.

Results: From 6/2021-6/2022, 16 patients were recruited. Median age was 71; two had recurrent disease. Four samples were unsuitable (necrotic tissue, delays in transport, incorrect diagnosis) and four were frozen immediately due to COVID restrictions. Organoids were established from 10 samples, including two of the four frozen. Histology and immunohistochemical staining (GFAP, CD44, Nestin, SOX-2) were consistent between organoids and matching tumour, with omics underway. Four samples underwent drug assays with temozolomide, lomustine and regorafenib; two patients had sufficient clinical data available for outcome correlation. GBM-10, a primary IDH-wildtype glioblastoma, demonstrated resistance to temozolomide with the patient progressing during Stupp-2(Fig2A). GBM-11, a recurrent IDH-wildtype glioblastoma with emergence 2 months after completing Stupp protocol, demonstrated resistance to both temozolomide and lomustine with the patient progressing rapidly and dying 2 months later(Fig2B,2C). GBM-11 demonstrated potential sensitivity to regorafenib(Fig2D).

Conclusion: These data demonstrate a high yield in culturing organoids from fresh tumour and confirm their fidelity. The potential utility of patient-derived tumour organoids to direct therapy selection in glioblastoma is demonstrated by the two initial cases. Further refinement is underway including exploration of clinical trial opportunities.





Theme

Translational Science

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Radiomic Features Predicting Cancerous Tissue In High Grade Glioma

Cara Crinnion[1], Lauren Causer[2], Stephen Dowdell[2], Peter Metcalfe[1], Martin Carolan[3], Senthilkumar Gandhidasan[3], Daniel Brungs[3]

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Abstract

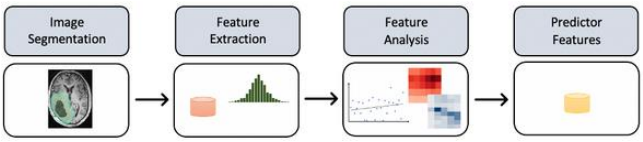
Aims: High grade gliomas (HGGs) are rapidly developing, poor prognosis tumours resultant of mutations in the glial cells. Magnetic resonance imaging (MRI) remains the most commonly employed imaging sequence for imaging HGGs. Often, increased contrast appears on the scans post-treatment which is unrelated to tumour growth. This phenomenon is known as pseudoprogression and results in difficulties accurately diagnosing true tumour progression. With HGG patients having a median survival time of 14 months, a quick diagnosis is vital to ensure optimal treatment management of these patients [1].

Radiomics is a field in medical imaging which extracts high-dimensional quantitative features from diagnostic medical images. The features obtained, which can be thought of as tumour descriptors, facilitate image diagnosis, prognosis, and therapy response in a clinical setting. Utilising this approach, it is hypothesised that the distinction between cancerous and healthy tissues are able to be identified in a quantitative manner.

Methods: This study obtained features of healthy and cancerous tissue from pre-radiochemotherapy T1-Gadolinium MRI scans. 'Cancerous' tissue was defined as the tissue encapsulated within the gross tumour volume (GTV) contour, and the 'healthy' tissue contour was created and defined as a 1.2cmx1cm2 volume of tissue greater than 5cm away from the GTV. Radiomic features from both regions were collected, enabling statistical analysis of the features to be performed.

Results: 108 features have been extracted. Preliminary findings show 2 predictive features indicative of the presence of cancer: Run Variance and Joint Energy, both of which are textural features extracted from the Gray Level Run Length Matrix (GLRM) and Gray Level Co-occurrence Matrix (GLCM), respectively. Further quantitative analysis is ongoing.

Conclusions: This study collected radiomic features from pre-radiochemotherapy, T1-Gad MRI scans of high grade glioma patients, from which 2 predictive radiomic features, Run Variance and Joint Energy, look promising as being indicative of cancer.



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Theme

Other

33

Elderly patients with glioblastoma should be assessed for adjuvant therapy protocols based on known prognostic factors rather than age: implications for accrual into GBM Elderly Protocols

Michael Back[1,2,3,4], Brendan Liu[1], Patrick Horsley[1], Venkat Venkatesha[1], Marina Kastelan[1,4], Helen Wheeler[1,4]

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Abstract

Aim: Adjuvant therapy regimen of elderly patients with Glioblastoma (GBM) may be based on age alone rather than prognostic factors. This audit reviews outcome of elderly patients managed with EORTC-NCIC (Stupp60Gy) Protocol.

Method and Materials: Consecutive patients with GBM managed from 2008-2020 with Stupp60Gy were assessed for primary endpoint of median overall survival (mOS). Analyses were conducted for known prognostic factors used in decision-making for patients aged <65 years and elderly subgroups 65-70 years, 70-74 years and >75 years.

Results: 447 patients received Stupp60Gy Protocol with medOS of 18.0 months (95%CI:16.9-19.1) and 2-year OS of 32%(95%CI:0.28-0.38). One hundred and twenty-three patients were potentially eligible for Elderly Protocol based on age criteria (57% aged 65-69yrs;33% aged 70-74yrs;10% aged >75yrs). MedOS was significantly different (p = .003)

between <65yrs group (19.1 months; 95%CI:18.1-20.7) and >65yrs (15.1 months; 95%CI:13.6-17.1). In both age categories better ECOG, more near-total resection and MGMT methylation predicted for improved medOS ($p<0.05$).

However when grouped by elderly subgroups, the mOS was 15.3 months (95%CI:13.6-17.5) in 65-69yr; 14.2 months (95%CI:12.2-18.0) in 70-74yr; and 15.3 months (95%CI:5.4-34.9) in >75yr groups ($p=0.55$). Additionally within each elderly subgroup, patients with one of three favourable prognostic features reached median survivals approaching younger patients. Presence of either good ECOG or near-total resection was associated with medOS >17 months; and for MGMT methylation medOS was >28 months.

Treatment was well tolerated with 85.5% of elderly patients not requiring admission within the ten weeks following start of IMRT. Of those admitted the majority resulted from persisting post-surgical neurological deficits or pseudoprogression events.

Conclusion: When assessed on prognostic factors rather than age, elderly patients had similar survival outcomes compared to younger cohort. This suggests that elderly patients presenting with favourable prognostic factors should be considered for aggressive intervention with standard rather than more conservative elderly protocols.

Theme

Other

3

Spatial transcriptomic analysis of Sonic Hedgehog Medulloblastoma identifies that the loss of heterogeneity and promotion of differentiation underlies the response to CDK4/6 inhibition

Tuan Vo[1], Brad Balderson[1], Kahli Jones[1], Joanna Crawford[1], Amanda Millar[2], Elissa Tolson[2], Thomas Robertson[3], Dharmesh Bhuva[4,5], Melissa Davis[4,2,5,6,7], Brandon Wainwright[2], Quan Nguyen[1], Laura Genovesi[2]

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Abstract

Background: Medulloblastoma (MB) is a malignant tumour of the cerebellum which can be classified into four major subgroups based on gene expression and genomic features. Single cell transcriptome studies have defined the cellular states underlying each MB subgroup, however the spatial organisation of these diverse cell states and how this impacts response to therapy remains to be determined.

Methods: Here, we used spatially resolved transcriptomics to define the cellular diversity within a sonic hedgehog (SHH) patient-derived model of MB and identify how cells specific to a transcriptional state or spatial location are pivotal in responses to treatment with the CDK4/6 inhibitor, Palbociclib. We integrated spatial gene expression with histological annotation and single cell gene expression data from MB, developing a analysis strategy to spatially map cell type responses within the hybrid system of human and mouse cells and their interface within an intact brain tumour section.

Results: We distinguish neoplastic and non-neoplastic cells within tumours and from the surrounding cerebellar tissue, further refining pathological annotation. We identify a regional response to Palbociclib, with reduced proliferation and induced neuronal differentiation in both treated tumours. Additionally, we resolve at a cellular resolution a distinct tumour interface where the tumour contacts neighbouring mouse brain tissue consisting of abundant astrocytes and microglia and continues to proliferate despite Palbociclib treatment.

Conclusions: Our data highlight the power of using spatial transcriptomics to characterise the response of a tumour to a targeted therapy and provide further insights into the molecular and cellular basis underlying the response and resistance to CDK4/6 inhibitors in SHH MB.

Theme

Adolescent and Young Adult, Paediatric and rare CNS Tumours

5

Capturing the patient voice: a review of patient-reported outcomes included in brain cancer clinical trials

Rachel Campbell[1,2], Yuenchen Lee[3], Dillon Srikumar[3], Glenn Stewart[3], Miesha Binta Noor[3], Nikita Papastamatis[3], Isabelle Afaras[3], Eng-Siew Koh[4,5], Mark B Pinkham[6], Haryana Dhillon[1,2]

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Abstract

Introduction

Patient-reported outcomes (PROs), including health-related quality of life (HRQL), provide unique information about the impact of disease and treatment from the patient perspective. Inclusion of PROs in brain cancer clinical trials enable assessment of the costs and benefits of treatment based on patient experiences to inform future treatment decision-making.

Aim

We aimed to identify all primary and secondary brain cancer trials registered in the Australia New Zealand Clinical Trials Registry (ANZCTR) to (i) determine how many trials include PROs; and (ii) describe trial characteristics.

Methods

The ANZCTR was searched from its inception in 2005 to March 2022 to identify all registered brain cancer trials including a PRO or not. Trial characteristics were extracted, including year of registration, phase, intervention type and population. PRO-specific information was extracted, including whether the PRO was a primary or secondary endpoint, assessment time-points, PRO type and measure.

Results

Sixty-five brain cancer trials were identified and 27 (42%) included a PRO. Identified trials were most commonly designed for participants with glioblastoma (52%; 35% of these included a PRO); 15% of trials were Phase 3 or 4 (10% of these included a PRO); and, 43% of all trials examined novel drug treatments (32% of these included a PRO). Of trials including PROs, most included a PRO as a secondary endpoint (78%). HRQL was most commonly specified as the key PRO endpoint (41%) with EORTC QLQ-C30 as the most commonly administered (23%) PRO measure.

Conclusion

Less than half of brain cancer trials registered on the ANZCTR included a PRO endpoint, highlighting potential missed opportunities in PRO assessment which capture the patient voice, particularly in trials intended to inform practice. These findings emphasise the need to incorporate meaningful PRO endpoints when designing future brain cancer clinical trials.

Theme

Survivorship, Psychology and Supportive Care, Other

POSTER ABSTRACTS

4

The fight against Glioblastoma: a novel aptamer-drug conjugate shows therapeutic potential

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Abstract

The limited success of current treatment options for glioblastoma, an aggressive brain cancer with poor survivability can be attributed to the blood-brain barrier (BBB). This barrier is known to prevent entry of most chemotherapeutic drugs to treat brain cancer thus, a novel targeted therapeutic capable of crossing the BBB to deliver drugs is essential. Aptamers, or chemical antibodies, are small single-stranded nucleotide sequences that can bind specifically and selectively to desired targets on the cell surface. Most importantly, aptamers can be modified as a drug delivery vehicle for therapeutic purposes. In this instance, we previously generated a bifunctional aptamer by combining a transferrin receptor and epithelial cell adhesion molecule (EpCAM) aptamer together and intercalated the chemotherapeutic doxorubicin (DOX) for treatment of brain metastases. We were able to demonstrate that the bifunctional aptamer-drug conjugate, termed TEPP-DOX, was successfully able to deliver drug payloads across the BBB to EpCAM positive brain metastases both in vitro and in vivo, and reduce metastases spread and tumourigenicity [1]. In this study, for the first time, this bifunctional aptamer-drug conjugate is being tested for treating the primary brain cancer, glioblastoma. To examine the potential of treating glioblastoma, the binding affinity of two bifunctional aptamers to glioblastoma was determined by flow cytometry, including with DOX conjugation, where a strong binding affinity towards the transferrin receptor on glioblastoma cells was observed. Next, the internalization and drug retention of aptamer-conjugates was visualized over a 96-hour period through confocal microscopy. With aptamer-DOX internalisation and retention visualized, the results of this study show that this conjugate would make an ideal therapeutic candidate for future studies.

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Theme

Translational Science

6

Screening for unmet needs of people affected by brain cancer: identifying brief screening measures

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Abstract

Introduction

People affected by brain cancer have diverse and complex needs. As part of the Brain cancer Rehabilitation, Assessment, Interventions for survivorship Need (BRAINs) program, we are adapting an existing electronic screening portal to identify the needs of patients and caregivers across the brain cancer trajectory.

Aim

To identify and develop appropriate screening measures for use in the BRAINs portal to assess unmet needs. We aimed to: (1) explore the appropriateness of an existing unmet needs screening measure (SCNS-ST9) for use in brain cancer survivors; and, (2) develop a brief screening measure to assess caregivers' unmet needs.

Methods

To address aim 1 secondary analyses were performed on data collected from 116 brain cancer survivors who completed a 34 item unmet needs survey (SCNS-SF34) at two time points; the SCNS-ST9 is a brief 9 item version of the SCNS. Data were analysed to determine the number of unmet needs missed by limiting screening to the SCNS-ST9.

To address aim 2 secondary analyses were performed on data collected from 188 caregivers who completed a 44 item unmet needs survey (SCNS-P&C). Psychometric analyses were performed to create a brief screening version of this measure.

Results

Analyses addressing aim 1 indicated only ≤11% of brain cancer survivors' unmet needs were missed by the SCNS-ST9 across time points. Preliminary psychometric analyses addressing aim 2 indicate the caregiver measure could be shortened from 44 to 8 items, assessing two domains: (1) psychological, emotional, work and social needs; and, (2) healthcare service and information needs.

Conclusion

Findings indicated the SCNS-ST9 missed ≤11% of brain cancer survivors' unmet needs, underscoring the potential for use of this instrument as a screening tool in clinical practice. The brief caregiver screening measure also shows promise for use in clinical care to identify caregivers' unmet needs and trigger referral for support.

Theme

Survivorship, Psychology and Supportive Care

7

Efficacy and Toxicity Profiles of Linear Accelerator-Based Hypofractionated Stereotactic Radiosurgery in the Management of Intact Brain Metastases

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Abstract

Aims: In the management of higher-risk brain metastases (BMs) that are large in volume or in eloquent anatomical locations, it can be challenging to achieve satisfactory disease control with stereotactic radiosurgery while balancing treatment-associated toxicities. In comparison to single-fraction stereotactic radiosurgery (sfSRS), hypofractionated stereotactic radiosurgery (hfSRS) is expected to offer superior or equal efficacy with lower toxicity profile. We report the therapeutic outcomes and incidence of radiation necrosis (RN) along with risk factors for RN in a consecutive cohort of patients to support this predicted benefit from hfSRS for high-risk BMs.

Methods: We retrospectively analysed 185 consecutive intact BMs with a median planning treatment volume (PTV) of 5.5 cm^3 from 152 patients who received hfSRS and were followed up for a median of 38 months with serial MRIs. The primary endpoint was the event of RN. Secondary outcomes reported were rates of local control (LC) and distant brain failure (DBF). Kaplan-Meier method was used to describe the incidence of RN, overall survival, and the incidence of DBF. Univariable Cox regression was used to identify the risk factors for RN.

Results: Median survival post SRS was 9.5 months. The cumulative incidence of RN was 13.2% (95% CI: 7.0-24.7%) and 18.1% of these patients with confirmed RN were symptomatic. Mean dose (HR 1.22, 95% CI: 1.05-1.42, p = 0.01) and BED10 delivered to PTV (HR 1.12, 95% CI: 1.04-1.2, p < 0.001) were significantly associated with RN. LC rate was 86% and the cumulative incidence of DBF was 36% with a median onset of 28.4 months.

Conclusions: The rate of RN in our cohort of patients with high-risk BMs was similar to that reported for sfSRS in an overall lower-risk population with smaller lesions. Therefore, in higher-risk BMs, hfSRS offers the opportunity to achieve effective disease control with an acceptable toxicity profile.

Theme

Brain Metastasis, Survivorship, Psychology and Supportive Care

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9

Developing a stepped care model for assessing unmet needs in people diagnosed with high grade glioma: defining criteria for stepped care intervention

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Abstract

Introduction

Stepped care models are effective and cost-efficient in delivering healthcare. People with brain cancer experience a range of symptoms and needs. As part of the Brain cancer Rehabilitation, Assessment, Interventions for survivorship Need (BRAINs) program, we are developing a stepped care referral pathway based on unmet needs.

Aim

To define step allocations based on levels of unmet need to inform the development of a stepped care referral pathway, and to map proposed step allocations to existing data.

Method

We adapted published criteria for defining level of unmet need (none, low, moderate, high) using the SCNS-ST9 (brief version of unmet needs survey (SCNS-SF34)). Data from T1 of a longitudinal cohort study of unmet needs in 116 people diagnosed with high grade glioma (HGG) was mapped to the criteria to test algorithms for use in an online portal for screening and referral based on the ADAPT clinical pathway.

Results

Using level of need, we identified a four-step pathway: Step 1 was defined as 'no' or 'satisfied' need across items, Step 2 included 'low' need for at least one item but no 'moderate' or 'high' need for any item, Step 3 included 'low' or 'moderate' need for at least one item but no 'high' need for any item, and Step 4 included 'high' need for at least one item. Of the 116 participants, 13% (n= 15) were classified as Step 1, 23% (n= 27) Step 2, 24% (n= 28) Step 3, and 40% (n= 46) Step 4.

Discussion

These criteria will be used to triage patients to a step allocation. The majority of people diagnosed with HGG were categorised as having high needs (Step 4), suggesting rapid intervention is required. Step allocations will guide timeframes for healthcare providers to review needs, and level and type of support required.

Theme

Survivorship, Psychology and Supportive Care

11

Extending the value of patient-reported outcome measures for cancer clinical trials: opportunities for COGNO to collaborate with CQUEST, the Cancer Australia Quality of Life technical service

Tim Luckett, Brendan Mulhern, Carrie-Anne Ng

CQUEST, UTS, Sydney, Australia

Abstract

Background and objectives

The Cancer Quality of Life Expert Service Team (CQUEST) is the Cancer Australia funded Quality of Life Technical Service, hosted by UTS (University of Technology Sydney).

One of CQUEST's aims is to extend the value of patient-reported outcome measures (PROMs) for cancer clinical trials by exploring innovative ways to measure, analyse and use health-related quality of life (HRQL) information. This poster will introduce state-of-the-science methods to COGNO members and extend an invitation for CQUEST to support the Group in these areas through its trials or sub studies.

Methods

The value of PROMs for COGNO's trials might be extended in four ways:

1. Innovative approaches to measuring both core and non-core domains of HRQL to facilitate a more accurate and holistic assessment of the impacts of disease and treatments on people with cancer.
2. Innovative approaches to HRQL data collection including: building capacity to ensure all Australians can contribute HRQL data to clinical trials; and advances in data capture technology (including computer adaptive testing).
3. Innovative approaches to interpreting and using HRQL data, including for decision-making in clinical settings.
4. Incorporating preferences into the measurement of HRQL in cancer trials to provide an enhanced understanding of people's prioritisation of different aspects of HRQL.

Results

We hope the presentation will result in collaboration between COGNO members and CQUEST to optimise the contributions that PROMs can make to cancer clinical trials and practice.

Conclusion

CQUEST invites COGNO members to collaborate on extending the value of HRQL data in cancer clinical trials.

Theme

Other

12

Dual targeting of EphA3 and Ephrin A5 to improve outcomes for GBM

Rochelle Dsouza[1,2], Niclas Skarne[1,2], Lachlan Harris[1,2], Seckin Akgul[1], Carolin Offenhauser[1], Quan Ngyuen[2], Craig Bell[2], Kristofer Thurecht[2], Ulrich Baumgartner[1], Rosalind Jeffree[3], Po-Ling Inglis[3], Bryan Day[1,2]

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Abstract

Introduction: Glioblastoma (GBM) is an aggressive brain cancer and is associated with very poor prognosis. Standard treatment involves surgical resection, post-operative radiation and TMZ chemotherapy. Further research into new therapeutic approaches which target chemo-resistant tumour propagating cells, are urgently required.

Results: The EphA3 receptor is frequently elevated in GBM, particularly in the mesenchymal subtype and expressed on tumour-initiating cells (Day et al. Cancer Cell 2013). 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 glial differentiation marker GFAP, are less proliferative and less stem cell-like. EphA3 is expressed on the vimentin-positive, highly proliferative, mesenchymal cells in GBM. IHC staining quantification, revealed a >75% coverage of tumour mass by EphA3 and ephrin A5. Ephrin A5 over-expression in-vivo showed a moderate reduction of GBM aggressiveness and downregulation of stem cell markers.

In-vivo Ephrin-A5 over-expression showed a moderate reduction of GBM aggressiveness and downregulation of stem cell markers. Spatial transcriptomics of ephrin-A5 over-expressing tumours revealed a reduction in proliferation markers including Ki67, MCM7 and PCNA. We detected an increase in expression of AC-like cell-state with a concomitant reduction of the MES-like and NPC-like cell-states. Consistently, over-expression of ephrin-A5 in primary GBM lines led to a reduction in neurosphere formation, Ki67 staining and growth rates.

Thus we propose that dual targeting of EphA3 and ephrin-A5 might better capture GBM tumour heterogeneity and lead to an extension GBM patient survival.

Conclusion: Whilst better understanding the biology of ephrinA5 expression, we also aim to validate antibody-based approaches to perform dual targeting of EphA3 and ephrin A5, leading to an extension GBM patient survival.

Theme

Translational Science

13

Outcomes of re-operation for glioblastoma in Tasmania – a five year single-centre experience

Venkata Santosh Rendu, Nova Thani, Rosemary Harrup

Royal Hobart Hospital, Hobart, Australia

Abstract

Background/Rationale:

Glioblastoma is a common malignant brain tumour in adults, which accounts for 2% of all malignancies. It carries a poor prognosis, with a median overall survival of 3 months without adjuvant treatment, and approximately 25% of people remaining alive at 24 months with current adjuvant chemoradiotherapy post initial surgery. Currently, there is no standard of care established for the management of recurrent disease, which has been shown to eventuate approximately 8 months following initial treatment.

Methods:

A retrospective case series of all glioblastoma re-operations in the last 5 years (01/01/2017 – 01/01/2022) conducted at the Royal Hobart Hospital in Tasmania, Australia, were investigated. A total of 19 cases were identified who underwent re-operation. Results were screened to ensure nil duplication/overlap. All cases had adjuvant chemoradiotherapy following original resection.

Results:

The age group of 45-64 years had the highest prevalence, with the most common locality of re-resection being in the left frontal region. Eight patients had fluoroscopic-guided surgery utilised at least once. 89% of the cohort underwent gross total resection of their recurrent lesion, whereas only 53% underwent gross total resection in the original surgery.

The median overall survival was approximately 7 months following re-resection for patients with IDH-wild type glioblastoma cohort, and 16 months overall, respectively. The progression-free survival for the entire group was approximately 7 months.[1] (refer to graphs below)

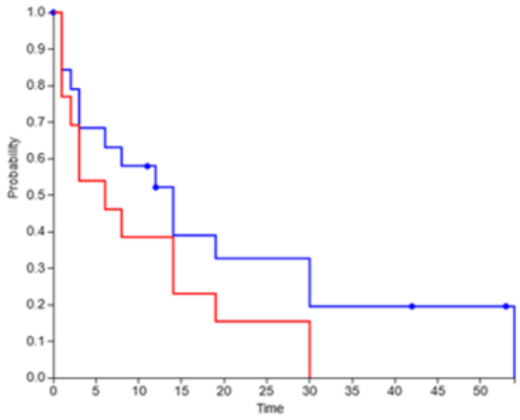
Conclusions:

The role of repeat cytoreductive surgery continues to be unclear, given the invariable recurrence of disease, and the lack of prospective data.

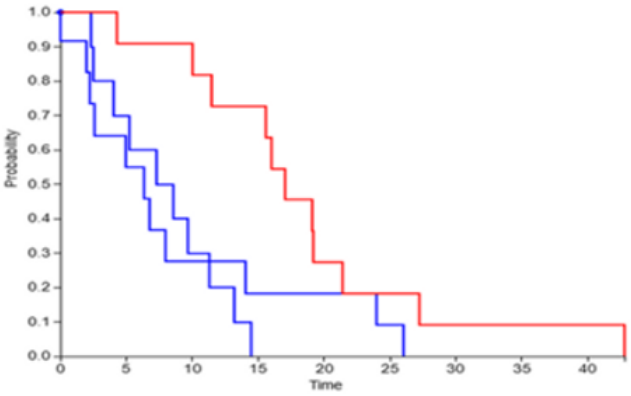
Given the poor prognosis, in select cases, further resection can be recommended for recurrent glioblastoma to relieve mass effect, as well as for further specimen collection/biobanking for future research.

We aim to contribute our data with the intent to optimise the multi-disciplinary treatment strategy, till further research/treatment breakthroughs may become evident.

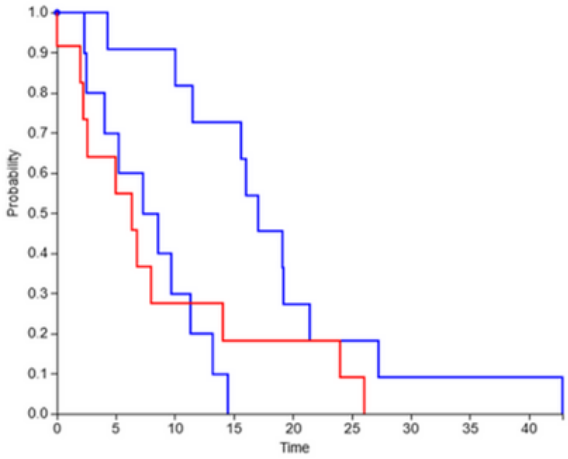
Survival Analysis for Cohort (Glioblastoma)



Overall Survival



Progression-free Survival



Theme

Survivorship, Psychology and Supportive Care, Pathology

14

Radiogenomics provides insights into gliomas demonstrating single-arm 1p or 19q deletion

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Abstract

Aims:

Adult-type intracranial gliomas with an isocitrate dehydrogenase mutation (IDH^{mut}) are further divided into those with or without 1p/19q-codeletion (combined loss of the short arm of chromosome 1 and the long arm of chromosome 19, $1p19q^{codel}$)[1]. Occasionally, 1p/19q testing reveals single-arm 1p- or 19q-deletion (unideletion), which remains within the diagnosis of astrocytoma, IDH^{mut}. Molecular assessment can, however, occasionally produce false positive or false negative 1p/19q results[2,3], raising the possibility that unideleted tumors could in reality be $1p19q^{codel}$. In this research, we used MRI (magnetic resonance imaging) features ("radiogenomics") to provide additional insights into unideleted gliomas, by determining

whether their MRI appearances were more consistent with 1p/1q-codeleted or non-codeleted gliomas.

Methods:

IDH^{mut} grade 2-3 gliomas with 1p/19q results were identified through previous research[4,5]. MRI features (T2-FLAIR mismatch and calcifications) were assessed by two neuroradiologists and compared across three groups: no 1p or 19q deletion; single arm 1p- or 19q-unideletion; and 1p/19q-codeletion.

Results:

121 patients were identified: 65 tumors without deletion, 12 unideleted and 44 codeleted. T2-FLAIR mismatch was identified in 4/12 unideleted tumors (33%), 32/65 tumors without deletion (49%) and 0/44 codeleted tumors (0%) – there was a significant difference between unideleted and codeleted tumors (p=0.0013), but no significant difference between unideleted and non-deleted tumors (p=0.39). Calcifications were demonstrated in none of the unideleted tumors, two (3%) of the tumors without deletion and 11 (25%) of the codeleted tumors. There was a trend (p=0.097) towards a difference between unideleted and codeleted tumors, but no significant difference between unideleted tumors and those without deletion (p=1).

Conclusions:

The MRI appearances support that tumours with single arm 1p- or 19q-deletion are equivalent to non-codeleted tumours, rather than IDH^{mut}/1p19q^{codel}. This provides reassurance that tumors with 1p- or 19q-unideletion are indeed non-codeleted, and additional 1p/19q testing is unnecessary.

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Theme

Radiology

16

Combining data from the world's first neuro-oncology registry trial (EX-TEM) with GEINO 14-01: A combined analysis to answer an important question

Lucy Gately[1,2], Mark Rosenthal[3], Sanjeev Gill[2], Zarnie Lwin[4,5], Peter Lau[6], Anthony Dowling[7,8], Rosemary Harrup[9,10], Mark Wong[11], Ross Jennens[12], Robert Campbell[13], Katharine Cuff[14], Elizabeth Ahern[15,16], Craig Underhill[17], Adam Cooper[18], Stephen Brown[19], Ian M Collins[20,21], Javier Torres[22], Peter Gibbs[1,8]

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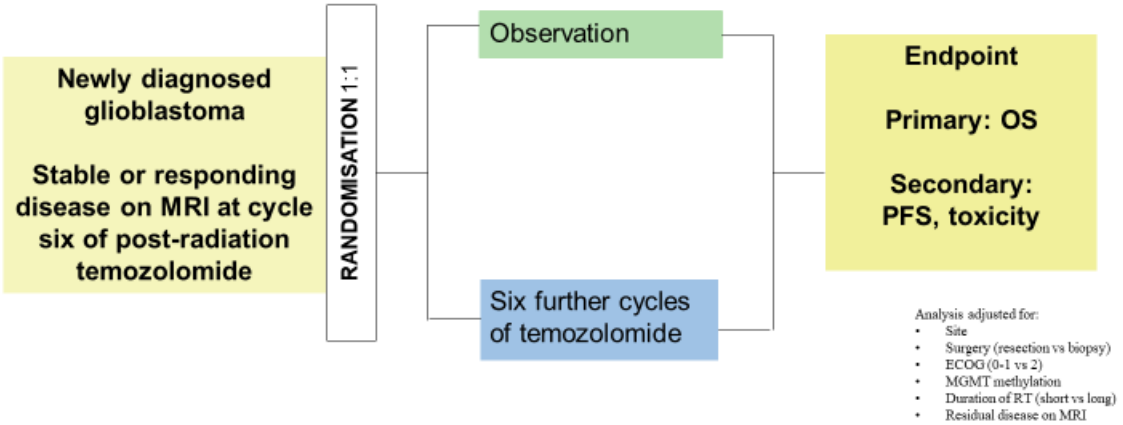
Abstract

Background: The optimal duration of post-radiation temozolomide in newly diagnosed glioblastoma remains unclear with no published phase III randomised trials evaluating this question. The practice-changing Stupp protocol used 6 months[1], however in 2017 a survey of current practices in Australia revealed that 50% of Oncologists routinely extend post-radiation temozolomide to 12 cycles, suggesting two emerging standards of care in the management of glioblastoma.

Methods: EX-TEM is the first phase III randomised registry trial to determine the impact on survival of extending post-radiation temozolomide to 12 months (see Figure 1). Utilising the BRAIN registry, which collects clinical data on patients diagnosed with brain tumours, the initial design was for 204 patients with newly diagnosed glioblastoma without progression at the end of six months of post-radiation temozolomide to be randomised in a 1:1 allocation to either six additional months (total of 12 months) or observation. The primary endpoint was 6-month progression free survival from date of cycle six (6mPFS), with 80% power to detect a 20% improvement, assuming 50% 6mPFS rate in the observation arm. Secondary endpoints included overall survival, major adverse events and necessity for temozolomide dose modification. Analyses were to be adjusted for study site, type of surgery, ECOG, MGMT methylation, duration of radiotherapy and residual disease on MRI at study entry. GEINO 14-01, is a near identical study which reported in 2020 on 159 enrolled patients, having failed to fully recruit, thus precluding a formal statistical comparison between the two study arms.

Progress: At the time of submission, 43 patients from 17 Australian sites have been recruited since March 2019. A formal plan to combine study data from EX-TEM and GEINO 14-01 is in place to ensure adequate statistical power to enable the first randomised comparison of the optimal duration of temozolomide, with an expectation of reporting in 2023.

Figure 1: Study schema



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Theme

Other

17

The BRAIN registry: Early uptake and initial data analysis in the COVID era

Lucy Gately[1], Kate Drummond[2,3], Mark Rosenthal[2], Anthony Dowling[4,3], Hui K Gan[5,3], David Campbell[6], Ron Freilich[7], Claire Phillips[8], Robert Campbell[9], Rosemary Harrup[10,11], Simone Reeves[12], Iwan Bennett[13], Peter Gibbs[1,3]

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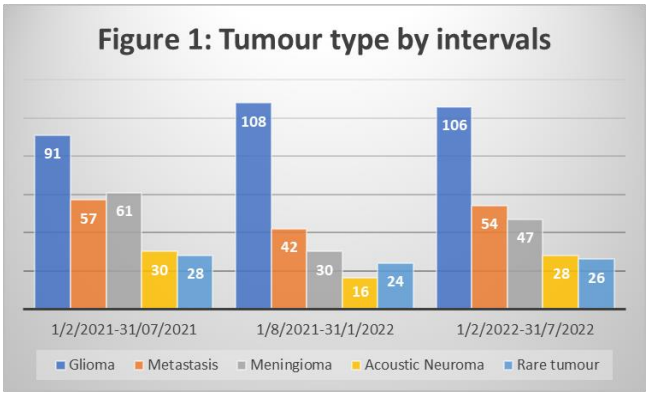
Abstract

Background: The multi-site BRAIN (Brain tumour Registry Australia: INnovation and translation) registry collects real-world data on patients diagnosed with brain tumours, commencing at diagnosis, including recurrence and treatment data, and capturing death data. It builds on a substantial initial database at Royal Melbourne Hospital and was activated in February 2021. It is now active at 10 sites across Victoria and Tasmania. Here we provide an update beyond 18 months of data collection, with an initial examination of impact of COVID.

Methods: A data audit was conducted from 1/2/2021 to 31/7/2022. Number and characteristics of patients were recorded and compared across 6-month intervals (i.e., 1/2/21-31/7/21, 1/8/21-31/1/22, 1/2/22-31/7/22).

Results: Since 2/2021, 748 patients have been registered in the BRAIN registry. Nearly half were glioma. There were similar registrations across the time intervals (36% vs 29% vs 35%, p=.23). Figure 1 shows the tumour types by interval. Compared with the first interval, there were significantly fewer resections of metastases(p=.03), meningiomas(p<.001) and acoustic neuromas(p=.003) in the second interval, corresponding to the early impact of COVID on health services. There was no significant difference between the first and third intervals, except for meningiomas(p<.001). BRAIN is currently supporting several quantitative, translational and qualitative projects across practice patterns, biomarkers, quality-of-care and survival. Substantial consumer engagement has been initiated, with consumer-led research projects in development.

Conclusion: BRAIN has been successfully implemented at multiple sites, supporting comprehensive data collection at major centres across Victoria and Tasmania, despite COVID workplace interruptions. A significant association between COVID timeperiods and rates of certain surgeries warrants further exploration. BRAIN has the capacity to be scaled nationally and internationally, with plans for broader engagement in 2023, to further support the power of registry-based data and registry-based trials. Further upgrades are underway to improve the collection of omics and survival data.



Theme

Other

19

Genetic Susceptibility to Glioma – Does Sex Matter?

Karen Alpen[1], Miroslaw Kapuscinski[1], Robert MacInnis[1,2], Claire Vajdic[3], Enes Makalic[1]

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Abstract

Background/Aims: Glioma is a familial disease with a two-fold risk associated with having a first-degree relative. Known genomic risk regions account for less than 40% of familial heritability[1]. Reported sex differences in glioma incidence, tumour progression, tumour molecular characteristics, survival and therapy responses together with reported sex differences in gene expression in the brain suggest that sex may play a role in glioma aetiology[2-5]. Our aim was to explore if glioma's missing heritability can be partly explained by sex-specific genetic susceptibility.

Method: We undertook a genome wide association analysis of three independent glioma case-control studies using a machine learning algorithm called DEPTH[6]. Unlike conventional marginal analysis of genome wide association studies (GWAS) data that consider each genomic marker independently, DEPTH tests groups of contiguous genomic markers simultaneously. DEPTH has been shown to discover risk regions missed by conventional GWAS analysis.[7]

Results: We identified 27 potential novel glioma risk regions that showed strong replication in at least two of the three independent datasets we analysed. Seventeen of the 27 regions were discovered in sex-specific datasets (eleven male and six female potential risk regions). Thirteen of the 27 regions contain genes that have previously been associated with glioma tumour progression or survival and of the remaining fourteen potential risk regions, four contain genes associated with other cancers, two contain genes associated with neurological disorders and one region contains genes associated with nervous system development.

Conclusions: These 27 potential glioma risk regions require further investigation to identify the causal genomic variant(s) and provide further insight into the heritability of glioma. Our findings indicate that sex may play a role in genetic susceptibility to glioma and should be considered in the development of risk prediction tools once more effective personalised treatments become available.

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Theme

Other

21

Targeting Androgen Receptor Signaling in Combination with Standard Care in Glioblastoma - A Novel Biomarker-Directed Therapeutic Strategy

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Abstract

Aims:

Glioblastoma (GBM) is a lethal brain cancer, with a 5-year survival rate <5%. Within GBM, there is a population of stem-like cells that are resistant to treatment, termed 'glioma stem cells'. Androgen receptor (AR) signalling is active in these cells. Thus, anti-androgen therapies have the potential to eradicate glioma stem cells. We have shown

that cytoplasmic AR is a biomarker that predicts tumors targetable with anti-AR therapy combined with chemotherapy. In GBM, ~55% of patients are cytoplasmic AR positive, suggesting that anti-AR therapy combined with standard-of-care therapy will improve survival outcomes for GBM.

Methods:

Cytoplasmic AR positive and AR negative patient-derived GBM cell lines will be tested for their response to anti-androgen therapies (abiraterone, enzalutamide and seviteronel) alone and in combination with temozolomide chemotherapy. Stem cell function will be assessed using a tumoursphere assay, and by measuring the expression of stem cell surface markers before and after therapy.

Results:

Preliminary data suggests AR antagonists are effective in monotherapy in vitro. Once we establish the best AR inhibitor used in synergy with chemotherapy, we will use this combination in vivo. Using orthotopic patient-derived xenograft models of GBM, we aim to demonstrate that anti-AR therapy plus standard therapy improves survival. We will gather the pre-clinical data to justify an Australian investigator-initiated Phase I clinical trial.

Conclusions:

Glioblastoma is a devastating disease, lacking effective or targeted treatments. Targeting AR to eradicate aggressive glioma stem cell populations is a promising therapeutic strategy to improve the efficacy of standard treatments, with the potential to greatly improve outcomes for GBM.

Theme

Translational Science

22

Understanding the roles of ephrin A5 in Glioblastoma and its potential as a therapeutic target

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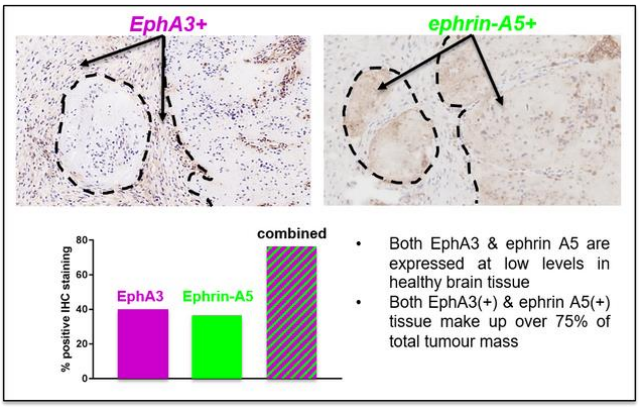
Abstract

Glioblastoma (GBM) is the most common and aggressive malignant primary brain cancer and is associated with very poor patient outcomes. Existing treatments have had limited success in improving overall survival. Thus, there is a need in identifying novel, tumor-specific molecules which will yield potential therapeutic targets.[1]

Several Eph receptors and ephrin ligands have been shown to be functionally overexpressed in cancer and have become attractive therapeutic targets. Day *et al.* 2013 demonstrated EphA3 to be a functional, tumor-specific target that is frequently elevated in GBM, particularly in the most aggressive subtype.[2] Furthermore, we have shown ephrin A5, the high affinity ligand of EphA3, to be expressed at comparable levels to its receptor in GBM. Our initial immunohistochemistry analysis suggests EphA3 and ephrin A5 to be expressed discretely on over 75% of the total tumor mass. However, unlike EphA3, the mechanisms of ephrin A5 function in GBM remain understudied.

Current work aims to better understand the biology and mechanisms of action of the ephrin A5 ligand. Preliminary data suggests ephrin A5 to exert a tumor-suppressive effect in GBM cell lines, with ephrin A5 overexpression promoting a less aggressive phenotype.



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Theme

Translational Science

24

LUMOS-2: Low and Intermediate Grade Glioma Umbrella Study of Molecular Guided Therapies

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Abstract

BACKGROUND: Grade 2 and 3 (G2/3) gliomas form the second largest group of malignant brain tumours in adults. There are no standardised treatments and few drug trials for these patients. The LUMOS pilot study confirmed the feasibility of performing molecular profiling in a timely fashion using tissue from craniotomy at relapse and established a Molecular Tumour Advisory Panel (MTAP) to provide tailored treatment recommendations. We now commence the LUMOS-2 study, in collaboration with the national Molecular Screening and Therapeutics (MoST) program and Cancer Screening Programme (CaSP) and will utilise this precision medicine umbrella study trial novel drugs for recurrent G2/3 glioma.

METHODS: LUMOS-2 is a multi-centre, signal-seeking umbrella trial matching molecular profiles of participants with recurrent IDH-mutant G2/3 glioma to corresponding targeted therapies or other biomarker-agnostic novel therapies for this disease entity. We currently have 4 planned arms (n=19 per arm). Participants with radiological evidence of progressive disease who are suitable for surgery will have molecular profiling performed on resected tumour tissue and optimal treatment recommendation from the MTAP. If an actionable or targetable molecular alteration is found, they will be offered corresponding targeted study therapies (brain penetrant PI3K or CDK4/6 inhibitors, or referred on to external trials e.g MoST treatment substudies); otherwise participants will be randomised to biomarker-agnostic treatments (novel immune checkpoint inhibitor or selective inhibitor of nuclear export compounds). Additional treatment arms are in development. The primary outcome of PFS6 will be evaluated using mRANO and RANO-LGG whilst secondary outcomes will include OS, response rate, toxicity and HRQoL measures. Correlative studies will examine biomarkers of response to these agents.

PROGRESS: The LUMOS-2 umbrella trial is a novel clinical trial which, when activated in Q1-2 of 2023, will provide multiple drugs for patients with relapsed G2/3 gliomas.

Theme

Translational Science, Pathology, Adolescent and Young Adult, Paediatric and rare CNS Tumours

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25

Developing a platform technology for targeted delivery of drugs to brain metastases

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Abstract

Prognosis for brain cancer, whether primary or metastasis, remains poor, even with advances in treatment for other cancers, due to the limited number of drugs that cross the blood brain barrier (BBB). While methods of overcoming this barrier have been developed and employed with current treatment options, the majority are highly invasive and non-specific, leading to neurotoxic side effects. A novel approach to address these issues is development of therapeutics targeting receptor mediated transport mechanisms on the BBB endothelial cell membranes. We have developed aptamers as targeted delivery agents that cross the BBB. Numerous studies have demonstrated that, despite theoretical implications of rapid renal clearance, nuclease degradation, and electrostatic repulsion, aptamers are effective agents for drug delivery. We have combined two

aptamers for the targeted delivery of chemotherapeutics to brain metastases which cross the BBB and specifically target cancer cells in the brain. Using this approach, we intercalated doxorubicin into this bifunctional aptamer targeting the transferrin receptor on the BBB and epithelial cell adhesion molecule on the metastatic cells. The ability of the doxorubicin loaded aptamer to transcytose the BBB and selectively deliver the drug to epithelial cell adhesion molecule-positive tumours was evaluated in an in vitro model and confirmed in vivo. We showed co-localised aptamer and doxorubicin fluorescent signals are clearly detectable within the brain lesions 75 minutes post administration. Following a short treatment schedule, brain metastases decreased following bifunctional-aptamer-doxorubicin treatment, as compared to control or free drug. As well, metastases decreased in bone and ovaries. Collectively, these results 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. We are now investigating this technology against primary brain cancers with different aptamers targeting other cell surface receptors.

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Theme

Brain Metastasis

26

Characteristics, Treatment and Survival Outcomes of Brain Metastases from Colorectal Cancer

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Abstract

Introduction

The brain is an uncommon site of colorectal cancer (CRC) metastases, affecting less than 4% of patients with metastatic CRC, and is associated with poor outcomes. Characterisation of these patients is vital to inform further research directions and to personalise treatment strategies.

Methods

Data from metastatic CRC patients was extracted from the Treatment of Recurrent and Advanced Colorectal Cancer registry, prospectively contributed by 32 Australian sites. Data analysed included patient demographics, disease characteristics, treatment and survival outcomes.

Results

Of the 3737 patients, 131 (3.5%) had de novo or developed brain metastases during their disease course, including 48 (1.3%) at first presentation with metastatic disease. Compared to those without brain metastases, patients with brain metastases at any point were more likely to be BRAF-mutated (21% vs 12%, p=0.015), have a rectal primary (42% vs 29%, p=0.005), have widespread metastatic disease (>2 sites 27% vs 16%, p<0.001), and have lung metastases (54% vs 30%, p<0.001). Patients with brain metastases were less likely to have liver (41% vs 62%, p<0.001) and peritoneal metastases (11% vs 20%, p=0.007). The presence of brain metastases at any time in metastatic CRC course was associated with a significantly shorter prognosis (median overall survival 7.6 vs 21.5 vs 26.7 months, p<0.001). Resection was pursued in 53 (41%) and stereotactic brain radiotherapy was pursued in 13 (9.9%) of patients with brain metastases, with a median overall survival from intervention of 23.4 months and 40.9 months respectively.

Conclusion

Brain metastases are rare in CRC and associated with poor survival outcomes. They are most commonly seen in patients with rectal primary and BRAF-mutated cancers and have a positive association with lung and a negative association with liver and peritoneal metastases. Surgical resection and stereotactic brain radiotherapy may lead to increased survival, although this retrospective analysis is limited by selection bias.

Theme

Brain Metastasis

27

IPAX-1: phase 1/2 study of 131I-iodo-phenylalanine (131I-IPA) combined with external radiation therapy as treatment for patients with recurrent glioblastoma multiforme

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Abstract

Background/Aims: A novel therapeutic approach using molecularly targeted radiation is in development for patients with recurrent GBM. Many tumor types, including GBM, overexpress the L-type amino transporter 1 (LAT-1)4, which is able to internalize the small-molecule amino acid derivative, 4-L-[131I] iodo-phenylalanine (131I-IPA). In preclinical research, combining 131I-IPA with external radiation therapy (XRT) yielded additive cytotoxic effects. Tumoral accumulation of 131I-IPA was confirmed in a proof-of-principle study using single doses of 2–7 GBq 131I-IPA as a monotherapy or in combination with XRT in patients with recurrent GBM. The objective of IPAX-1 was to evaluate the safety, tolerability, dosing schedule, and preliminary efficacy of 131I-IPA in combination with second-line radiotherapy in patients with recurrent GBM.

Methods: IPAX-1 is a multi-center, open-label, single-arm, dose-finding phase 1/2 study. In phase 1, patients received intravenous 131I-IPA at a dose level of 2 GBq administered in one of three different dosing regimens: single dose group with 2 GBq before radiation, 3 (f)-fractionated-parallel group: 3 x 0.67 GBq during XRT and 3 (f)-fractionated-sequential group: 0.67 GBq x 1 → XRT → 0.67 GBq x 2. XRT is delivered in 18fractions of 2 Gy each.

Results: 10 patients were included. Survival from start of TLX101 therapy showed mPFS2 of 4.27 m (95% CI 2.28-6.36), mOS2 of 9.9 m (95% CI 2.5-17.3), and mOS1 of 36.5 m (95% CI 22.03-58.07).

Conclusions: There were no clinically relevant laboratory, urinalysis, vital signs, or ECG changes. There were no notable differences in safety and tolerability between groups. Injections of single or fractionated doses of 131I-IPA containing a total activity of 2 GBq in combination with XRT in patients with recurrent GBM were well tolerated. Survival data look promising; a phase 1/2 study in first line setting is planned.

Theme

Translational Science, Brain Metastasis

28

Implementation of Identify Surface Guidance for Intracranial Stereotactic Radiosurgery (SRS)

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Abstract

Introduction

Intracranial SRS planning techniques routinely involve non-coplanar couch angles, which inhibit the use of cone-beam computed tomography (CBCT) for verification of patient position following couch motion. An advantage offered by surface guided radiotherapy (SGRT) is that it can be used at all couch angles and does not involve any radiation dose. Compared to CBCT, real-time sub-millimetre shift accuracy may also be possible[1].

Aim

To implement the use of Identify SGRT for intracranial SRS.

Method

Identify version 2.3.1 was installed on a Truebeam v2.7 and was commissioned using tests as recommended by AAPM

TG302[1]. An evaluation of available immobilisation solutions was undertaken, with a recommendation of the open-faced Encompass mask. The mask allows for the anterior surface region of interest (ROI) to be used for intrafraction monitoring. The sensitivity of the recommended ROI against patient setup errors was verified with anthropomorphic phantoms and human subjects. A treatment imaging/SGRT workflow was created to allow for data collection used to support the implementation for intracranial SRS. Correlated clinical localisation data for Identify, EPID and CBCT across a patient cohort with various optimal couch angles is reviewed to validate the accuracy of intrafraction patient motion during treatment.

Results

Results show that Identify correlated well to radiographic shifts detected by treatment-acquired EPID and CBCT images. Figure 1 shows an individual patient movement in the longitudinal versus time. This is also correlated to the couch angle, showing that over time and with each subsequent couch rotation, Identify is able to record and monitor intrafraction patient motion at sub-millimetre detection accuracy, appropriate for intracranial SRS.

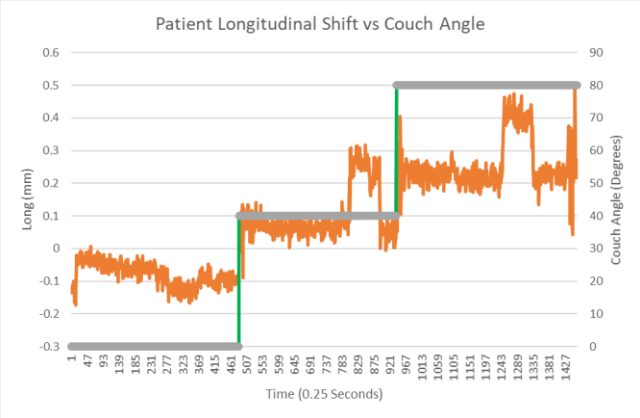

Figure 1.

Conclusion

Appropriate immobilisation equipment was evaluated and a treatment workflow was created to collect data. This was used to verify the system accuracy and the implementation of Identify surface guidance for intracranial SRS.

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Theme

Brain Metastasis

29

To assess trends in treatment and outcomes for Queenslanders with glioblastoma over a 10-year period

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Abstract

Aim: To assess trends in treatment and outcomes for Queenslanders with glioblastoma over a 10-year period.

Methods: Data from people the Queensland Oncology Repository was analysed retrospectively. Multivariate analyses (MVA) were performed to identify relationships between variables.

Results: 2,334 Queenslanders were diagnosed with glioblastoma between 2009 and 2019 of which 66% were living in metropolitan regions and of those who had surgery (n=1,883[sp1]), 68.8% received this in the public sector. Histological diagnosis was confirmed in 81%, 18% were based on clinical diagnosis only, and 1% at autopsy or via death certificate. 519 (22%) underwent biopsy only and 1,364 (58%) underwent debulking surgery. On MVA, debulking surgery (as opposed to biopsy only) was associated with tumour location outside frontal lobe, age <70, <2 comorbidities and if performed in a private hospital (OR 1.96, 95% CI 1.54- 2.50; p <0.001). [sp1] [MP2] After debulking surgery, 45% received adjuvant combination chemotherapy (CT) and radiotherapy (RT), 36% adjuvant RT alone and 3% adjuvant CT alone. After biopsy alone or no surgical intervention, 56[sp3] % received no further treatment, 21% combination CT and RT, 19% RT alone and 4% CT alone. Median survival was 2.1months for untreated patients and 10.1months for patients receiving any treatment. For those that received debulking surgery, increased mortality was associated with age >70, indigenous status, low socioeconomic status and ≥2 comorbidities. There was no significant variation in treatment received or survival based on patient location (metropolitan versus rural or remote location), or treatment location (public versus private sector).

Conclusion: Survival after glioblastoma is poor, as expected. In general, treatment and outcomes for people living in rural or remote areas of Queensland do not differ to those living in major cities. Reasons why indigenous status is associated with greater mortality warrants further evaluation.

Theme

Other

30

Are the cognitive needs of brain cancer survivors being met? : healthcare professional perspectives

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Abstract

Background: Despite the 5-year survival rate following primary brain tumour diagnosis increasing, and the prevalence of cognitive impairment in brain cancer survivors, supportive care primarily remains focused on physical or mental health. Little is known about the extent of screening for cognitive impairment or the cognitive interventions available to brain cancer survivors in routine care.

Aim: To explore current practice of assessment and intervention, particularly the applicability of a memory strategies intervention (LaTCH), for cognition in brain cancer survivors.

Methods: Qualitative methods were used to conduct semi-structured focus group (n=3) and individual interview (n=4) discussions. Participants were brain cancer care coordinators and health professionals throughout Australia. Focus groups and interviews were audio recorded and transcribed. Data were analysed thematically, and an interpretivist design was used to structure data interpretation.

Results: Participants included 10 care coordinators, with roles spanning from radiation oncology, inpatient clinical nursing, outpatient clinical care and occupational therapy. We identified 5 themes. The major overarching theme captured the unmet needs in this population. Specific areas of concern were lack of standardised cognitive assessment; and, limited to no cognitive interventions. Participants endorsed the suitability of LaTCH for a certain group of brain cancer survivors, with an unmet need still apparent for those with severe cognitive, behavioural, or language impairments.

Conclusion: Our results confirm the need for and limited availability of cognitive assessment and intervention for brain cancer survivors. LaTCH has the potential to fill this unmet need for some survivors, but further work is required to develop effective interventions to address more severe and complex needs.

Theme

Survivorship, Psychology and Supportive Care

31

Survival outcomes and health-related quality of life in older lower grade glioma and glioblastoma patients

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Abstract

Introduction: There is a paucity of research on clinical outcomes and health-related quality of life (HRQoL) of older patients with lower grade gliomas (LGG), who have poorer survival than younger patients. This study reports the prognostic factors and HRQoL of elderly LGG patients, and compares this population to glioblastoma patients of similar age.

Methods: A retrospective analysis was conducted on LGG and glioblastoma patients aged ≥50 treated at a tertiary hospital from 2002-2020. Treatment modalities and tumour

characteristics were examined. HRQoL was assessed on follow-up visits via the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and Brain Cancer Module (QLQ-BN20). The Kaplan-Meier method and log-rank tests were used for survival analysis.

Results: The study included 106 patients (median age 58), of whom 50 had LGG (astrocytoma 22, oligodendroglioma 28) and 56 had glioblastoma. Median progression-free survival (PFS) was 6.1, 5.3 and 1.2 years for astrocytoma, oligodendroglioma and glioblastoma, respectively. Median overall survival (OS) was 12.4, 9.8 and 2.2 years for astrocytoma, oligodendroglioma and glioblastoma, respectively (Figure 1). There was a statistically significant decrease in PFS and OS for patients ≥60 and those who did not have a gross macroscopic resection. Greater than 50% T2-FLAIR mismatch had no significant impact on survival in IDH-mutant disease. MRI necrosis was an adverse prognostic factor in glioblastoma patients. Compared to normative data, post-surgical elderly LGG patients showed reductions across all functional domains, particularly in role, social and cognitive function (Figure 2). Fatigue, insomnia and financial difficulties resulted in the highest patient burden on the QLQ-C30. In the QLQ-BN20, headache, future uncertainty and drowsiness had the greatest impact.

Conclusion: Subtype of glioma, age and extent of resection were significant prognostic factors. HRQoL was impaired across multiple domains. Further studies are warranted to investigate treatment strategies that will improve survival and HRQoL in this population.

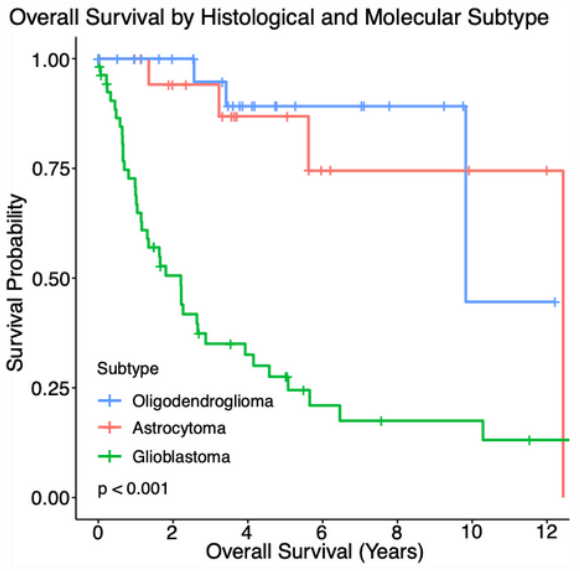

Figure 1. Kaplan-Meier survival analysis showing overall survival based on tumour subtype. Tick marks represent censoring.

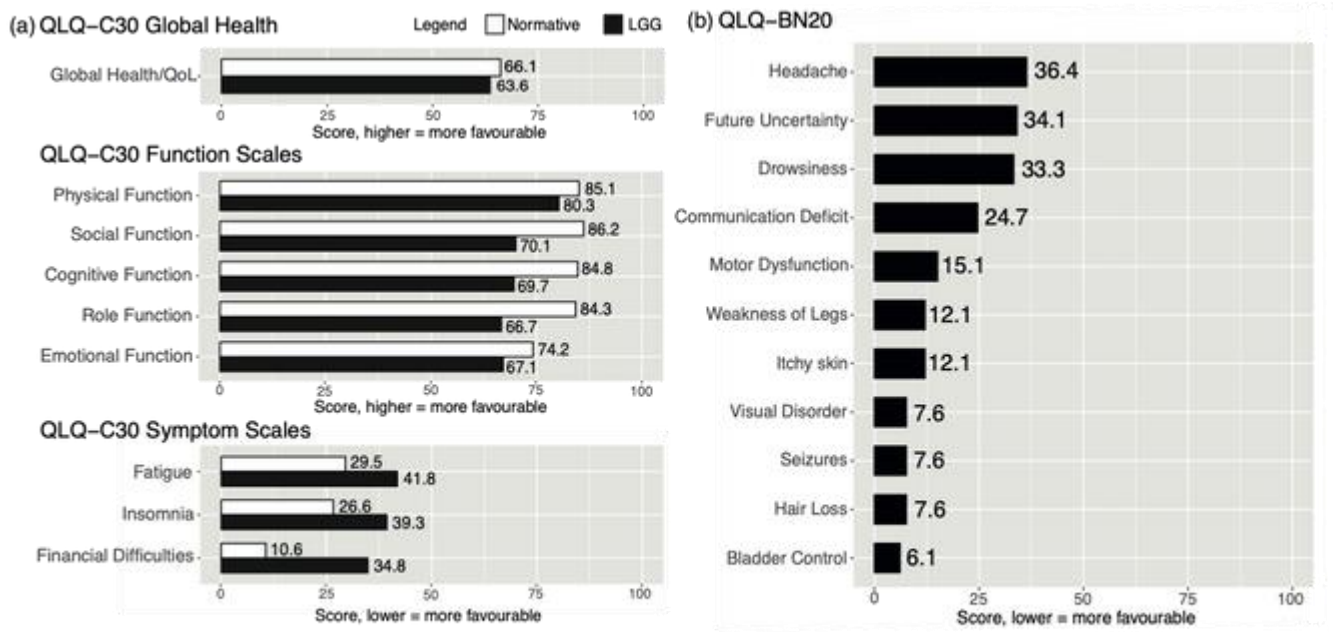

Figure 2. Comparison of EORTC QLQ-C30 questionnaire scores between LGG patients and the general population normative data (a). Higher scores in the QLQ-C30 Function Scales and lower scores in the QLQ-C30 Symptoms Scales represent better outcomes. EORTC QLQ-BN20 questionnaire scores of LGG patients are also depicted (b), with lower scores being more favourable.

Theme

Survivorship, Psychology and Supportive Care, Radiology

32

Optimising an Online Intervention for Carers of People with a Brain Tumour

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Abstract

Aims: An online intervention was developed to address the unmet needs of carers of people with a primary brain tumour.

Methods: A pilot evaluation with 10 carers assessed the effectiveness of the intervention. Acceptability and usability were measured through online data analytics (Google Analytics – unique page views and time on page), surveys and phone interviews. Questionnaires measured the potential impact on distress (The Distress Thermometer), depression, anxiety (The 14-item Hospital Anxiety and Depression Scale), carer competence (Carer Competence Scale), carer preparedness (Caregiving Preparedness Scale) and unmet needs (11-item Supportive Care Needs Scale – Brain Tumour Specific instrument for carers).

Results: Results showed that the intervention had high levels of usability and acceptability and positively impacted levels of depression. The qualitative findings highlighted how it met carer needs through the comprehensive amount of information and resources, and that it validated and normalised carer experiences. The interviews provided valuable information that has led to further refinement of the intervention.

Conclusions: Design adaptations have been undertaken, and users can now navigate the online intervention according to needs such as: Newly diagnosed; Starting treatment; After treatment and Coping. Finally, the inclusion of more videos of carers sharing their experiences aligned with interview and survey findings. Recruitment for the main RCT evaluation of the intervention has commenced. It is hoped that 100 carers of people with a brain tumour will be recruited to access and evaluate the intervention.

Theme

Translational Science, Survivorship, Psychology and Supportive Care

34

PSMA expression correlates with improved overall survival and VEGF expression in glioblastoma

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Abstract

Background

Prostate Specific Membrane Antigen (PSMA) is a transmembrane glycoprotein usually associated with prostate cancer. In prostate cancer, 68Ga-PSMA PET images the extent of disease and correlates with immunohistochemistry (IHC) PSMA staining. PSMA has also been found on the neo-vasculature of different malignancies. This study sought to examine the correlation between PSMA expression and vascular endothelial growth factor (VEGF) expression via IHC in IDH1/2 wild type Glioblastoma samples as well as their prognostic impact.

Methods

We examined 247 IDH1/2 wild type Glioblastomas (2009-2014) by IHC. We established a scoring system for IHC staining intensity and density from 0-3 for VEGF and PSMA.

Clinicopathological variables from chart review included age, gender, location of tumour, histological grade, and overall survival. Overall survival (OS) was censored at date of last follow-up where relevant. Patients were dichotomized into PSMA expression high (3+) and low (0-2+) and these cohorts were compared using log-rank analysis. PSMA-VEGF association was evaluated by the Chi-squared test.

Results

Thirty-five patients (14%) had high PSMA expression. Sixty-nine patients (28%) had high VEGF expression. OS was significantly better in those with high PSMA vs low PSMA (16.1 vs 10.8 mo, p=0.02). High PSMA expression also correlated with high (3+) VEGF expression (p=0.001).

Conclusion

This preliminary analysis suggests those with higher PSMA had significantly improved OS. While VEGF levels are usually associated with higher grade and poorer prognosis, high

VEGF expression was associated with high PSMA expression in this study.

Patients with high PSMA expression may have significant uptake on PSMA PET leading to a new therapeutic target in Glioblastoma. The combination of 177Lu-PSMA and bevacizumab may be a potential treatment combination in these patients.

Theme

Translational Science, Pathology

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A prospective, multi-centre trial of FET PET in glioblastoma patients – the TROG 18.06 FIG Study: Nuclear Medicine and Radiation Oncology credentialling program results demonstrate moderate to high interobserver agreement

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Abstract

Background: FET-PET In Glioblastoma (FIG) is an Australian prospective multi-centre study evaluating the impact of serial [18F]fluoroethyl-L-tyrosine positron emission tomography (FET-PET) imaging in Glioblastoma. Participants undergo FET-PET imaging pre-chemo-RT (FET-PET1), one-month post-chemo-RT and at suspected progression (FET-PET3). FET-PET analysis includes biologic target volume (BTV) delineation by Nuclear Medicine (NM) physicians. Radiotherapy (RT) target volume definition is per standard care (GTV_{MR}) with Radiation Oncologist (RO) deriving hybrid RT volumes (GTV_{MR-FET}) incorporating BTV post-RT. We describe here aspects of the NM and RO trial credentialling program.

Methods: Each trial site completed (1) BTV delineation by ≥2 NM physicians (3xFET-PET1, 3xFET-PET3) on six cases and (2) GTV_{MR}, GTV_{MR-FET} and organs at risk (OAR) delineation by ≥1 RO on three cases (3xFET-PET1). Pairwise Dice similarity coefficient (DSC) and intraclass correlation coefficient (ICC) assessed volume overlap and inter-observer agreement, respectively. GTV_{MR} and GTV_{MR-FET} differences were assessed using Wilcoxon signed-rank test.

Results: Data from 19 NM physicians and 19 ROs across 10 FIG sites has been analyzed to date. Acknowledging an NM case resubmission rate of 25%, resulted in moderate to excellent (ICC=0.75, 0.52-0.95; DSC=0.81±0.10) BTV agreement. RO-defined GTV_{MR-FET} were significantly larger ($p<0.0001$) compared to GTV_{MR} for case 1 (42.8±4.4 vs. 26.5±4.8 cm^3), case 2 (87.8±10.8 vs. 56.5±11.3 cm^3), and case 3 (18.3±2.1 vs. 9.3±1.0 cm^3), respectively. GTV_{MR} showed moderate to excellent agreement (ICC=0.90,0.69-1.0; DSC=0.84±0.06) and GTV_{MR-FET} showed good to excellent agreement (ICC=0.97, 0.87-1.0; DSC=0.86±0.05). OAR delineation demonstrated highest overlap agreement for brainstem (DSC=0.86±0.06) but lowest agreement for optic chiasm (DSC=0.47±0.25).

Conclusion: The comprehensive FIG trial credentialling program has expanded expertise in FET-PET interpretation and RT volume incorporation. Quantitative assessment resulted in moderate to excellent inter-observer agreement, though NM BTV and RO chiasm delineation remain areas of focus for the prospective phase.

Theme

Other