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BRITISH NEURO-ONCOLOGY SOCIETY ANNUAL MEETING 2021

PRECISION MEDICINE AND THE FUTURE OF NEURO-ONCOLOGY PRACTICE

ABSTRACT BOOK

THURSDAY 8TH AND FRIDAY 9TH JULY 2021
VIRTUAL CONFERENCE

BNOS BRITISH NEURO-ONCOLOGY SOCIETY

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12 CPD POINTS

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Are patients with brain tumours being given timely DVLA advice?

Oral Presentation - Main Stage (5 minutes)

Mr. Shumail Mahmood [1], ***Mr. Yazan Hendi*** [1], ***Mr. Hasan Zeb*** [1], ***Mr. Yasir A Chowdhury*** [2], ***Mr. Ismail Ughratdar*** [3]

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Aims

Over 11,000 patients are diagnosed with a primary brain tumour annually in the UK, with many more being diagnosed with a secondary brain tumour. UK law stipulates that all individuals with a brain tumour must inform the Driver and Vehicle Licensing Agency (DVLA) and may be required to surrender their driving license depending on their specific tumour and symptoms. Despite this guidance, we found that patients continue to arrive at the neuro-oncology clinic without the correct DVLA advice being given. This can potentially lead to patients with brain tumours continuing to drive on the public highway, which poses a severe hazard as the risk of seizures could endanger the public. This retrospective study looks to review what information was provided to patients with brain tumours upon initial diagnosis and determine the adequacy of this; ultimately aiming to improve the quality of information given to future neuro-oncology patients.

Method

A structured questionnaire was designed, asking patients who have been treated for a brain tumour at the Queen Elizabeth Hospital in Birmingham about any information they received about driving when they were first diagnosed. The questionnaire comprised of 11 questions designed to gather an understanding of what information was given to patients about driving. The study secured local audit approval. 75 patients identified from the weekly neuro-oncology MDT list were contacted. All patients included in this audit were required to stop driving and inform the DVLA about their condition as per the DVLA guidelines. Their responses were collated and analysed. Using this data, we determined if there were inadequacies in the information that was given to these patients about driving, and how this process may be improved in the future.

Results

60 patients (80%) possessed driving licenses when first diagnosed and 17% of these (n=10) were not told to stop driving; 8 of whom were diagnosed in primary/secondary care. 39 patients (65%) were first diagnosed in primary/secondary care, however, only 21% of these (n=8) were told to stop driving by primary/secondary care consultants. The remaining 31 patients (81%) were only told to stop driving after referral to tertiary care, by consultant neurosurgeons at the Queen Elizabeth Hospital. Conversely, of the 12 patients first diagnosed at the Queen Elizabeth Hospital, 85% were told to stop driving at diagnosis, suggesting a notable difference in informing patients between primary/secondary care and tertiary care. Patients also commented on the quality of the information received, as 10 individuals (21%) mentioned needing more information about getting their license back, and 5 individuals (11%) mentioning being given conflicting or incorrect information from different members of the MDT.

Conclusion

The results show that in practice, there are inconsistencies about mandatory DVLA advice which should be clearly provided to patients with a new diagnosis of a brain tumour. Only 78% of patients were told to stop driving at diagnosis, suggesting that the remainder could be liable to continue driving despite their diagnosis. Furthermore, many patients diagnosed in primary/secondary care are not being told to stop driving until after

referral to tertiary care which can take weeks, causing delays in them being given this information, which can pose risks to themselves and the public. These delays may be alleviated by giving patients a simplified resource when they are first diagnosed which clearly explains the driving rules. We therefore propose developing a one-page resource based on DVLA guidance and distributing this to patients and referring healthcare professionals at first diagnosis. A subsequent re-audit can evaluate if this intervention improves the current situation.

BrainApp: Using near-patient sensing through a mobile app and machine learning in brain tumour patients

Oral Presentation - Main Stage (5 minutes)

Dr. Nur Aizaan Anwar [1], ***Dr. Matthew Williams*** [1]

1. *Imperial College London*

Aims

1. To assess the feasibility, acceptability, and performance of a mobile app, 'BRIAN', developed by The Brain Tumour Charity (BTC), in collecting data on quality of life (QOL), activity and sleep, for predicting disease progression in adult brain tumour patients.
2. To generate a prospectively collected dataset of patient measures obtained through mobile devices in brain tumour patients and healthy volunteers.
3. To assess compliance and performance of micro-challenges (hand coordination, visual memory, speech and facial features) in study participants using a mobile application.
4. To assess differences and systematic variation in micro-challenge performance between healthy volunteers and brain tumour patients.
5. To assess factors associated with micro-challenge performance in brain tumour patients, the relationship between micro-challenges and standard measures of QoL and disease progression.
6. To assess the diagnostic performance of different machine learning models in detecting brain tumour progression.

Method

This abstract describes the protocol for a multi-centre observational non-randomised phase II trial for adult brain tumour patients and healthy volunteers in the UK. Participants will use the BRIAN mobile app, developed by BTC to help individuals cope with a brain tumour, and share their journey with both researchers and clinicians. Participants will be required to enter information on their medical background, mood, and QOL; have the option to link fitness trackers to the app; as well as perform mini-games which assess speech, coordination, facial features and reaction time. Patients will have their brain imaging and histopathology report submitted to the sponsor. We will then investigate the correlation and temporal relation of these multimodal data with conventional measures of disease progression. We will use traditional statistical methods initially (i.e. descriptive statistics and multilevel modelling), which will then inform the development of a machine learning model in predicting brain tumour progression.

Results

The BRIAN app is currently being beta-tested by healthy volunteers from the Computational Oncology Lab, Imperial College London. We are in the process of obtaining ethical approval for the trial.

Conclusion

This study may enable the development of a tool that allows us to detect earlier signs of disease progression, and so offer earlier treatment and preservation of quality of life; and hence the best course of action. Such a tool would also be non-invasive, cheap, quick, and can be used by patients in the comfort of their own homes.

Bridging the Gap: Development of a Patient Public Involvement Group

Oral Presentation - Main Stage (5 minutes)

Mrs. Claire Goddard [1], ***Dr. Helen Benghiat*** [2], ***Mr. Frederick Berki*** [1], ***Mr. Peter Buckle*** [3], ***Mr. William Garratt*** [1], ***Dr. Margaret O'Hara*** [4], ***Ms. Elizabeth Walker*** [3], ***Prof. Colin Watts*** [5], ***Dr. Victoria Wykes*** [5]

1. *University Hospitals Birmingham NHS Foundation Trust,* ***2.*** *Department of Radiotherapy, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK,* ***3.*** *BERTI, Queen Elizabeth Hospital Birmingham,* ***4.*** *Patient & Public Involvement & Engagement in Research, Queen Elizabeth Hospital Birmingham,* ***5.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Every year, the Queen Elizabeth Hospital Birmingham (QEHB) neuro-oncology team review over 2000 individuals with brain tumour. Patient and public involvement (PPI) has been fragmented to date. Initially we invited two patient advocates and a core group of allied health professionals to meet virtually to discuss development of a local PPI group, its aims, specific goals, and timescales to maintain momentum. In March 2021 we launched *"BERTI: Brain tumour Education and Research paTient and public Involvement group, West Midlands*". Our inaugural meeting will be virtual in April 2021 and will be followed by three meetings per year.

Method

- We developed information leaflets to promote the BERTI initiative. A membership form has been developed to record baseline information (non-clinical) e.g. contact details, which tumour type the individual is interested in, which aspect of BERTI they are interested in (Education, Research or Clinical service development).
- Patient advocates have reviewed all patient and public facing forms.
- All forms have been checked by Information Governance at QEHB to ensure General Data Protection Regulation compliant.
- Contact details and non-clinical data will be stored in a password protected database on a NHS computer network.
- Information to ensure members can unsubscribe from this group is easy to find and will be done immediately.
- A BERTI email account has been set up with a core group of professionals having access who are all fully trained in data protection and have GDPR certification.
- We will produce an annual BERTI newsletter.

Results

BERTI is a group for people affected by brain tumours in any way. We include patients, friends and family, health professionals and researchers who are committed to improving the care of people with a brain tumour. It is run between the QEHB and University of Birmingham (UoB).

BERTI provides a forum to meet other people affected by brain tumours and

- Share experiences
- Understand the condition better
- Work with clinical staff and researchers to improve clinical care and facilitate research for people living with brain tumours.

We will meet three times per year, virtually at the moment but face to face once Covid restrictions ease. We will have a formal talks explaining certain aspects of brain tumour or research initiatives. Throughout, there will be dedicated time set aside for group discussions to promote a genuine two-way dialogue between healthcare/research professionals and individuals affected by brain tumour.

Conclusion

The PPI group will be allowed to evolve rather than start out too prescriptive. It will capitalise on its strengths and skills of its composite members. There are no set models rather principles that will provide the foundations for a group which is supported to fulfil their specific purpose.

The views of the PPI group will be presented at the quarterly Neuro-Oncology Multi-disciplinary team business meetings to provide a forum to discuss issues. We aim to foster a PPI friendly environment, deliver real engagement and involvement across the group.

CaPaBLE: Comparing the Patient Generated Index to standard quality of life measures in patients and caregivers affected by high-grade brain tumours - Preliminary analysis

Oral Presentation - Main Stage (5 minutes)

Ms. Lillie Pakzad-Shahabi [1], ***Mr. James Tallant*** [2], ***Prof. Mary Wells*** [3], ***Dr. Matthew Williams*** [4]

1. *John Fulcher Neuro-Oncology Laboratory, Brain Tumour Research Centre of Excellence, Imperial College London; Computational Oncology Group, Institute for Global Health Innovation, Imperial College London,* ***2.*** *Division of Cancer, Charing Cross Hospital, Fulham Palace Road, Imperial College Healthcare NHS Trust,* ***3.*** *Nursing Directorate, Imperial College Healthcare NHS Trust; Department of Surgery and Cancer, Imperial College London,* ***4.*** *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust; Computational Oncology Laboratory, Institute of Global Health Innovation, Imperial College London*

Aims

High grade gliomas are rare but have the highest number of cancer deaths in the under-40s. Treatment options are limited, resulting in a clinical focus on maintaining quality of life (QoL). However standard QoL assessment tools are time consuming, may not reflect an individual's priorities, and are rarely used in clinical practice. Moreover, the impact of caring for someone with a high grade glioma is seldom assessed.

An alternative approach to assessing quality of life is to use a patient - or carer-generated index (PGI/CaGI), which asks patients & carers to raise, rank and number their concerns. This may offer a route to individualised QoL assessments within clinical and research settings.

The CaPaBLE study tests the feasibility and acceptability of the PGI and CaGI methodology in patients with high-grade glioma and their caregivers. This paper highlights key similarities and differences of the PGI/CaGI to standard QoL questionnaires.

Method

CaPABLE is an observational phase 2 non-randomised study following patients and their caregivers over 6 months starting at either first diagnosis or recurrence (https://www.isrctn.com/ISRCTN45555598). Patients and caregivers complete both standard questionnaires (EORTC QLQ C30 & BN20 and CargoQOL) and PGI/CAGI at 5 timepoints over the 6 month period. Each time the patients/caregivers complete the PGI/CAGI they are asked to identify up to 5 main topics of concern for their QoL, to score these, and rank their importance.

For this analysis, we grouped topics into themes, compared the stability of themes over time and to EORTC domains. Analyses of EORTC measures are conducted using standard scoring approaches. Here we present an initial analysis of occurrence of PGI/CaGI themes compared to EORTC domains, but do not consider scores or ranking.

Results

6 patients (4 male) and 5 caregivers (3 female; 4 paired with patients; one unpaired) have completed both standard questionnaire and PGI/CaGI at three or more time points, with a total of 19 (patient) and 18 (caregiver) assessments. On average people reported 3 topics at each assessment.

The PGI generated 59 topics (32 themes); the CaGI, 50 topics (23 themes) and themes were consistent over time. The most common domain raised by patients was "social life" (13). Caregivers raised "personal life and family" (12 and "planning ahead" (7) more commonly.

Of the 32 PGI themes, 23 align with EORTC domains. 9 PGI themes were not represented in the EORTC questionnaires, and 14 EORTC domains did not appear in the PGI. Of the 23 CaGI themes, 17 align with 7 CarGOQOL domains. 6 CaGI themes were not represented in the CarGOQOL and 3 CarGOQOL domains did not appear in the CaGI.

Conclusion

PGI and CaGI themes coincide with the main domains of EORTC (i.e., cognitive, social, role, physical, emotional functioning, future uncertainty). However, there were significant discrepancies: PGI (e.g., intimacy, ability to drive, and COVID related restrictions) and CaGI (e.g. personal life & family) highlighted themes that are not in the standard questionnaires. Both PGI/CaGI and standard questionnaires agree that symptom-related issues such as pain and seizures are not the main priority when it comes to QoL. In addition, CarGOQOL reports positive aspects of care, whereas CaGI only raised negative areas.

This study is the first to show the feasibility of PGI/CaGI in a brain tumour patient & caregiver population. PGI/CaGI are notably quicker to complete and provide insights not captured by standard questionnaires. We are continuing to recruit patients and caregivers, and have submitted a protocol amendment to carry out qualitative interviews with patients and caregivers, to explore their views further.

Developing guidelines for the management of brain tumour related epilepsy

Oral Presentation - Main Stage (5 minutes)

Ms. Elizabeth Vacher [1], ***Mr. Miguel Rodriguez Ruiz*** [1], ***Dr. Jeremy Rees*** [1]

1. *UCL Institute of Neurology*

Aims

Brain Tumour Related Epilepsy (BTRE) has a significant impact on Quality of Life with implications for driving, employment and social and domestic activities. Management of BTRE is complex due to the higher incidence of pharmacoresistance and the potential for interaction between anti-cancer therapy and anti-epileptic drugs (AEDs). Neurologists, oncologists, palliative care physicians and clinical nurse specialists treating these patients would benefit from up-to-date clinical guidelines. We aim to review the current evidence to adapt current NICE guidelines for Epilepsy and to outline specific recommendations for the optimal treatment of BTRE, encompassing both primary and metastatic brain tumours.

Method

A comprehensive search of the literature from the past 20 years on BTRE was carried out in three databases: Embase, Medline and EMCARE. A broad search strategy was used and the evidence was evaluated and graded based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Results

All patients with BTRE should be treated with AEDs. There is no proven benefit for the use of prophylactic AEDs, although there are no randomised trials testing newer agents. Seizure frequency varies between 10-40% (Class 2a evidence) in patients with Brain Metastases (BM) and from 30% (high-grade gliomas) to 90% (low-grade gliomas) (Class 2a evidence) in patients with Primary Brain Tumours (PBT). In patients with BM, risk factors include number of BM and melanoma histology (Class 2b evidence). In patients with PBT, risk factors include frontal and temporal location, oligodendroglial histology, IDH mutation and cortical infiltration (Class 2b evidence). There is a low incidence of seizures (13%) after stereotactic radiosurgery for BM (Class 2b evidence). Non-enzyme inducing AEDs are recommended as first line treatment for BTRE, but up to 50% of patients with BTRE due to PBT remain resistant (Class 2b evidence).

Conclusion

The review has highlighted the relative dearth of high quality evidence for the management of BTRE, and provides a framework for further studies aiming to improve seizure control, quality of life, and indications for AEDs.

Longitudinal Connectome Analyses following Low-Grade Glioma Neurosurgery: Implications for Cognitive Rehabilitation

Oral Presentation - Main Stage (5 minutes)

Mr. Anujan Poologaindran [1], ***Mr. Mike Hart*** [1], ***Mr. Tom Santarius*** [1], ***Mr. Stephen Price*** [1], ***Mr. Rohit Sinha*** [1], ***Mr. Mike Sughrue*** [1], ***Dr. Yaara Erez*** [1], ***Dr. Rafael Romero-Garcia*** [1], ***Prof. John Suckling*** [1]

1. *University of Cambridge*

Aims

Low-grade gliomas (LGG) slowly grow and infiltrate the brain's network architecture (**the connectome**). Unlike strokes that acutely damage the connectome, LGGs intricately remodel it, leading to varying deficits in executive function (i.e. attention, concentration, working memory). By longitudinally mapping the "*mesoscale*" architecture of the connectome, we may begin to systematically accelerate domain-general cognitive rehabilitation in LGG patients. In this study, we pursued the following aims: 1) track cognitive and connectome trajectories following LGG surgery, 2) determine optimal time period for cognitive rehabilitation, and 3) distinguish patients with perioperative predictors of long-term cognitive deficits (>1 year).

Method

With MRI and cognitive data from n=629 individuals across the lifespan, we first validated the structural, functional, and topological relevance of the multiple demand (MD) system for higher-order cognition. Next, in n=17 patients undergoing glioma surgery, we longitudinally acquired connectome and cognitive data: pre-surgery, post-surgery Day 1, Month 3, & 12. We assessed how glioma infiltration, surgery, and rehabilitation affected MD system trajectories at the single-subject level. Deploying transcriptomic and graph theoretical analyses, we tested if perioperative connectome modularity can accurately distinguish long-term cognitive trajectories.

Results

Controlling for age and sex, the MD system's multi-scale architecture in health was positively associated with higher-order cognition (Catell's fluid intelligence). Pre-operative glioma infiltration into the MD system was negatively associated with the number of long-term cognitive deficits (OCS-Bridge cognitive battery), suggesting its functional reorganisation. Mixed-effects modelling demonstrated the resilience of the MD system to infiltration and resection, while the early post-operative period was critical for effective neurorehabilitation. Graph analyses revealed perioperative modularity can distinguish patients with long-term cognitive deficits at one-year follow-up. Transcriptomic analyses of inter-module connector hubs revealed increased gene expression for mitochondrial metabolism and synaptic plasticity.

Conclusion

This is the first serial functional mapping of LGG patient trajectories for domain-general cognition. By assessing the mesoscale architecture, we demonstrate how connectomics can help overcome the intrinsic heterogeneity in LGG patients and predict long-term rehabilitation trajectories. We discuss how to identify neurobiologically-grounded personalised targets for '*interventional neurorehabilitation*' following LGG surgery.

Oral Presentation - Main Stage (7 minutes)

Activation of Raf signalling in NF2-null Schwann cells leads to sustained proliferation; an investigation of a new and inducible model for human schwannoma.

Oral Presentation - Main Stage (7 minutes)

Ms. Charlotte Lespade [1], ***Dr. Liyam Laraba*** [2], ***Mx. Evyn Woodhouse*** [3], ***Ms. Marie Srotyr*** [4], ***Prof. Alison C. Lloyd*** [5], ***Prof. David B. Parkinson*** [3]

1. *Peninsula Medical School, University of Plymouth, UK,* ***2.*** *Plymouth University,* ***3.*** *Peninsula Medical School, Faculty of Health, University of Plymouth, Plymouth, UK,* ***4.*** *University of Plymouth, UK,* ***5.*** *MRC Laboratory for Molecular Cell Biology, UCL, UK*

Aims

The NF2 gene encodes the tumour suppressor Merlin, which is deleted in 100% of patients with the familial tumour predisposition syndrome neurofibromatosis type 2 but also in 70% of those who develop sporadic schwannomas. The Raf-TR mouse model uses a tamoxifen-inducible Raf-kinase/ oestrogen receptor fusion protein (Raf-TR) expressed in myelinating Schwann cells to mimic a nerve injury response in Schwann cell by activating Raf/MEK/ERK signalling in the absence of peripheral nerve injury.

We will assess whether Raf/MEK/ERK activation on an NF2 null background leads to tumourigenesis within the vestibular nerves and dorsal root ganglia (DRGs), two tumour sites identified in the Periostin-Cre mouse model in which schwannoma formation is spontaneous, with a view to generating an inducible NF2 null schwannoma mouse model.

Method

Mice with a Schwann cell specific loss of Merlin were crossed with mice carrying a tamoxifen-inducible Raf-TR gene to generate Raf-TR$^{+/-}$; P0-Cre$^{+/-}$; NF2$^{fl/fl}$ (Cre+) mice which were NF2 null and compared to Raf-TR$^{+/-}$; P0-Cre$^{-/-}$; NF2$^{fl/fl}$ (Cre-) littermate controls. Mice were injected with tamoxifen or vehicle for five consecutive days and their vestibular nerves and dorsal root ganglia (DRGs) were analysed at various timepoints . An EdU proliferation assay was used to quantify the proliferation in the vestibular ganglia, as well as the DRGs. Rates of proliferation were compared to Cre- age-matched littermate controls treated with tamoxifen or vehicle.

Results

In the Periostin-Cre NF2 null schwannoma model, tumours form spontaneously in the DRGs and vestibular ganglia. In our new model, we see a clear increase in proliferation at 21 d post-injection in the NF2 null (Cre+) tamoxifen-treated mice compared to control (Cre-) tamoxifen-treated controls in both DRGs and vestibular ganglia. Cre- tamoxifen-treated mice do not show increased proliferation compared to Cre- vehicle controls. Taken together, this shows that activation of the Raf/MEK/ERK pathway in Schwann cells only causes a sustained proliferation response on an NF2 null background in the DRGs and vestibular ganglia. We are assessing later timepoints to further characterise tumour development in these mice.

Conclusion

Combining the Raf-TR mouse model to create a demyelinating phenotype with an NF2 null background leads to vastly increased rates of proliferation at the sites of schwannoma tumourigenesis within the peripheral nervous system: the DRGs and the vestibular ganglia. The high proliferation in the vestibular ganglia in particular is similar to the development of vestibular schwannomas in patients with Neurofibromatosis type 2. The new mouse model used in this study shows potential to be very useful as an inducible schwannoma tumour model, in which we can study the early events of tumour formation.

Artificial intelligence for early prediction of treatment response in glioblastoma

Oral Presentation - Main Stage (7 minutes)

Dr. Markand Patel [1], ***Dr. Jinfeng Zhan*** [2], ***Dr. Kal Natarajan*** [1], ***Dr. Robert Flintham*** [1], ***Dr. Nigel Davies*** [1], ***Dr. Paul Sanghera*** [1], ***Dr. James Grist*** [3], ***Prof. Vinay Duddalwar*** [4], ***Prof. Andrew Peet*** [5], ***Prof. Vijay Sawlani*** [1]

1. *Queen Elizabeth Hospital Birmingham,* ***2.*** *The Affiliated Hospital of Qingdao University,* ***3.*** *University of Birmingham,* ***4.*** *University of Southern California,* ***5.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Treatment response assessment in glioblastoma is challenging. Patients routinely undergo conventional magnetic resonance imaging (MRI), but it has a low diagnostic accuracy for distinguishing between true progression (tPD) and pseudoprogression (psPD) in the early post-chemoradiotherapy time period due to similar imaging appearances. The aim of this study was to use artificial intelligence (AI) on imaging data, clinical characteristics and molecular information within machine learning models, to distinguish between and predict early tPD from psPD in patients with glioblastoma.

Method

The study involved retrospective analysis of patients with newly-diagnosed glioblastoma over a 3.5 year period (n=340), undergoing surgery and standard chemoradiotherapy treatment, with an increase in contrast-enhancing disease on the baseline MRI study 4-6 weeks post-chemoradiotherapy. Studies had contrast-enhanced T1-weighted imaging (CE-T1WI), T2-weighted imaging (T2WI) and apparent diffusion coefficient (ADC) sequences, acquired at 1.5 Tesla with 6-months follow-up to determine the reference standard outcome. 76 patients (mean age 55 years, range 18-76 years, 39% female, 46 tPD, 30 psPD) were included. Machine learning models utilised information from clinical characteristics (age, gender, resection extent, performance status), O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and 307 quantitative imaging features; extracted from baseline study CE-T1WI/ADC and T2WI sequences using semi-automatically segmented enhancing disease and perilesional oedema masks respectively. Feature selection was performed within bootstrapped cross-validated recursive feature elimination with a random forest algorithm and Naïve Bayes five-fold cross-validation to validate the final model.

Results

Treatment response assessment based on the standard-of-care reports by clinical neuroradiologists showed an accuracy of 33% (sensitivity/specificity 52%/3%) to distinguish between tPD and psPD from the early post-treatment MRI study at 4-6 weeks. Machine learning-based models based on clinical and molecular features alone demonstrated an AUC of 0.66 and models using radiomic features alone from the early post-treatment MRI demonstrated an AUC of 0.46-0.69 depending on the feature and mask subset. A combined clinico-radiomic model utilising top common features demonstrated an AUC of 0.80 and an accuracy of 74% (sensitivity/specificity 78%/67%). The features in the final model were age, MGMT promoter methylation status, two shape-based features from the enhancing disease mask (*elongation* and *sphericity*), three radiomic features from the enhancing disease mask on ADC (*kurtosis*, *correlation*, *contrast*) and one radiomic feature from the perilesional oedema mask on T2WI (*dependence entropy*).

Conclusion

Current standard-of-care glioblastoma treatment response assessment imaging has limitations. In this study, the use of AI through a machine learning-based approach incorporating clinical characteristics and MGMT pro-

moter methylation status with quantitative radiomic features from standard MRI sequences at early 4-6 weeks post-treatment imaging showed the best model performance and a higher accuracy to distinguish between tPD and psPD for early prediction of glioblastoma treatment response.

Characterizing immune cell subsets of tumour infiltrating lymphocytes (TILs) in brain metastases

Oral Presentation - Main Stage (7 minutes)

Dr. Priyakshi Kalita-de Croft [1], ***Ms. Haarika Chittoory*** [1], ***Dr. Peter Simpson*** [2], ***Prof. Sunil Lakhani*** [1]

1. *University of Queensland,* ***2.*** *The University of Queensland*

Aims

The heterogeneity of TILs are not well characterized in brain metastasis. To address this, we performed a targeted analysis of immune cell subsets in brain metastasis tissues.

Method

We performed multiplex immunofluorescence (mIF) on a limited cohort of brain metastases arising from breast cancers (n=20). Using RNA-interference validated antibodies, we quantitated the subsets of immune cells in formalin-fixed paraffin embedded whole sections. The panel of proteins analyzed included PanCK, CD8, CD4, Vista and Iba1 and an average of 15000 cells per sample were analysed. We also analysed an independent publicly available cohort at the RNA level to corroborate our findings.

Results

We found that increased density of tils (high>30%; low <30%) correlated with survival and they were two distinct phenotypes. The tumours with low tils had significantly higher expression of the immune-checkpoint molecule Vista in tumour cells ($p<0.01$) as well as in their microenvironment ($p<0.001$). Contrastingly, the brain metastatic tumours with high tils displayed higher expression of microglia. Low tils-tumours display CD8+ T-cells that exclusively co-express Vista ($p<0.01$) compared to high tils group where CD8+ T-cells significantly co-express Iba1 ($p<0.05$). Interestingly no definite phenotypes were observed in CD4+ T-cells. These results were also found in an independent cohort where Vista was a highly ranked gene within the CD8+ T-cell population.

Conclusion

Variety of immune escape routes may be involved in brain metastasis. This may be executed by increasing the expression of T-cell inhibitory molecule Vista or by increased activated microglia which may release immunosuppressive cytokines. Further studies are required to provide mechanistic insights into these phenomena.

Chemotherapy strategies for young children newly diagnosed with desmoplastic/extensive nodular medulloblastoma up to the era of molecular profiling – a comparative outcomes analysis of prospective multi-center European and North American trials.

Oral Presentation - Main Stage (7 minutes)

Prof. Jonathan Finlay [1], ***Dr. Martin Mynarek*** [2], ***Dr. Girish Dhall*** [3], ***Dr. Lucie Lafay-Cousin*** [4], ***Dr. Claire Mazewski*** [5], ***Prof. David Ashley*** [6], ***Dr. Sarah Leary*** [7], ***Prof. Bruce H Cohen*** [8], ***Dr. Giles Robinson*** [9], ***Prof. Russell Geyer*** [7], ***Prof. Diana Tait*** [10], ***Mr. Joseph Stanek*** [1], ***Prof. Amar Gajjar*** [11], ***Prof. Stefan Rutkowski*** [12]

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Aims

Survival has been poor in several multi-center/national trials since the 1980s, either delaying, avoiding or minimizing brain irradiation in young children with medulloblastoma. The introduction of German regimens supplementing "standard" chemotherapy with both intravenous high-dose (HD-MTX) and intraventricular (IVENT-MTX) methotrexate, and North American regimens incorporating marrow-ablative chemotherapy with autologous hematopoietic cell rescue (HDCx+AuHCR), have reported encouraging outcomes. We performed a comparative outcomes analysis of these differing strategies for young children with desmoplastic/extensive nodular medulloblastoma.

Method

Data from 12 trials reported between 2005 and 2020 for children <six-years-old with desmoplastic/extensive nodular medulloblastoma were reviewed; event-free (EFS) survival+/-standard errors were compared.

Results

The German HIT-SKK'92 and HIT-SKK'00 trials incorporating HD-MTX and IVENT-MTX reported 85+/-8% and 95+/-5% 5-10-year EFS respectively; a third trial (ACNS1221) incorporating HIT-SKK therapy but *without* IVENT-MTX reported only 49+/-10% EFS. Three trials (Head Start I and II combined and CCG-99703) employing induction chemotherapy *without* HD-MTX, followed by one or three HDCx+AuHCR cycles, reported 3-5-year EFS of 67+/-16% and 79+/-11%. Two trials employing HD-MTX-containing induction chemotherapy (Head Start III and ACNS0334), followed by one or three HDCx+AuHCR cycles, reported 3-5-year EFS of 89+/-6% and 100%, respectively. Finally, four trials utilizing *neither* IVENT-MTX *nor* HDCx+AuHCR (UK-CNS-9204, CCG-9921, COG-P9934 and SJYC07) reported 2-5 year EFS of 35+/-11%, 77+/-9%, 58+/-8% and 53+/-9% respectively.

Conclusion

A trend towards better EFS for young children with desmoplastic/extensive nodular medulloblastoma is observed in trials including *either* HD-MTX and IVENT-MTX *or* including HD-MTX-containing induction chemotherapy and HDCx+AuHCR. Trials excluding HD-MTX, IVENT-MTX and HDCx+AuHCR have poorer outcomes.

Efficacy and Safety of CyberKnife Stereotactic Radiosurgery in Acromegaly.

Oral Presentation - Main Stage (7 minutes)

Dr. Desiree Seguna [1], Dr. Scott Akker [1], Dr. James Ahlquist [2], Dr. Aparna Pal [3], Dr. Antonia Brooke [4], Dr. rachel lewis [1], Dr. PN Plowman [1], Dr. Jane Evanson [1], Ms. Pratistha Panday [5], Prof. William Martyn Drake [1]

1. *St Bartholomew's Hospital,* ***2.*** *Southend University Hospital,* ***3.*** *The Churchill Hospital, Oxford,* ***4.*** *Royal Devon and Exeter Hospital,* ***5.*** *Queen Mary*

Aims

Objective: Active acromegaly is associated with increased mortality. While surgery is the mainstay of treatment, it is not always curative. In selected cases, CyberKnife stereotactic radiosurgery (CK SRS) can be used as adjuvant treatment in patients with persistent disease.

Method

Methodology: Biochemical response was measured using serum IGF-1 levels, calculated as a percentage of the upper limit of normal (% ULN). Levels were recorded prior to treatment, at 6-12 months post-treatment and at the most recent follow-up. Anterior pituitary hormone deficits were assessed before and after treatment. Tumour size was followed-up using MRI.

Results

10 patients (7 male, mean age 36 yrs [+/- 12.6, SD]) with acromegaly were treated with CK SRS. 9 were treated following failure to attain biochemical remission with TSS. 1 had primary CK SRS. 2 had previous conventional fractionated external beam radiotherapy.

Median tumour diameter was 6 mm (IQR 5.2-10.5 mm), with cavernous sinus invasion in 2 cases. The dose was 20-24Gy/1#. 4 patients were on dopamine agonist, 4 on somatostatin analogue and 2 on pegvisomant. Mean follow-up 31.6 months (+/- 13.5 months, SD).

Median IGF-1 % ULN was 146% pre-treatment (IQR 126.5-208.5), 109% at 6-12 months (IQR 76.5-131%) and 71% (IQR 59-91%) at last follow-up. Mean radiological follow-up 16.6 months (+/- 15.9 months, SD). No cases showed tumour enlargement.

One patient developed secondary hypothyroidism. Side-effects: headache (7 patients), blurred vision (1 patient), fatigue/nausea (1 patient). No new visual fields defects, cranial nerve palsies, cerebrovascular events or secondary tumours.

Conclusion

Conclusions: CK SRS appears safe and effective in selected patients with acromegaly, when there is failure to attain biochemical cure with surgery and in patients intolerant or resistant to medical treatment.

Elevated 2HG does not cause features of tumorigenesis

Oral Presentation - Main Stage (7 minutes)

Dr. Julie Adam [1], Dr. Alina Finch [2], Dr. Catarina Sepulveda [3], Dr. Martin Ducker [4], Dr. Maria Blanca Torroba [5], Dr. Daniel Krell [6], Prof. Skirmantas Kriaucionis [7], Prof. Francis Szele [4], Prof. Peter Ratcliffe [1], Prof. Tomoyoshi Soga [8], Prof. Kamil Kranc [9], Prof. Ian Tomlinson [10], Dr. Chiara Bardella [11]

1. *Target Discovery Institute, University of Oxford,* ***2.*** *Institute of Cancer and Genomic Sciences, University of Birmingham,* ***3.*** *Centre for Regenerative Medicine, University of Edinburgh,* ***4.*** *Department of Physiology, Anatomy and Genetics, University of Oxford,* ***5.*** *Department of Physiology, Anatomy and Genetics,* ***6.*** *the wellcome centre for human genetics university of Oxford,* ***7.*** *Ludwig Cancer Research, University of Oxford,* ***8.*** *Institute for Advanced Biosciences, Keio University,* ***9.*** *Centre for Haemato-Oncology, Barts Cancer Institute, University of London,* ***10.*** *IGMM, University of Edinburgh,* ***11.*** *Istitute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Gliomas are the most frequent brain tumours, representing 75% of all primary malignant brain tumours in adults. IDH1 (and IDH2) driver mutations occur in >80% of low grade gliomas and secondary GBMs, in <10% of primary GBMs and other cancers. How IDH1/2 mutations contribute to tumorigenesis is mostly unknown. IDH1/2 convert isocitrate to α-ketoglutarate, but when mutated possess a novel enzymatic function that reduces α-ketoglutarate to D2-hydroxyglutarate (2HG). Indeed 2HG accumulates in IDH1/2-mutant tumours, and this discovery suggested that 2HG may have a role in IDH1/2-mutant tumours onset and progression, possibly by causing dysregulations of various enzymes in the cells. Studies are undergoing to clarify the causative role of 2HG in IDH1/2-mutant tumours, but it is still not clear whether 2HG is the driver/oncometabolite. Our aim is to understand the role of 2HG in developing and adult mouse tissues and whether its accumulation might cause features of gliomagenesis.

Method

A constitutive D2hgdh Knock-out mouse (D2hgdh KO) was generated and the relative molecular and cellular analysis were performed.

Results

Brains dissected from D2hgdh KO mice appeared to be histologically normal. No differences were found in the proliferation and labelling retaining capacity of neural stem and progenitors cells (NSC/NPC) of the D2hgdh KO mice compared to controls. A comprehensive metabolites analysis showed that D2hgdh KO mouse accumulated 2HG in various organs and tissues, included total brains and in the NSC/NPC microdissected from the subventricular zone, the site of origin of many human gliomas. The DNA amount of 5mC and 5hmC extracted from brains of D2hgdh KO mice was similar to controls. A normal number of haematopoietic progenitors was also found.

Conclusion

Although D2hgdh KO mice accumulated 2HG in all tissues analysed, they did not develop any abnormalities and remained completely asymptomatic. This suggests that a mere increment of 2HG in developing and adult tissues may be not sufficient to cause tumorigenesis (and gliomagenesis), leading some doubts on the oncogenic roles of the 2HG in IDH1/2-mutant tumours.

Evaluation of Intraoperative Surgical Adjuncts and Resection of Glioblastoma (ELISAR GB): A UK and Ireland, multicentre, prospective observational cohort study

Oral Presentation - Main Stage (7 minutes)

Dr. Georgios Solomou [1], ***Dr. Ali Gharooni*** [2], ***Dr. Rory J Piper*** [3], ***Mr. Angelos G Kolias*** [2], ***Dr. Daniel M Fountain*** [4], ***Prof. Keyoumars Ashkan*** [5], ***Dr. Melissa Gough*** [6], ***Dr. Danyal Z Khan*** [7], ***Prof. Puneet Plaha*** [8], ***Ms. Kathrin Whitehouse*** [9], ***Prof. Michael Jenkisnon*** [10], ***Mr. Stephen Price*** [11], ***Prof. Colin Watts*** [12]

1. *School of Medicine, Keele University, Staffordshire, UK,* ***2.*** *Neurosurgery Division, Department of Clinical Neurosciences, Cambridge University, Cambridge, UK,* ***3.*** *Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK,* ***4.*** *Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, UK,* ***5.*** *Department of Neurosurgery, King's College Hospital NHS Foundation Trust, London,* ***6.*** *School of Medical Education, Newcastle University Medical School, Newcastle Upon Tyne, UK,* ***7.*** *Welcome/EPSRC Centre for Interventional and Surgical Sciences, National Hospital for Neurology and Neurosurgery, London, UK,* ***8.*** *Oxford University Hospitals NHS Foundation Trust,* ***9.*** *Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK,* ***10.*** *The Walton Centre, Liverpool,* ***11.*** *University of Cambridge,* ***12.*** *Queen Elizabeth Hospital, Birmingham*

Aims

Extent of resection is associated with better survival in patients with glioblastoma. Numerous surgical adjuncts can be used to achieve maximal safe resection - including fluorescence-guidance with 5-aminolevulinic acid (5-ALA), neuronavigation, intraoperative ultrasound (IoUS), intra-operative MRI (iMRI), tractography, electro-physiological monitoring and awake surgery. We evaluated the availability, use and operative aim and success associated with these adjuncts.

Method

This is a prospective cohort study of 27 of 31 neurosurgical centres in the UK and Ireland from 6 January to 19 March 2020. Consecutive cases were identified through neuro-oncology multidisciplinary meetings. Eligible cases included adults with a supratentorial histopathologically confirmed glioblastoma with pre/post-operative reported T1-weighted MRI with contrast deemed suitable for resection. Outcomes included the availability and usage of surgical adjuncts, and the percentage of operations that achieved their aim of complete resection, defined as complete resection of enhancing tumour (CRET) on post-operative T1-MRI. We present the initial descriptive statistics from this national study.

Results

232 patients with glioblastoma were included. In 142 patients (61.2%) the surgical aim was CRET. 5-ALA and neuronavigation were available in all centres (Figure 1). The most commonly used neurosurgical adjunct was neuronavigation (88.2%) (Figure 2). The proportion of patients receiving 5-ALA in CRET and debulking-only groups was 65.0% and 48.9%, respectively. 35 different combinations of adjuncts were found in total, with 13 unique combinations only used in one instance (Figures 1 & 2). CRET was achieved in 69/142 (45.8%) patients in which was the aim. 9/90 (10%) patients in the debulking-only group achieved CRET, of which 7/9 (77.8%) had received 5-ALA. Of the three most frequently used combination of adjuncts for patients deemed feasible for CRET, the most successful in terms of achieving CRET was the combined use of neuronavigation, 5-ALA and IoUS, with post-operative CRET at 47.4% (Figure 3).

Conclusion

ELISAR-GB has collated prospective data to demonstrate the current use of intraoperative adjuncts in the UK and Ireland. There is marked heterogeneity with regards to combinations of adjuncts used. A CRET of 47% is lower

than would be expected compared to previously published literature, possibly due to a more stringent definition of complete resection in this study. Based on these early descriptive results, there is no clear combination of adjuncts that shows superiority and use of 5-ALA does not always result in CRET when it is the surgical aim. Of interest, 5-ALA is being used for operations that do not aim for complete resection, a change in indication. The FUTURE GB trial will provide more conclusive evidence on the efficacy of surgical adjuncts to maximise extent of resection.

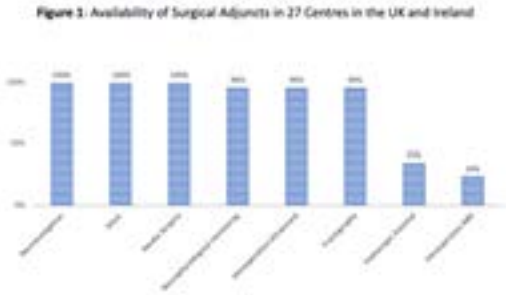


Figure 1.png

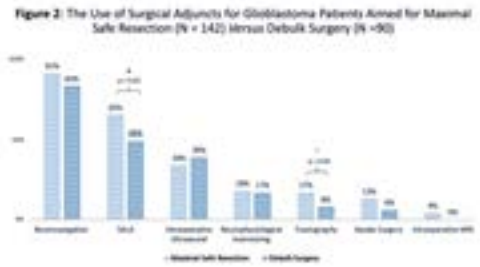


Figure 2.png

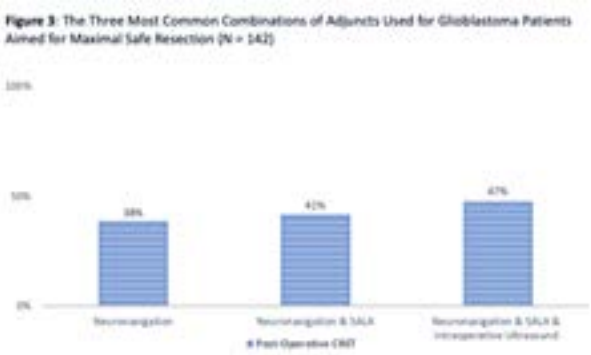


Figure 3.png

Excessive new origin firing underlies selective glioma stem cell cytotoxicity induced by replication stress response inhibition

Oral Presentation - Main Stage (7 minutes)

Ms. Emily Clough [1], ***Mrs. Karen Strathdee*** [1], ***Dr. Ross Carruthers*** [1]

1. *Institute of Cancer Sciences, University of Glasgow*

Aims

Glioblastoma (GBM) is a treatment refractory cancer of extreme unmet need which exhibits treatment resistance due to a subpopulation of GBM cancer stem cells which have constitutive DNA damage response activation driven by elevated replication stress (RS). RS response inhibition is potently cytotoxic to GSC, however mechanistic understanding will be key to biomarker discovery and successful clinical translation.
We investigated response to combined ATR and PARP inhibition (CAiPi) to gain mechanistic insight and inform biomarker development.

Method

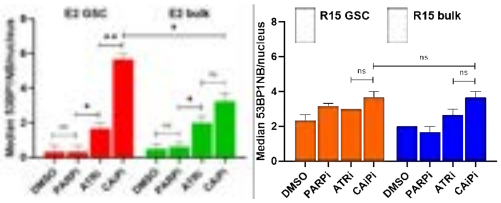
A panel of patient-derived GBM cell lines were cultured as stem enriched (GSCs) or stem depleted (bulk), to characterise response to combined ATR inhibition (VE821 5μM) and PARP inhibition (Olaparib 1μM), by CellTiter-Glo viability assay.
Mechanistic investigations included immunofluorescence of 53BP1 nuclear bodies and DNA fibre analysis. Studies into the importance of PARP trapping included another PARPi Veliparib (1μM), and investigations into inhibition of origin firing used the CDK inhibitor Roscovitine.

Results

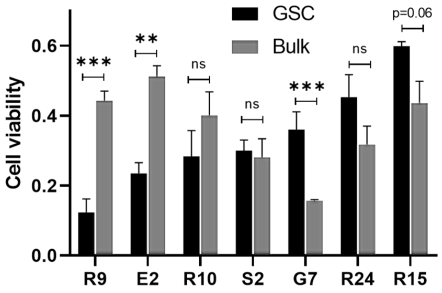
Responses to CAiPi in a panel of primary paired GBM GSCs vs differentiated progeny were heterogenous. CAiPi is selectively GSC cytotoxic in a subpopulation of tumours. DNA fibre analysis identified increased new origin firing with PARPi, which was correlated with increased PARP trapping. Inhibition of origin firing by exposure to roscovitine rescued the CAiPi cytotoxic phenotype, suggesting origin firing has an important role in selective GSC cytotoxicity.
A population of treatment-sensitive GSCs with increased numbers of 53BP1 nuclear bodies in G1 phase with CAiPi were identified, indicative of under-replication of DNA in S phase.

Conclusion

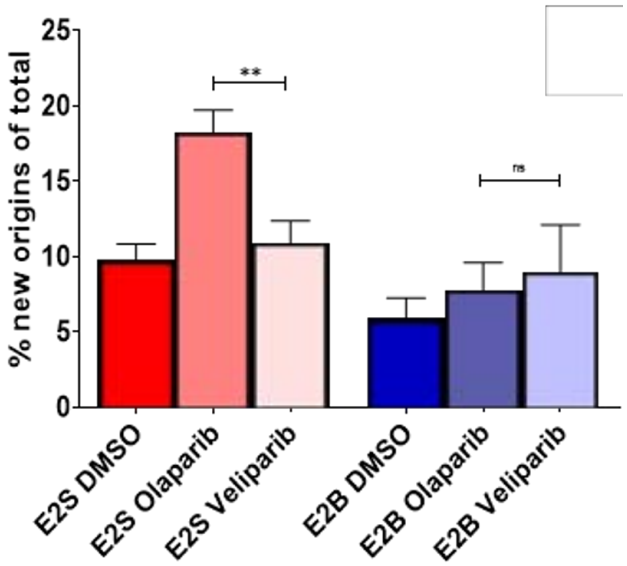
Selective GSC cytotoxicity is induced by CAiPi via dysregulation of replication, by both DNA under-replication resulting in DNA lesions, and the novel finding of increased new origin firing in GSC due to PARPi.



53bp1nb gbm.png



Caipi response gbm.png



Neworigins gbm.png

Fully automated deep learning system for detecting sarcopenia on brain MRI in glioblastoma

Oral Presentation - Main Stage (7 minutes)

Ms. Radvile Mauricaite [1], Dr. Ella Mi [2], Dr. Jiarong Chen [2], Dr. Andrew Ho [3], Ms. Lillie Pakzad-Shahabi [4], Dr. Matthew Williams [1]

1. *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust,* ***2.*** *Computational Oncology Laboratory, Institute of Global Health Innovation, Imperial College London,* ***3.*** *Norfolk and Norwich University Hospitals NHS Foundation Trust,* ***4.*** *John Fulcher Neuro-Oncology Laboratory, Brain Tumour Research Centre of Excellence, Imperial College London*

Aims

Glioblastoma multiforme (GBM) is an aggressive brain malignancy. Performance status is an important prognostic factor but is subjectively evaluated, resulting in inaccuracy. Objective markers of frailty/physical condition, such as measures of skeletal muscle mass can be evaluated on cross-sectional imaging and is associated with cancer survival. In GBM, temporalis muscle has been identified as a skeletal muscle mass surrogate and a prognostic factor. However, current manual muscle quantification is time consuming, limiting clinical adoption. We previously developed a deep learning system for automated temporalis muscle quantification, with high accuracy (Dice coefficient 0.912), and showed muscle cross-sectional area is independently significantly associated with survival in GBM (HR 0.380). However, it required manual selection of the temporalis muscle-containing MRI slice. Thus, in this work we aimed to develop a fully automatic deep-learning system, using the eyeball as an anatomic landmark for automatic slice selection, to quantify temporalis and validate on independent datasets.

Method

3D brain MRI scans were obtained from four datasets: our in-house glioblastoma patient dataset, TCGA-GBM, IVY-GAP and REMBRANDT. Manual eyeball and temporalis segmentations were performed on 2D MRI images by two experienced readers. Two neural networks (2D U-Nets) were trained, one to automatically segment the eyeball and the other to segment the temporalis muscle on 2D MRI images using Dice loss function. The cross sectional area of eyeball segmentations were quantified and thresholded, to select the superior orbital MRI slice from each scan. This slice underwent temporalis segmentation, whose cross sectional area was then quantified. Accuracy of automatically predicted eyeball and temporalis segmentations were compared to manual ground truth segmentations on metrics of Dice coefficient, precision, recall and Hausdorff distance. Accuracy of MRI slice selection (by the eyeball segmentation model) for temporalis segmentation was determined by comparing automatically selected slices to slices selected manually by a trained neuro-oncologist.

Results

398 images from 185 patients and 366 images from 145 patients were used for the eyeball and temporalis segmentation models, respectively. 61 independent TCGA-GBM scans formed a validation cohort to assess the performance of the full pipeline. The model achieved high accuracy in eyeball segmentation, with test set Dice coefficient of 0.9029 ± 0.0894, precision of 0.8842 ± 0.0992, recall of 0.9297 ± 0.6020 and Hausdorff distance of 2.8847 ± 0.6020. High segmentation accuracy was also achieved by the temporalis segmentation model, with Dice coefficient of 0.8968 ± 0.0375, precision of 0.8877 ± 0.0679, recall of 0.9118 ± 0.0505 and Hausdorff distance of 1.8232 ± 0.3263 in the test set. 96.1% of automatically selected slices for temporalis segmentation were within 2 slices of the manually selected slice.

Conclusion

Temporalis muscle cross-sectional area can be rapidly and accurately assessed from 3D MRI brain scans using

a deep learning-based system in a fully automated pipeline. Combined with our and others' previous results that demonstrate the prognostic significance of temporalis cross-sectional area and muscle width, our findings suggest a role for deep learning in muscle mass and sarcopenia screening in GBM, with the potential to add significant value to routine imaging. Possible clinical applications include risk profiling, treatment stratification and informing interventions for muscle preservation. Further work will be to validate the prognostic value of temporalis muscle cross sectional area measurements generated by our fully automatic deep learning system in the multiple in-house and external datasets.

GlioCova: Treatment and hospital admissions for patients with GBM in England

Oral Presentation - Main Stage (7 minutes)

Ms. Radvile Mauricaite [1], ***Ms. Kerlann Le Calvez*** [1], ***Dr. Matthew Williams*** [2]

1. *Computational Oncology Laboratory, Institute of Global Health Innovation, Imperial College London,* ***2.*** *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust*

Aims

Data on the treatment and outcomes of patients with primary brain tumours in England is sparse. The GlioCova project uses linked national data from England to explore the incidence, treatment, outcomes, and treatment costs of all adult brain tumour patients in all 50,000 patients in England from 2013 – 2018. Here we present initial results from patients with glioblastoma (GBM).

Method

We used a linked dataset from the national cancer registration system in England including all adult patients diagnosed with a malignant or benign brain tumour between 2013 and 2018 (51,775 patients in total).
Glioblastoma patients were selected based on ICD-10 codes (C70, C71, C72), morphology codes (9440, 9441, 9442), and grade (G4, G3, GX and NA) from the national cancer registry. We extracted data on treatment (radiotherapy, chemotherapy, brain surgery or biopsy) and measured how many patients who had adjuvant Temozolomide completed 6 cycles.

Results

We identified 15,294 glioblastoma patients. Most had glioblastoma morphology (14,924), followed by gliosarcoma (264) and giant cell glioblastoma (106). Almost all had a cranial tumour (C71) while 17 had a tumour originating in the spinal cord, cranial nerves or other part of central nervous system (C72). Median age was 66 (IQR=17) and 60% were male. 51.9% (7,935) underwent surgery; an additional 18.2% (2,784) had a biopsy; 3,701 (24.2%) out of 15,294 patients received radiotherapy (only) and 316 (2.1%) received chemotherapy (only). 5,520 (36.1%) received both radiotherapy and chemo. Out of 4,101 GBM patients receiving temozolomide after radiotherapy, only 1,535 (37.4%) completed 6 cycles. The 7,935 GBM patients who had surgery had a median length of stay in hospital of 5 days (IQR=6) while those that had a biopsy had a median of 3 days (IQR=6).

Conclusion

We have presented a description of treatment of all GBM patients in England over a five-year period. This is the first time we have been able to understand detailed treatment patterns at a national scale, and significantly extends previous analyses. Further work will look at patient safety indicators, variation across centres and costs of treatment.

Acknowledgements

We would like to thank the GlioCova Expert Advisory Group for their input and discussion.
This work uses data provided by patients and collected by the NHS as part of their care and support.

Identification of novel therapeutic targets for histone 3 mutated children's brain tumour, using unique tumour cell surface proteomic signatures

Oral Presentation - Main Stage (7 minutes)

Ms. Anya Snary [1]***, Prof. Richard Grundy*** [2]***, Dr. Rob Layfield*** [1]***, Dr. Ruman Rahman*** [1]***, Dr. Farhana Haque*** [3]

1. *University of Nottingham,* ***2.*** *The Children's Brain Tumour Research Centre, University of Nottingham,* ***3.*** *University of Lincoln*

Aims

Improvements in the treatments for childhood and adolescent brain tumours, High-Grade Glioma (pHGG) and Diffuse Intrinsic Pontine Glioblastoma (DIPG), have not advanced much and they continue to carry a very poor prognosis. These brain tumours are now defined by mutations affecting histone 3 proteins, indeed 80% of DIPGs harbour histone H3.1 and H3.3 K27M somatic mutations whilst 30% of pHGGs exhibit H3.3 G34R or G34V mutations. We hypothesized that the histone 3 mutant tumours will have distinct mutation specific surfactome (cell membrane proteins) signature.

Method

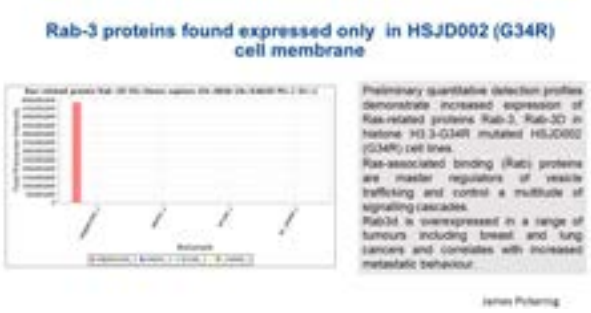
We therefore analysed the cell surface proteomics of pHGG and DIPG, in order to identify novel targets for therapy. We have at first isolated the cell membrane fractions from a range of patient cells carrying different histone 3 mutations (G34R, G34V), relative to wild type histone 3. A comparative quantitative mass-spectrometry analyses of these cell surface membrane fractions is then performed.

Results

The results obtained to date demonstrated unique differential cell membrane expression patterns which correlated to specific mutation type. For example, increased expression of Ras-related proteins Rab-3, Rab-3D is detected only in histone H3.3-G34R mutated cell line in comparison.

Conclusion

Identification and analyses of these unique cell membrane proteins' association with specific in H3.3 mutation in pHGG, will help to identify precise mutation specific therapeutic targets, benefiting the patients to receive therapy based on tumour's molecular signature.



Rab3 and g34r mutation.jpg

Initial experience with navigated intraoperative ultrasound for brain tumour surgery

Oral Presentation - Main Stage (7 minutes)

Mr. Adam Nunn [1], ***Mr. Neil Barua*** [1]

1. *Southmead Hospital*

Aims

The use of intraoperative ultrasound (iUS) has been associated with prolonged survival in patients with high grade glioma. However, iUS remains an under-utilised surgical adjunct in many neurosurgical units due to greater familiarity with CT and MR imaging. Navigated intraoperative ultrasound (NiUS) facilitates co-registration of pre-operative MR imaging with iUS, offering a number of advantages over standard neuronavigation. The aim of this study was to describe our initial experiences with NiUS for brain tumour resection in adults.

Method

We prospectively collected data on patient demographics, tumour location and histology, extent of resection and early post-operative outcome in 9 consecutive patients. Brainlab neuronavigation (BrainLab, Germany) and the BK5000 cranial ultrasound probe (BK Medical, Denmark) were used in all cases. We also collected data on surgical intent and the use of surgical adjuncts including neurophysiology monitoring, DTI and 5ALA.

Results

NiUS was used in 9 patients (6 male, 3 female). iUS scans were successfully co-registered in all cases. Histological diagnoses were GBM (7 patients), melanoma (1 patient) and oligodendroglioma (1 patient). NiUS was used in conjunction with the following techniques and adjuncts – awake craniotomy (2), DTI (all cases), neurophysiology monitoring (4 cases) and 5ALA (7 cases). Gross total resection was achieved in 8 patients. The mean operative time was 4 hours and 7 minutes, which is significantly lower than that reported in a recently published series involving intra-operative MRI. No patients suffered any deterioration in neurological status in the early post-operative period.

Conclusion

NiUS was rapidly assimilated into our surgical workflow with successful co-registration in all cases. NiUS was used successfully in conjunction with awake craniotomy, neurophysiology monitoring, DTI and 5ALA for both enhancing and non-enhancing tumours. Based on our early experience we offer learning points on patient positioning, set up of equipment and interpretation of iUS. Further studies are required to determine the impact of NiUS on patient outcome.

Preliminary evidence of antitumour activity of Ipatasertib (Ipat) and Atezolizumab (ATZ) in glioblastoma patients (pts) with PTEN loss from the Phase 1 Ice-CAP trial (NCT03673787)

Oral Presentation - Main Stage (7 minutes)

Dr. Crescens Tiu [1], Dr. Liam Welsh [2], Mr. Timothy Jones [3], Dr. Anna Zachariou [4], Mr. Toby Prout [4], Dr. Alison Turner [4], Mr. Rob Daly [4], Dr. Nina Tunariu [5], Ms. Ruth Riisnaes [4], Mr. Bora Gurel [4], Mr. Mateus Crespo [4], Ms. Suzanne Carreira [4], Dr. Igor Vivanco [4], Dr. Ben Jenkins [4], Prof. Christina Yap [4], Dr. Anna Minchom [5], Prof. Udai Banerji [5], Prof. Johann deBono [5], Dr. Juanita Lopez [5]

1. *Royal Marsden Hospital and the I,* ***2.*** *Royal Marsden Hospital,* ***3.*** *St George's University Hospital NHS Foundation Trust,* ***4.*** *Institute of Cancer Research,* ***5.*** *Royal Marsden Hospital and the Institute of Cancer Research*

Aims

Despite improved understanding of effector T-cell trafficking into the central nervous system, initial trials with anti-PD1/PD-L1 immune checkpoint inhibitors (ICIs) have failed to meet their primary endpoints. PTEN loss of function is frequent in GBM and has been correlated with not only poor overall prognosis, but also impaired antitumour responses, including reduced T cell infiltration into tumour and reduced efficacy of ICIs.

Ipatasertib is a novel, potent, selective, small-molecule inhibitor of Akt. We have shown that Ipatasertib efficiently depletes $FOXP3^+$ regulatory T cells from the tumour microenvironment (TME) resulting in increased infiltration of effector T cells in solid tumours (Lopez 2020, AACR).

We hypothesize that the use of AKT inhibition in PTEN glioblastomas may deplete the TME of suppressive immune cells, and render malignant brain tumours more responsive to ICIs. We present updated data for the combination of Ipat+ATZ in patients with glioblastoma.

Method

Patients with relapsed WHO grade IV GBM with stable neurological symptoms ≥5 days prior to enrolment, requiring <3mg Dexamethasone were recruited into two cohorts of this early phase, open-label, single-centre trial studying the combination of Ipatasertib (Ipat) and Atezolizumab (ATZ): a dose finding cohort (A2; n=9) and an expansion cohort (B3; n=7, recruitment ongoing).

The Ice-CAP A2 cohort assessed safety, pharmacodynamic, and preliminary clinical activity of Ipat (200mg or 400mg OD) + ATZ (1200mg Q3W) in pts with potentially resectable relapsed WHO Grade IV GBM. Pts had a 14-21-day run-in phase of Ipat then surgical tumour resection. Combination Ipat+ATZ commenced post surgery. Patients who declined surgery or who were deemed high risk for surgery proceeded directly to combination. Patients in the expansion cohort B3 commenced directly on Ipat+ATZ at the RP2D of 400mg Ipat with ATZ.

Results

16 evaluable recurrent GBM pts were enrolled across two cohorts. Median age 56 yrs (25-71 yrs). Median ECOG PS 1. Median lines of prior therapy 1 (range 1-4). 10 pts had PTEN loss by IHC (H<30) and/or PTEN mutations on next generation sequencing.

No DLTs, treatment-related (TR) serious adverse events (AEs), or immune-related AEs were observed. Most common TR AEs were G1 diarrhoea (44%), mucositis (17%), rash (28%).

Clinical benefit rate (CR, PR and SD> 6 cycles) at clinical cutoff date (23/02/21) in patients with PTEN aberration was 30% (3/10). A 58-year-old man with PTEN loss had MRI at Cycle 5 showing worsening enhancement suggestive of disease progression. Resection of the lesion showed intense lymphocyte infiltration and pathological CR. He is currently on Cycle 22 with no evidence of disease. Two other patients with PTEN loss with radiological stable disease per RANO criteria remain well on study for >6 cycles.

Conclusion

Combination Ipat+ATZ appears safe and tolerable in GBM pts, with 400mg Ipatasertib OD + 1200mg ATZ Q3W declared as RP2D. Early efficacy signals were detected with PTEN loss being a promising predictive biomarker for response to combination. An expansion cohort enriched with pts with PTEN loss is ongoing.

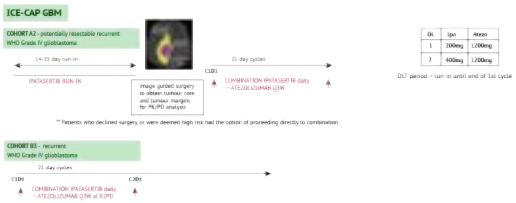


Figure 1 ice-cap gbm schema.png

Figure 2 gbm a2andb3 pfs only.jpg

Proteomic analysis of genetically stratified low-grade meningioma.

Oral Presentation - Main Stage (7 minutes)

Mrs. Yeasmin Akther [1], ***Dr. CLAIRE ADAMS*** [1], ***Dr. Vikram Sharma*** [1], ***Dr. Claudia Barros*** [1], ***Dr. Matthew Banton*** [1], ***Prof. Oliver Hanemann*** [1]

1. *University of Plymouth*

Aims

Meningioma is the most common primary intracranial tumour. Although ~80% are benign WHO grade I and show high rates of recurrence. Surgery is the main therapeutic approach, yet location can hamper complete resection and chemotherapies are ineffective. Moreover, accurate biomarkers for clinical management are lacking. Approximately 60% sporadic meningiomas harbour mutations in the *NF2*gene, while mutations in genes including *TRAF7*, *KLF4*, *AKT1*, *SMO* and *PIK3CA*have been identified majority in the *NF2*-positive low grade-tumours. Moreover, mutations in TRAF7 mostly co-occur with a $KLF4^{K409Q}$ or with $AKT1^{E17K}$ mutation. The mutations and their molecular manifestations consequently affect the signalling pathways at the protein level. The molecular mechanisms behind meningioma tumourigenesis are still obscure and the identification of specific biomarker is necessary to enable their implementation in routine diagnostics and therapeutics. Therefore, we aim to identify novel biomarkers and therapeutic targets of genetically stratified low-grade meningioma by characterising the proteomic landscape.

Method

Frozen tumour samples have already been analysed for $NF2^{-/-}$ by next generation sequencing and genotyped for common mutational hotspots in non-NF2 meningioma such as TRAF7, KLF4 and AKT1 and grouped in to three different mutational groups: $AKT1^{E17K}$/*TRAF7*, $KLF4^{K409Q}$/*TRAF7*and $NF2^{-/-}$ and all these mutations will be compared to normal healthy meninges. For global proteomics, proteins were separated by SDS-PAGE followed by in-gel tryptic digestion and sample preparation for LC-MS/MS analysis. Raw mass spectrometry data files were processed by MaxQuant (1.6.2.10) and Perseus software (1.6.1.3). Quantitative phospho-proteomics was performed using TMT 10plex labelling approach followed by motif analysis using motif-X algorithm. GO enrichment analyses were performed using (DAVID) v6.8 against all human proteins. Potential candidates from expression data analysis will be validated via Western Blot and immunohistochemistry.

Results

We have quantified 4162 proteins across all mutational meningioma subgroups and normal meninges (n=31). Hierarchical clustering analysis showed distinct proteomic profiles of mutational subgroups revealing clusters of differentially expressed proteins. Comparative analysis showed 10 proteins were commonly significantly upregulated ($\log_2$ fold-change≥1; p<0.05) among all mutational subtypes *vs.* normal meninges, indicating proteomic landscapes of mutational subtypes to be highly variable. In contrast, 257 proteins were commonly significantly downregulated ($\log_2$ fold-change≤-1; p<0.05) and enriched with molecular functions including aldehyde dehydrogenase and oxido-reductase. Mutational subtype-specific analysis identified 162 proteins significantly upregulated in $AKT1^{E17K}$/*TRAF7 vs.* remaining sample groups to be enriched in the oxidative phosphorylation pathway. However, only 14 and 7 proteins were commonly significantly upregulated in $KLF4^{K409Q}$/*TRAF7* and $NF2^{-/-}$ mutant meningioma subtypes respectively. Several of these up-regulated proteins including ANNEXIN-3, CRABP2, CLIC3 and Endoglin were already verified via WB. Lastly, analyses of 6600 phospho-sites (n=8) predicted regulatory kinases including CHEK1, CHEK2 and LCK.

Conclusion

Global proteomic and phos-phoproteomics analysis has led to the identification of proteins differentially expressed in mutant subtypes. Results of this study to date suggest that a proteomic approach is an effective tool to identify distinct patterns in genetically distinct meningioma subgroups. Further validation and functional verification (with inhibitory or knockdown approaches) of potential candidates will allow us to identify potential drug targets/biomarkers for meningiomas.

Readmission and reoperation rates after resection of malignant primary brain tumours in England 2013-2017

Oral Presentation - Main Stage (7 minutes)

Mr. Adam Wahba [1], ***Mr. Nick Phillips*** [2], ***Prof. Peter Hutchinson*** [3], ***Prof. David Cromwell*** [4], ***Mr. Ryan Mathew*** [2]

1. *Royal College of Surgeons of England and Sheffield Teaching Hospitals NHS Trust,* ***2.*** *University of Leeds and Leeds Teaching Hospitals NHS Trust,* ***3.*** *Neurosurgery Division, Department of Clinical Neurosciences, Cambridge University, Cambridge, UK,* ***4.*** *Royal College of Surgeons of England and London School of Hygiene & Tropical Medicine*

Aims

Morbidity and mortality following resection of malignant primary brain tumours is high. The benefits of reoperation for recurrent tumours are uncertain and it is not known how frequently patients in England undergo further tumour resections. The aim of this study was to describe 30-day and one-year readmission rates, the clinical reasons for readmission and the rate of resections for recurrent tumours.

Method

Patient data was extracted from Hospital Episode Statistics (the hospital administrative data for NHS hospitals in England) for all supratentorial, malignant, primary brain tumour resections performed from April 2013 to March 2017. All subsequent non-elective readmissions to any NHS hospital and all readmissions for further tumour resection within 30 days and one year were analysed for the primary clinical diagnosis and primary procedure performed.

Results

A total of 6,982 patients were identified and the 30-day and one-year readmission rates were 18.6% (n=1,298) and 57.4% (n=4,007), respectively. The rates of reoperation for tumour resection were 0.5% (n=33) and 6.2% (n=432), respectively. The commonest reasons for 30-day readmission were post-operative complications (17.9% of admissions), general medical complications (17.3%) and surgical site infection (9.6%). The most frequently performed neurosurgical procedures were for treatment of surgical site infection (37.6% of procedures). The commonest reasons for readmission within one year were general medical complications (17.4%), seizures (14%), systemic infections (11.4%) and post-operative complications (11%). Almost half of all neurosurgical procedures performed within one year were reoperation for tumour resection (45.6%), while treatment of surgical site infection (17.9%) and CSF shunt insertions and revisions (9.1%) were also common.

Conclusion

This study provides a descriptive analysis of the rates of readmission, diagnosis on readmission, and the need for further neurosurgical procedures. The rate of non-elective readmissions within one year is high and these data may be useful for service planning and for counselling patients about their treatment. Additionally, these data contribute to the development of quality indicators, for benchmarking and comparing quality of care provision between neurosurgical units. Further research, with linkage to histology data and performance status, would support an analysis of the role of resection of recurrent, malignant, primary brain tumours.

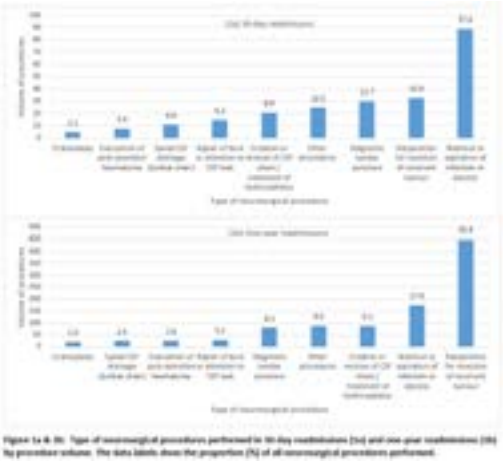


Figure1 aw.png

Figure2 aw.png

	30-day		1-year	
	Volume	%	Volume	%
Total number of patients	6982	100	6982	100
Patients readmitted	1298	18.6	4007	57.4
- For any procedure (including diagnostic imaging)	838	12.0	2975	42.6
- For neurosurgical procedure	230	3.3	843	12.1
- Reoperation for tumour resection	33	0.5	432	6.2
- No procedure performed	497	7.1	1945	27.8
Total readmissions	1480	100	7848	100
- For any procedure (including diagnostic imaging)	962	65.0	5140	65.5
- For neurosurgical procedure	237	16.0	980	12.5
- Reoperation for tumour resection	33	2.2	448	5.7
- No procedure performed	518	35.0	2708	34.5
Readmitted to neurosurgery	412	27.8	1318	16.8
Readmitted to other specialty	1068	72.2	6530	83.2

Table 1: 30-day and one-year readmission and re-operation rates following resection of malignant primary brain tumours in neurosurgical units in England.

Table1 aw.png

Selection of headache cases for expedited scanning to assist prompt diagnosis of brain tumour

Oral Presentation - Main Stage (7 minutes)

Dr. Robin Grant [1], ***Dr. Karolis Zienius*** [2], ***Mr. Will Hewins*** [3], ***Dr. David Maxwell*** [4], ***Dr. David Summers*** [5], ***Mrs. Lesley McKinlay*** [6], ***Dr. Paul M Brennan*** [7], ***Dr. Lorna Porteous*** [8]

1. *Edinburgh Centre for Neuro-Oncology,* ***2.*** *Research Fellow, Edinburgh Centre for Neuro-Oncology,* ***3.*** *Research Psychologist, Neurosciences, Royal Infirmary of Edinburgh,* ***4.*** *Protocol Based Referral Lead, NHS Lothian,* ***5.*** *Consultant Neuro-Radiologist, Royal Infirmary of Edinburgh,* ***6.*** *Superintendent Neuroradiographer,* ***7.*** *Reader in Neurosurgery, University of Edinburgh,* ***8.*** *GP Lead for Cancer & Palliative Care in Lothian, NHS Lothian*

Aims

Patients with brain tumours and headache commonly have poorer cognitive skills, either overtly or covertly, when cognitively tested. Cognitive changes reflect, tumour mass, fronto-temporal location or hydrocephalus, Previous work has demonstrated that the “semantic Verbal Fluency Test (SVFT) -“How many animals can you think of in a minute?” is a useful fast screening test for cognitive issues. Median SVFT in patients with brain tumour on admission is 10 animals.

Most GPs can now order “direct access cerebral imaging (DACI)” in patients with headache suspicious of cancer. The waiting times for scanning can be many weeks. The aim of this study was to determine whether low SVFT scores: might be useful to help stratify or expedite DACI. We present data from referrals through and electronic Protocol Based Referral (PBR) pathway for CT scanning over 3 years, to determine whether SVFT might be a useful adjunct to history and examination.

Method

From 2017, in Edinburgh/Lothians, Scotland, an electronic PBR was developed with involvement of Primary Care Cancer Lead, PBR lead, Neurology, Neurosurgery and Neuro-Imaging for outpatient imaging of patients in the community with Headache Suspicious of Cancer, to expedite their scans. The PBR sat alongside the routine outpatient DACI system. If the forms were correctly filled in Neuro-Radiology prioritised their appointments. The referrer (GP) was asked to complete the ePBR form and SVFT at the time of referral. Other data were also gathered, including: Past Medical History of cancer; other symptoms/signs; and co-morbid conditions and medications filled automatically from the GP system. This formed the dataset. We also retrospectively assessed a) whether English was first language b) past history of Pain Clinic Attendance or Functional Illness and subsequent final diagnosis of headache/condition, through evaluation of electronic GP referral letters through SCI Gateway system of those cases where SVFT was recorded.

Results

Between March 2017 - November 2019, 669 scans through PBR pathway. (62% females; Mean age 53 years: 60% cases <60 years). SVFT was completed in only 381/669 (57%). Median SVFT was 17. Eleven of 381 cases had cancer (2.9%). 10 cases with cancer had SVFT <17 animals (median 10) (5.32%). One case had SVFT >=17 (35 animals) (0.5%) - CT scan showed small multiple intra-cerebral calcified and non-calcified lesions, consistent with metastases. 12% with PMH cancer had a tumour.

Other possible reasons for low SVFT were: co-existing presumed dementia/mild cognitive impairment (19); non native English speakers (12); headache after traumatic brain injury (5); significant small vessel disease/vascular(5); intracranial cysts (4)(pineal / arachnoid, Giant Cell Arteritis (4) (all new - symptomatic); Chiari 1 malformations (2), PMH – encephalitis (1). Interestingly, there were 53 cases with known psychiatric/pain conditions on drugs (e.g. codeine/antidepressants/antipsychotics) with SVFT < 17 words/min.

Conclusion

People with Headache “Suspicious of Cancer” + SVFT <17 words in a minute are more likely to have a tumour (5.32% vs 0.5%) or other secondary cause for poor cognition.

Other probable causes /associations, with SVFT <17 are age, poor English skills, co-existing dementia. SVFT score may be a useful adjunct or “red flag,” to consider, to expedite DACI scan in patients with “Headache Suspicious of Cancer”. A SVFT >=17 in those with Headache Suspicious of Cancer, does not exclude the possibility of an intracranial tumour. Excluding cases with recognised causes for low SVFT e.g. dementia and those with existing chronic pain/psychiatric disease further increases the likelihood of a secondary cause for headache. SVFT should be tested in the persons native language.

A larger prospective study is required to establish whether these pilot study data and to examine whether chronic pain, functional neurology are negative predictive factors for secondary headache.

Spatiotemporal changes in along-tract profilometry of cerebellar peduncles in cerebellar mutism syndrome

Oral Presentation - Main Stage (7 minutes)

Mr. Sebastian Toescu [1], ***Dr. Lisa Bruckert*** [2], ***Dr. Rashad Jabarkheel*** [2], ***Dr. Derek Yecies*** [3], ***Dr. Gerald Grant*** [2], ***Dr. Kshitij Mankad*** [1], ***Prof. Christopher Clark*** [1], ***Mr. Kristian Aquilina*** [1], ***Prof. Heidi Feldman*** [2], ***Dr. Katie Travis*** [2], ***Dr. Kristen Yeom*** [2]

1. *UCL Great Ormond Street Institute of Child Health,* ***2.*** *Stanford University,* ***3.*** *Stanford*

Aims

Cerebellar mutism syndrome occurs in 25% of children following resection of posterior fossa tumours. Characterised by mutism, emotional lability and cerebellar motor signs, the syndrome is usually reversible over weeks to months. Its pathophysiology remains unclear, but evidence from diffusion MRI studies has implicated damage to the superior cerebellar peduncles in the development of this condition. The objective of this study was to describe the application of automated tractography of the cerebellar peduncles to provide a high-resolution spatiotemporal profile of diffusion MRI changes in cerebellar mutism syndrome.

Method

A retrospective case-control study was performed at Lucille Packard Children's Hospital, Stanford University. Thirty children with midline medulloblastoma (mean age ± standard deviation 8.8 ± 3.8 years) underwent volumetric T1-weighted and diffusion MRI at four timepoints over one year. Forty-nine healthy children (9.0 ± 4.2 years), scanned at a single timepoint, were included as age- and sex-matched controls. Cerebellar mutism syndrome status was determined by contemporaneous casenote review. Automated Fibre Quantification was used to segment each subject's cerebellar peduncles (Figure 1), and fractional anisotropy was computed at 30 nodes along each tract. A non-parametric permutation-based method was used to generate a critical cluster size and p-value for by-node ANOVA group comparisons. Z-scores for patients' fractional anisotropy at each node were calculated based on values from controls' corresponding nodes; these were analysed using mixed ANOVA with post-hoc false discovery rate-corrected pairwise t-tests.

Results

13 patients developed cerebellar mutism syndrome. Automated fibre segmentation successfully identified the cerebellar peduncles in the majority of participants, but was more robust at follow-up timepoints (78.7% vs. 44.7% pre-operatively). Fractional anisotropy was significantly lower in the distal regions of the left superior cerebellar peduncle pre-operatively ($p=0.0137$) in patients compared to controls, although patients could not be distinguished pre-operatively with respect to cerebellar mutism syndrome status (Figure 2). Post-operative reductions in fractional anisotropy in children with cerebellar mutism syndrome were highly specific to the distal left superior cerebellar peduncle, and were most pronounced at follow-up timepoints ($p=0.006$; Figure 3). There were no significant differences in other cerebellar peduncles, either in along-tract fractional anisotropy or Z-scores, with respect to cerebellar mutism syndrome status.

Conclusion

A novel application of an automated tool to extract diffusion MRI data along the length of the cerebellar peduncles is described in a longitudinal retrospective cohort of paediatric medulloblastoma. Changes in fractional anisotropy in the cerebellar peduncles following tumour resection are described in a heretofore unprecedented level of spatiotemporal detail. In particular, children with post-operative cerebellar mutism syndrome show changes in the distal regions of the left superior cerebellar peduncle, and these changes persist up to a year post-operatively. These findings will have direct clinical implications for neurosurgeons performing resection

of midline paediatric posterior fossa tumours.

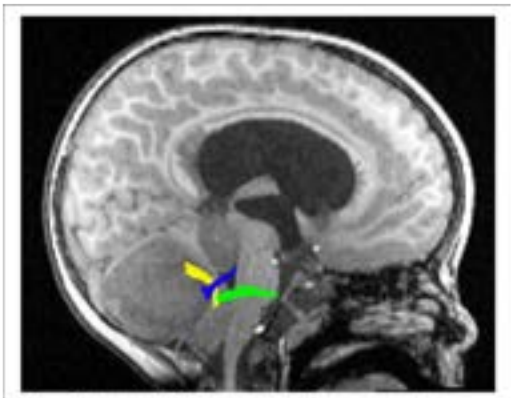


Figure 1. Example of AFQ-segmented tracts in a representative subject with a medulloblastoma. Blue; superior cerebellar peduncle; yellow, inferior cerebellar peduncle; green, middle cerebellar peduncle.

Fig1bnos.png

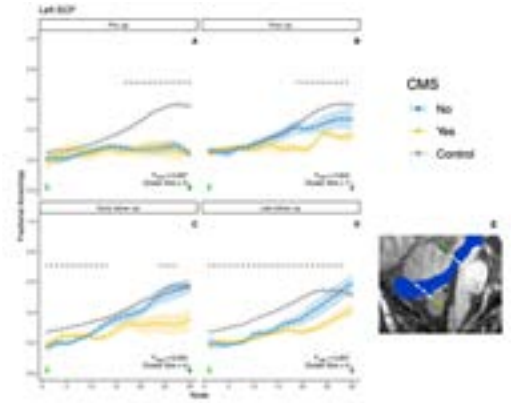


Figure 2. Longitudinal along-tract profilometry results for the left superior cerebellar peduncle in patients and controls. **A**, pre-operative; **B**, post-operative; **C**, early follow-up; **D**, late follow-up. Coloured points indicate group mean at each node; ribbon indicates standard error of the mean per group. * indicates by-node ANOVA p-value (p_{node}) lower than the p_{FDR}, calculated by non-parametric permutation method, at that individual node; * indicates $p_{node} < p_{FDR}$ at more than λ adjacent nodes, where λ is the cluster size for a given tract and timepoint. Cluster size and p_{FDR} indicated for each tract and timepoint. **E**, representative example of a segmented left SCP in a post-operative scan. Coloured green arrows in E correspond to node number on plots.

Fig2bnos.png

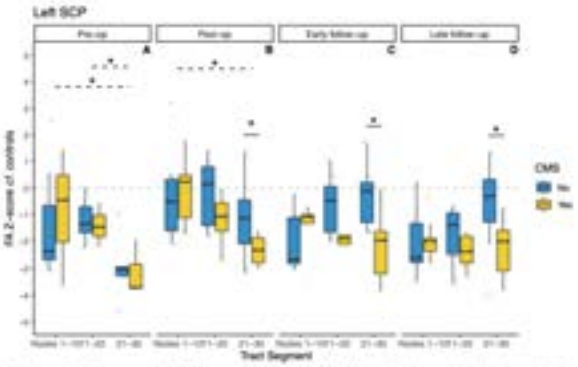


Figure 3. Z-score of FA for patients with CMS (yellow) and without (blue), compared to controls, within tract segments (proximal / middle / distal thirds) of the left superior cerebellar peduncle. **A**, pre-operative; **B**, post-operative; **C**, early follow-up; **D**, late follow-up. Grey dotted line indicates $z = 0$. False discovery rate adjusted p values: °, p<0.01; *, p<0.05. Solid lines indicate *post-hoc* pairwise significance tests between CMS groups within tract segments; dotted lines indicate *post-hoc* pairwise significance tests between tract segments.

Fig3bnos.png

Stereotactic radiosurgery combined with immune checkpoint inhibition for the treatment of melanoma brain metastases is associated with high levels of extracranial disease control and survivorship - an abscopal effect?

Oral Presentation - Main Stage (7 minutes)

Dr. Philip Webb [1], ***Mr. Mark Zorman*** [1], ***Mrs. Rhona Watson*** [1], ***Mrs. Gemma Austin*** [1], ***Ms. Carol Thurgood*** [1], ***Dr. Nick Coupe*** [1], ***Dr. Miranda Payne*** [1], ***Dr. Claire Hobbs*** [1]

1. *Oxford University Hospitals NHS Foundation Trust*

Aims

Melanoma brain metastases (MBM) are a common presentation to the neuro-oncology MDT. Stereotactic radiosurgery (SRS) is a highly effective treatment for cerebral metastases, with at least 70% control rates of individual metastases,[1] whilst immune checkpoint blockade has revolutionised the management of metastatic melanoma in recent years.[2] Recent studies have demonstrated that immune checkpoint inhibition alone also has activity in the brain, with MBM response rates of 50% or more.[3, 4] When MBM are treated with combination immunotherapy and SRS together, 12-month intracranial progression free survival (PFS) rates of 85% have been achieved.[4, 5] The aim of the current study was to evaluate the local control of MBM treated at our tertiary referral centre, which benefits from specialist neuro-radiology peer review of SRS contour volumes, and further to investigate whether overall survival is also improved, and what the mechanism of this may be.

Method

A retrospective analysis of all patients treated with SRS for brain metastases at our teriary SRS centre between June 2017 – January 2020 was performed. Inclusion criteria included patients treated for MBM, who received at least 2 doses of any combination of immune checkpoint inhibition concurrently with (defined as at the time of or commenced within 3 months of) SRS. The primary endpoints were the intracranial and extracranial response rates and survival rate at 12 months. Response was defined as complete response, partial response or stable disease. Secondary endpoints included the rate of imaging-defined radionecrosis, median lesional progression free survival ($mPFS_{lesion}$), non-lesional intracranial PFS ($mPFS_{intracranial}$), extracranial PFS ($mPFS_{extracranial}$) and overall survival (mOS), measured from the start date of SRS to the date of event or censored at the start date of data collection. Kaplan-Meier curves and survival statistics were generated using SPSS v26.

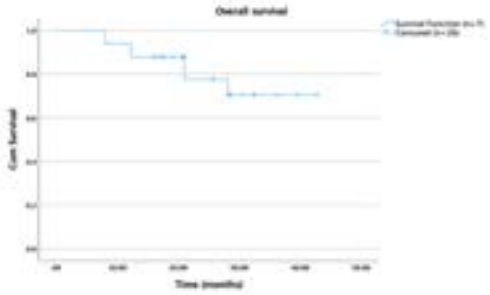
Results

33 MBM from 18 patients were identified. The median follow up was 25.8 months (minimum 12 months). Of the 18 patients: the median age was 60 (IQR 48 – 72); 17 (94%) patients were ECOG performance status 0-1; the median number of extracranial disease sites was 2 (pre-immunotherapy) and 1 (pre-SRS); the median duration of immunotherapy treatment was 17.6 (12.9 – 28.5) months, and the median number of metastases treated per patient was 2. Of the 33 metastases: 31 (94%) were supratentorial; 6 (18%) underwent prior neurosurgical resection; the median GTV volume (cc) of unresected metastases was 0.5cc (0.1 – 2.7), and 21 (64%) were treated with single fraction SRS. The median OS and PFS for all subtypes were not reached. The rates of OS, PFS_{lesion}, $PFS_{intracranial}$ and $PFS_{extracranial}$ at 12 months were 93.9%, 87.9%, 81.8% & 75.8% respectively.

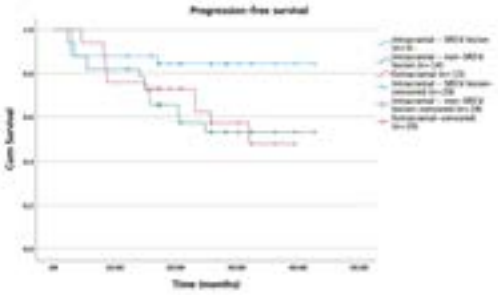
Conclusion

Our cohort of MBM patients appear to perform favourably when compared with the current literature. When compared to a recent extensive systematic review of modern management of MBM, our lesional control rate is as good as the weighted average of concurrent SRS + immunotherapy studies (87.9% vs 85.4% 12-month PFS),

however we demonstrate a significantly improved 12-month OS rate (93.9% vs 52.8%) compared to the same (mOS of 15.8 – 17.4 months in other studies).[6,7] Our extra-lesional PFS is high and, compared to extracranial PFS rates from 51% at 6-months to 70.4% at 9-months in the literature,[3,4] our 75.8% control at 12 months suggests that extracranial control could drive the OS benefit. This suggests a benefit of SRS beyond the local control of MBM and questions whether patients without brain metastases may benefit from body SABR to extracranial metastases, to elicit a similar, potentially abscopal type effect.



Os curve.png



Pfs curves.png

Survival Outcomes following LINAC based Stereotactic Radiosurgery/Stereotactic Radiotherapy (SRST) treatment of brain metastases: The Wessex Experience.

Oral Presentation - Main Stage (7 minutes)

Dr. Mark Noble [1], ***Dr. Jeng Ching*** [1], ***Dr. Enrico Clarke*** [1]

1. *University Hospital Southampton NHS Foundation Trust*

Aims

Since 2016, the University Hospital Southampton NHS Foundation Trust (UHSFT) has been commissioned by NHS England to deliver SRST to brain metastases. At UHSFT, all referrals are discussed at the Wessex Neurosciences multidisciplinary team meeting. Referrals that satisfy the criteria set by NHS England (estimated prognosis greater than 6 months, absence or controlled extracranial disease or potentially controllable extracranial disease with a Karnofsky Performance Status >70%) will be offered SRST. This retrospective study was performed to assess overall survival rates of patients with brain metastases treated with SRST with further tumour subtype analysis. We also benchmarked our results with other SRST centres.

Method

Retrospective data collection was performed for all the patients who have been treated with SRST. Patients who received SRST to a single metastasis, multiple metastases and/or to the resection cavity between 01/01/2017 to 30/09/2019 were included in this study. All treatment was delivered using a LINAC based SRST platform. Prescription doses ranged from 13.5 Gy to 21 Gy in a single fraction, 21 to 24 Gy in 3 fractions and 25 Gy in 5 fractions. Patients are treated using a stereotactic thermoplastic immobilisation shell and dynamic conformal arc therapy with ExacTrac ™ and Cone Beam CT imaging. Dates of death were obtained from the NHS Digital Spine and survival analysis using median overall survival was performed using the Kaplan Meier Method.

Results

277 patients were treated between 01/01/17 and 30/9/2019. The median overall survival from the Kaplan Meier Method was shown to be 14.7 months and the 6-month overall survival was 71% for all patients.
Sub-group analysis of individual tumour sites showed: lung (n=110) median OS 12.1 months, melanoma (n=58) median OS 26.4 months, breast (n=46) median OS not reached (67% still alive) but 18 months survival was 70%, renal (n=22) median OS 15.4 months and colorectal (n=19) median OS 6 months. “Other” tumour sites (n=22) included patients with ovarian, neuroendocrine, sarcoma, testis, oesophagus, unknown primary and gallbladder which were grouped together due to small patient numbers. 41% of patients treated were alive at the time of analysis.

Conclusion

Patients with brain metastases treated with SRST at UHFST have similar outcomes compared to other SRST centres. These patients have a median overall survival of 14.7 months. However, 29% of patients analysed did not survive more than 6 months. Further collection and analysis of the data might improve patient selection and their outcomes.

The role of brain biopsy in the diagnosis of CNS lymphoma

Oral Presentation - Main Stage (7 minutes)

Ms. JOY ROACH [1], ***Dr. Mark Fabian*** [1], ***Mr. Paul Grundy*** [1]

1. *University Hospital Southampton NHS Foundation Trust*

Aims

Primary CNS lymphoma is the third most common primary CNS tumour after glioblastoma and diffuse astrocytoma with high grade diffuse large B cell being the most common subtype. Without treatment the median survival is 1.5-3.3 months and with treatment this improves to 10-20 months. Tissue biopsy remains the gold standard investigation for the diagnosis of CNS lymphoma and as neurosurgeons we are frequently asked to biopsy lesions suspicious for lymphoma to confirm the diagnosis. Although brain biopsy carries a relatively low risk with a complication rate of 1-2% cerebral lymphoma lesions have a higher propensity to bleed. In patients with a history of lymphoma (either CNS or systemic) where radiological features concur with CNS lymphoma we aim to investigate whether radiological diagnosis alone would be sufficient in diagnosis, in order to reduce the need for a brain biopsy.

Method

A retrospective review of the case notes, imaging, neuro-oncology MDT discussions and histological reports for all adult patients who underwent a brain biopsy over a five-year period between January 2015 and January 2020 was performed. This identified a total of 478 biopsies performed over the five-year period and of these 458 cases were discussed in the neuro-oncology MDT. The most likely and differential diagnosis based on imaging was recorded for each case along with the final integrated diagnosis from histological analysis of biopsy samples.

Results

Of the 458 patients discussed in the MDT, a differential diagnosis of CNS lymphoma based on radiological features was recorded in 127 cases and confirmed on histological examination in 65 cases. CNS lymphoma was recorded as the most likely diagnosis based on radiological features in 54 cases and confirmed in 45 cases. A past history of lymphoma was identified in 11 biopsy patients. The latency between initial lymphoma diagnosis and a cerebral lesion appearing ranged from 7 months to 29 years. The 11 patients with a history of lymphoma were reviewed in the MDT and imaging features were consistent with recurrence in 7 cases. The diagnosis of lymphoma recurrence was confirmed in 6 out of 7 cases (86%). There will have been a number of patients with a history of lymphoma that did not have a biopsy as the diagnosis was clear cut but we are unable to quantify this.

Conclusion

The treatment for lymphoma depends on the performance status of the patient varying from whole brain radiotherapy with oral temozolomide for those with a poor performance status to MATRix treatment in patients with a good performance status. Treatment-related mortality with MATRix therapy is 4-7% and understandably there is a reluctance to treat suspected lymphoma recurrence even in patients with a known history of lymphoma. However, our experience over the last five years demonstrates that in patients with a history of lymphoma where the imaging findings and MDT discussion were all consistent with a recurrence of lymphoma we found that in nearly all our cases (6 out of 7) this diagnosis was confirmed with histological analysis exposing the patients to an invasive and potentially unnecessary procedure.

The role of diffusion tensor imaging metrics in machine learning-based characterisation of paediatric brain tumors and their practicality for multicentre clinical assessment

Oral Presentation - Main Stage (7 minutes)

Dr. Heather Rose [1], ***Dr. Huijun Li*** [2], ***Dr. Christopher D Bennett*** [3], ***Dr. Jan Novak*** [4], ***Dr. Yu Sun*** [5], ***Dr. Lesley MacPherson*** [6], ***Dr. Shivaram Avula*** [7], ***Prof. Theodoros Arvanitis*** [8], ***Prof. Christopher Clark*** [9], ***Prof. Simon Bailey*** [10], ***Dr. Dipayan Mitra*** [11], ***Prof. Dorothee Auer*** [12], ***Prof. Richard Grundy*** [13], ***Prof. Andrew Peet*** [14]

1. *Institute of Cancer and Genomic sciences, The University of Birmingham, Birmingham,* ***2.*** *Birmingham Children's Hospital, Birmingham, Children's Hospital of Nanjing Medical University, Nanjing,* ***3.*** *Institute of Cancer and Genomic sciences, The University of Birmingham,* ***4.*** *Birmingham Children's Hospital, Birmingham, United Kingdom, School of Life and Health Sciences, Aston University,* ***5.*** *The University of Birmingham, Birmingham, Birmingham Children's Hospital, Birmingham,* ***6.*** *Radiology, Birmingham Women's and Children's Hospital,* ***7.*** *Radiology, Alder Hey Children's NHS Foundation Trust,* ***8.*** *Institute of Digital Healthcare, WMG, University of Warwick,* ***9.*** *UCL Great Ormond Street Institute of Child Health,* ***10.*** *Sir James Spence Institute of Child Health, Royal Victoria Infirmary,* ***11.*** *Neuroradiology Department, Newcastle upon Tyne Hospitals, Newcastle upon Tyne,* ***12.*** *Sir Peter Mansfield Imaging Centre, University of Nottingham,* ***13.*** *The Children's Brain Tumour Research Centre, University of Nottingham,* ***14.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Magnetic resonance imaging (MRI) is a valuable tool for non-invasive diagnosis of paediatric brain tumours. The rarity of the disease dictates multi-centre studies and imaging biomarkers that are robust to protocol variability. We investigated diffusion tensor MRI (DT-MRI), combined with machine learning, as an aid to diagnosis and evaluated the robustness of the imaging metrics.

Method

A multi-centre cohort of 52 clinical DT-MRI scans (20 medulloblastomas (MB), 21 pilocytic astrocytomas (PA), 11 ependymomas (EP)) were analysed retrospectively. Histograms for regions of solid tumour for fractional anisotropy (FA), mean diffusivity (MD), pure anisotropic diffusion (q) and pure isotropic diffusion (p) were compared to assess diagnostic capability. Linear discriminate analysis (LDA) was used for classification and validated using leave-one-out-cross-validation (LOOCV).

Results

Histogram medians for FA, MD, q and p were all different between tumor groups (P<.0001, Kruskal Wallis test). Median MD, p and q values were highest in PA, then EP and lowest in MB (P<.0001, Pairwise Wilcox test). FA median was higher for EP than PA (P=.004) with no significant difference between EP and MB (P=.591). ROC analysis showed that median MD, q and p perform best as a diagnostic marker (AUC= 0.92 to 0.99). LOOCV showed an overall accuracy of the LDA classification, ranging between 67% - 87%. FA values were highly dependent on protocol parameters, whereas pure anisotropic diffusion, q, was not.

Conclusion

DT-MRI metrics from multi-centre acquisitions can classify paediatric brain tumours. FA is the least robust metric to protocol variability and q provides the most robust quantification of anisotropic behaviour.

The use of cannabinoid and non-cannabinoid supplementary therapies in patients undergoing treatment for Glioblastoma reveals an urgent need for guidance

Oral Presentation - Main Stage (7 minutes)

Mr. Babar Vaqas [1], ***Dr. Louise Dulley*** [1], ***Dr. Ruchi Maniar*** [2]

1. *Queens Hospital, Romford,* ***2.*** *Kettering General Hospitals NHS Foundation Trust*

Aims

Glioblastoma (GBM) is currently an incurable malignancy with a very poor prognosis for the majority of patients. Many patients undergo debulking surgery, radiotherapy and chemotherapy however therapeutic options are limited, and this can lead to patients sourcing their own treatments. There is some evidence that cannabinoids have the effect of inhibiting GBM tumour growth through a variety of pathways, some of which include CB2 cannabinoid receptor pathway activation. We undertook a patient questionnaire to understand what alternative therapies patients are accessing and why, with a focus on cannabinoid use.

Method

We undertook a prospective observational questionnaire based qualitative study of 50 … consecutive patients undergoing treatment for glioblastoma at our centre.

Results

43 patients responded to our questionnaire. 33% of patients were taking some kind of supplementary therapy with 25% taking cannabis derivatives, mainly CBD oil. There were no clear discriminators amongst our cohort including age or sex when considering the likelihood of taking cannabis derivatives. 6 out of 11 (55%) patients taking cannabis derivatives reported some positive effects with improved sleep and general wellbeing being most commonly reported. Patients reported spending between £10-£300 per month with an average of £42 per month. Cannabis products were obtained via the internet or from friends.

Conclusion

This small cohort of patients indicates that a significant proportion of glioblastoma patients investigate and use alternative therapies, in particular cannabis oil. NICE guidance for clinicians simply notes there is insufficient evidence to support the use of cannabis oil in the treatment of this disease. Given the publicity and interest in the utility of cannabis oil to treat cancers this leaves patients to research the use of these agents without access to robust clinical data to guide their use or indeed to conclude they are not beneficial. The accessing of these compounds, potentially by a sizeable number of patients, leaves them vulnerable to unregulated perhaps unscrupulous drug sources. This small study has further highlighted the unmet need for information and guidance on supplementary treatments for glioma patients and this poses a challenge to all those treating this group of patients to answer a question our patients are clearly wanting answered.

Oral Presentation - Video on demand (5 minutes)

Brain tumour related epilepsy with co-existing non epileptic attacks: Characteristics of a clinically challenging cohort

Oral Presentation - Video on demand (5 minutes)

Dr. Shanika Samarasekera [1], ***Dr. Di Liang*** [2]

1. *Queen Elizabeth Hospital, Birmingham,* ***2.*** *Queen Elizabeth Hospital Birmingham*

Aims

The co-existence of non-epileptic attacks (NEAD) in patients with brain tumour related epilepsy (BTRE) is poorly described. Non epileptic attacks (NEAD) co-occur in up to 30% of patients with epilepsy PWE. Adverse life events are associated with development of NEAD; their co-occurrence in those with BTRE is potentially un-surprising . We sought to characterise the evolution of symptoms in this cohort.

Method

Clinical trajectories of patients with BTRE and co-existing NEAD were characterised. The diagnosis of NEAD was based on the epilepsy specialist's observation of attacks and /or capture of attacks on video. Some patients had additional video EEG correlate.

Patients had been referred because of persisting symptoms in spite of escalating antiepileptic therapy.

Results

Of eight patients, six were initially misdiagnosed with escalating seizures. One patient developed NEAD de novo following tumour biopsy, the remaining patients developed NEAD following onset of BTRE. Onset of NEAD was not temporally linked with the diagnosis of a brain tumour. In five patients, NEAD onset occurred when seizures were controlled (< 1 seizure/ month). All patients reported fear of developing uncontrolled seizures as being associated with their symptoms and identified their NEAD as more disabling than their epilepsy.

Patients were eventually managed with polytherapy -two found adjunctive clobazam helpful and four were offered antidepressant/ anxiolytic medication. Behavourial strategies including mindfulness were also discussed. At time of last follow up, seven patients had on-going NEAD symptoms in spite of good seizure control.

Conclusion

NEAD can co-occur with BTRE and should be considered in those with rapidly escalating symptoms in spite of antiepileptic therapy and radiologically stable lesions. Both making the diagnosis of NEAD and providing ongoing support is challenging. These patients require a multidisciplinary approach with support from allied specialties including neuropsychiatry and neuropsychology.

BrainWear: Longitudinal, objective assessment of physical activity in 42 High Grade Glioma (HGG) patients

Oral Presentation - Video on demand (5 minutes)

Dr. Seema Dadhania [1], ***Ms. Lillie Pakzad-Shahabi*** [2], ***Ms. Kerlann Le Calvez*** [1], ***Dr. Waqar Saleem*** [3], ***Dr. James Wang*** [1], ***Dr. Waleed Mohammed*** [3], ***Mr. Sanjay Mistry*** [4], ***Dr. Matthew Williams*** [1]

1. *Computational Oncology Laboratory, Institute of Global Health Innovation, Imperial College London,* ***2.*** *John Fulcher Neuro-Oncology Laboratory, Brain Tumour Research Centre of Excellence, Imperial College London,* ***3.*** *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust,* ***4.*** *Imperial College NHS Trust*

Aims

In patients with HGG, we know that QoL and physical function decline with progressive disease (PD) and fatigue is a strong predictor of survival in recurrent disease. Despite notable technical advances in therapy for in the past decade, survival has not improved. The role of physical function as a predictor of QoL, treatment tolerance and as an early indicator of worsening morbidity (e.g. tumour recurrence) is an area of growing importance. Recent advancements in wearable technology allow us the opportunity to gather high-quality, continuous and objective data BrainWear is a feasibility study collecting longitudinal physical activity (PA) data from patients with primary and secondary brain tumours and we hypothesise changes in PA over time, are a potentially sensitive biomarker for PD both at diagnosis and relapse.

Method

Here we show early analysis of this novel dataset of 42 HGG patients and will present:

1) feasibility and acceptability

2) how digitally captured PA changes through treatment and at PD/hospitalisation

3) the correlation between patient reported outcomes (PRO) and PA data

4) how PA in HGG patients compares with healthy UK Biobank participants

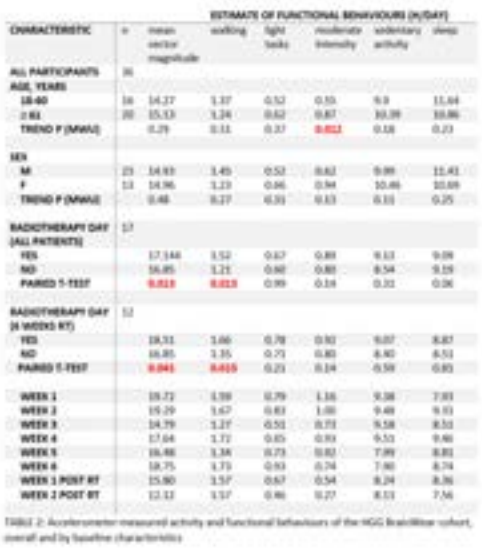
PA data is collected via a wrist-worn accelerometer. Raw accelerometer data is processed using the UK Biobank Accelerometer Analysis pipeline in python 3.7, and evaluated for good quality wear-time. Overall activity is represented as vector magnitude in milligravity units(mg) and a machine-learning classifier classifies daily activity into 5 separate groups (walking, tasks-light, moderate, sedentary and sleep). Descriptive statistics summarise baseline characteristics and unadjusted mean used to present vector magnitude and accelerometer-predicted functional behaviours (in h/day) by age, sex, radiotherapy and weekend days. Mixed effect models for repeated measures are used for longitudinal data evaluation of PA.

Results

Between October 2018 and March 2021, 42 patients with a suspected HGG were recruited; 16 females and 26 males with a median age of 59. 40 patients had surgery and 35 patients had adjuvant primary radiotherapy, 23 of whom had a 6-week course. They have provided 3458 days of accelerometer data, 80% of which has been classified as good quality wear-time. There are no statistical differences in mean activity between gender, patients >60 years show statistical difference in time spent doing moderate activity compared to those <60 years, and there are significant differences in mean vector magnitude and walking between radiotherapy and non-radiotherapy days. In patients having a 6-week RT course, time spent in daily moderate activity falls 4-fold between week 1 and the second week following RT completion (70 minutes to 16 minutes). HGG versus healthy UK Biobank participants shows significant differences in all measures of PA.

Conclusion

Here we present preliminary analysis of this highly novel dataset in adult high grade glioma patients, and show digital remote health monitoring is feasible and acceptable with 80% of data classified as high quality wear-time suggesting good patient adherence. We are able to objectively describe how PA changes through standard treatments and understand the inter and intra-patient variation in PA, and whether there are correlates with patient-centred measures, clinical measures and early indicators of worsening disease. We will present further data on changes in PA prior to hospitalisation and at disease progression, and discuss some of the challenges of running a digital health trial. The passive and objective nature of wearable activity monitors gives clinicians the opportunity to evaluate and monitor the patient in motion, rather than the episodic snapshot we currently see, and in turn has the potential to improve our clinical decision making and potentially outcomes.



		ESTIMATE OF FUNCTIONAL BEHAVIOURS (H/DAY)					
CHARACTERISTIC	n	mean vector magnitude	walking	light tasks	moderate intensity	sedentary activity	sleep
ALL PARTICIPANTS	36						
AGE, YEARS							
18-60	16	14.27	1.37	0.52	0.55	9.9	11.64
≥ 61	20	15.13	1.24	0.62	0.87	10.39	10.86
TREND P (MWU)		0.29	0.11	0.37	0.012	0.18	0.23
SEX							
M	23	14.93	1.45	0.52	0.62	9.99	11.41
F	13	14.96	1.23	0.66	0.94	10.46	10.69
TREND P (MWU)		0.48	0.27	0.31	0.13	0.11	0.25
RADIOTHERAPY DAY (ALL PATIENTS)	17						
YES		17.144	1.52	0.67	0.89	9.13	9.09
NO		16.85	1.21	0.60	0.80	8.54	9.19
PAIRED T-TEST		0.013	0.013	0.99	0.19	0.33	0.06
RADIOTHERAPY DAY (4 WEEKS RT)	12						
YES		18.51	1.66	0.78	0.92	9.07	8.87
NO		16.85	1.35	0.71	0.80	8.40	8.51
PAIRED T-TEST		0.041	0.015	0.23	0.14	0.59	0.83
WEEK 1		19.72	1.59	0.79	1.16	9.38	7.93
WEEK 2		19.29	1.67	0.83	1.00	9.48	9.33
WEEK 3		14.79	1.27	0.51	0.73	9.58	8.53
WEEK 4		17.64	1.72	0.65	0.93	9.53	9.46
WEEK 5		16.46	1.34	0.73	0.82	7.99	8.81
WEEK 6		18.75	1.73	0.93	0.74	7.90	8.74
WEEK 1 POST RT		15.90	1.57	0.67	0.54	8.24	8.36
WEEK 2 POST RT		12.12	1.57	0.46	0.27	8.13	7.56

TABLE 2: Accelerometer measured activity and functional behaviours of the NGG BrainWear cohort, overall and by baseline characteristics

Table2.png

Brainwear.png

Differential cerebrovascular risks in glioblastoma and meningioma patients: a population-based matched cohort study in Wales (United Kingdom)

Oral Presentation - Video on demand (5 minutes)

Mr. Michael TC Poon [1], ***Dr. Kai Jin*** [1], ***Dr. Paul M Brennan*** [1], ***Dr. Jonine Figueroa*** [1], ***Prof. Cathie Sudlow*** [1]

1. *University of Edinburgh*

Aims

There is limited evidence on cerebrovascular risks in glioblastoma and meningioma patients. We aimed to compare cerebrovascular risks of these patients with the general population.

Method

We used population-based routine healthcare and administrative data linkage in this matched cohort study. Cases were adult glioblastoma and meningioma patients diagnosed in Wales 2000-2014 identified in the cancer registry. Controls from cancer-free general population were matched to cases (5:1 ratio) on age (±5 years), sex and GP practice. Factors included in multivariable models were age, sex, index of multiple deprivation, hypertension, diabetes, high cholesterol, history of cardiovascular disease, and medications for cardiovascular diseases. Outcomes were fatal and non-fatal haemorrhagic and ischaemic stroke. We used flexible parametric models adjusting for confounders to calculate the hazard ratios (HR).

Results

Final analytic population was 16,921 participants, of which 1,340 had glioblastoma and 1,498 had meningioma. The median follow-up time was 0.5 year for glioblastoma patients, 4.9 years for meningioma patients, and 6.6 years for controls. The number of haemorrhage and ischaemic stroke was 154 and 374 in the glioblastoma matched cohort, respectively, and 180 and 569 in the meningioma matched cohort, respectively. The adjusted HRs for haemorrhagic and ischaemic stroke were 3.74 (95%CI 1.87-6.57) and 5.62 (95%CI 2.56-10.42) in glioblastoma patients, respectively, and were 2.42 (95%CI 1.58-3.52) and 1.86 (95%CI 1.54-2.23) in meningioma patients compared with their controls.

Conclusion

Glioblastoma and meningioma patients had higher cerebrovascular risks; these risks were even higher for glioblastoma patients. Further assessment of these potentially modifiable risks may improve survivorship.

Evaluating the impact of a joint Clinical Nurse Specialist and Allied Health Care Professional clinic for neuro-oncology patients attending Velindre Cancer Centre, Cardiff

Oral Presentation - Video on demand (5 minutes)

Ms. Rachel Evans [1], ***Mrs. Rhian Burke*** [1], ***Ms. Cathryn Lewis*** [1], ***Mrs. Helena Goode*** [1], ***Ms. Sarah Ellam*** [1], ***Mrs. Amy Gee*** [1], ***Mrs. Deborah Mullan*** [1], ***Ms. Rehana Begum*** [1], ***Dr. James Powell*** [1], ***Dr. Jillian MacLean*** [1], ***Dr. Najmus Iqbal*** [1], ***Dr. Owen Tilsley*** [1], ***Mrs. Lisa Love-Gould*** [1], ***Mrs. Kate Baker*** [1]

1. *Velindre Cancer Centre*

Aims

Key governing guidelines recognise that the holistic and complex needs of neuro-oncology patients are best served by a cohesive multidisciplinary team (MDT). Achieving a joint Clinical Nurse Specialist (CNS) and Allied Healthcare Professional (AHP) clinic (including Speech and Language Therapy, Physiotherapy, Dietetics and Occupational Therapy) for neuro-oncology patients has been a longstanding vision at Velindre Cancer Centre (VCC) in Cardiff. A successful funding application to Welsh Government in July 2020 allowed the establishment of a virtual “one stop shop” clinic with CNS and AHPs available along the care trajectory to improve patient and carer quality of life. The project reports on whether this innovative clinic model successfully achieved the desired coordinated, anticipatory and holistic care.

Method

The project utilised service improvement methodology principles with aims inherent within quarterly time-frames. This included robust data collection on patient attendances and interventions, improving patient education and self-management and wide patient, care and staff engagement by means of questionnaires and semi-structured interviews. The mixed methods approach yielded rich quantitative and qualitative data.

Results

The data demonstrates an increasing demand for the joint neuro-oncology clinic indicating that additional resources may be required. From triangulation of patient, carer and wider team engagement the key benefits were perceived to be having accessibility to the team in a convenient way, the provision of support and timely information and the overall perception of enhanced holistic care.

Conclusion

The data demonstrates the huge successes of the joint neuro-oncology clinic so far, including improvements to patient and carer quality of life, wider VCC benefits and cost saves. The persuasive case was presented to Welsh Government, and ongoing endorsement has been achieved for the next financial year.

Functional neurological disorders in patients with brain tumours.

Oral Presentation - Video on demand (5 minutes)

Dr. Charmaine Toh [1], ***Dr. Dorothy Joe*** [2], ***Dr. Katia Cikurel*** [2], ***Ms. Julia Johnson*** [3], ***Mr. Francesco Vergani*** [4], ***Mr. Jose-Pedro Lavrador*** [4], ***Mr. Ranjeev Bhangoo*** [4], ***Prof. Keyoumars Ashkan*** [4], ***Dr. Paul Shotbolt*** [5], ***Dr. Najma Khan-Bourne*** [6], ***Dr. Gerald Finnerty*** [7]

1. *Department of Basic and Clinical Neuroscience, King's College London, London,* ***2.*** *Department of Neurology, King's College Hospital NHS Foundation Trust, London,* ***3.*** *Speech and Language Therapy, King's College Hospital NHS Foundation Trust, London,* ***4.*** *Department of Neurosurgery, King's College Hospital NHS Foundation Trust, London,* ***5.*** *Department of Neuropsychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London,* ***6.*** *Department of Neuropsychology, King's College Hospital NHS Foundation Trust, London,* ***7.*** *Department of Basic and Clinical Neuroscience, King's College London, London; Department of Neurology, King's College Hospital NHS Foundation Trust, London*

Aims

Signs and symptoms that develop in people with brain tumours are often attributed to their tumour. The prevalence and management of functional neurological symptoms in brain tumour patients have received little attention. This is surprising because functional neurological symptoms complicate management greatly and misdiagnosis can lead to inappropriate treatment and iatrogenic side-effects. Therefore, we investigated the presentation, diagnosis and management of functional neurological disorders (FND) in patients who had a brain or meningeal tumour.

Method

A retrospective case review was performed from 2017 - 2021 to identify adult brain tumour patients who developed a functional neurological disorder that caused significant disability necessitating expedited investigations. All patients attended a regional neuro-oncology centre. We recorded type of brain tumour and diagnostic investigations. The onset of functional symptoms was divided into three time windows: before tumour diagnosis, after diagnosis and before treatment or after tumour treatment. A neuropsychological review looked for evidence of previous adverse life events. Therapeutic interventions for functional neurological disorder and their outcomes were documented. The case review was combined with a systematic review of the literature to identify the published presentations of functional neurological disorder in the adult brain tumour population. MEDLINE, EMBASE and PsycINFO databases were searched for studies published between January 1980 and February 2021.

Results

Six patients (5 female, 1 male) were identified from the case review with a median age of 41 (range 29 - 56) years old. Four patients had non-epileptic attack disorder, which was diagnosed with videotelemetry of habitual attacks. One patient had a functional hemiparesis with normal central motor conduction time. One patient had a functional speech disorder with normal EEG. Half of these patients had functional neurological symptoms prior to surgery/oncological treatment. Five patients (83%) were referred for further neuropsychiatric or psychological evaluation. A history of significant psychological trauma prior to the brain tumour diagnosis was elicited in four (66%) patients.

Conclusion

Patients with either a brain or meningeal tumour may develop functional neurological symptoms. Our findings suggest the possibility that diagnosis of a brain tumour may precipitate a debilitating functional neurological dis-

order. The neurobiological basis for functional neurological disorders is being actively investigated. There are suggestions in the literature that some brain diseases increase the risk of developing a functional neurological disorder. Further work is needed to determine whether this is true for patients with brain tumours. Increased awareness of functional neurological disorders will improve management. Withdrawal of unnecessary treatment, such as anticonvulsant drugs, reduces the risk of iatrogenic side effects. Initiation of multi-disciplinary care pathways, e.g. physiotherapy, speech and language therapy and psychological treatments, promotes recovery. Collectively, these interventions improve our patients' quality of life.

Raised cardiovascular disease mortality after central nervous system tumour diagnosis Analysis of 171,926 from UK and USA

Oral Presentation - Video on demand (5 minutes)

Dr. Kai Jin [1], ***Dr. Paul M Brennan*** [1], ***Mr. Michael TC Poon*** [1], ***Prof. Cathie Suldow**** [1], ***Dr. Jonine Figueroa*** [1]

1. *University of Edinburgh*

Aims

Whether patients with malignant central nervous system (CNS) tumours may be at risk of dying from cardiovascular disease (CVD) is unknown. We examined CVD mortality risk in malignant CNS tumours patients compared to the general population in the US and UK.

Method

Data from 56,731 malignant CNS tumours were analysed from SAIL Wales, UK (N=3,624) diagnosed 2000-2015; and the US-based cancer registry (SEER, N=53,107) diagnosed 2005-2015. Age-, sex-, and calendar-year- adjusted standardised mortality ratios (SMRs) were calculated for CVD comparing CNS tumour patients with the general population. Hazard ratios were calculated using Cox regression models to identify factors associated with CVD mortality.

Results

CVD was the most common non-cancer cause of death for malignant CNS tumour patients in SAIL (UK) and SEER (US). The leading types of CVD death were heart (SAIL 56%, SEER 65%) and cerebrovascular (SAIL 40%, SEER 29%) diseases. Malignant CNS tumours patients had over 2-fold higher CVD mortality than the general population (SAIL SMR=2.14, 95% CI=1.61-2.79, SEER SMR=2.21, 95% CI=2.06-2.36) with substantially greater risk in younger adult patients (< 50 years) and within the first year after their cancer diagnosis. Cerebrovascular disease has greater mortality risk (SAIL SMR=6.55, 95% CI 4.15-9.83, SEER SMR=3.60, 95% CI 3.14-4.11) than that of heart disease (SAIL SMR=1.88, SEER SMR=1.94) compared to the general population. Age, sex, race/ethnicity in USA, and no surgery were associated with CVD mortality.

Conclusion

Patients with malignant CNS tumours had higher risk for CVD mortality supporting further research to improve mortality outcomes.

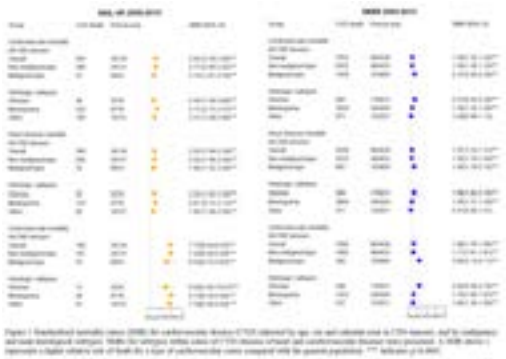


Figure 1 smr overall.jpg

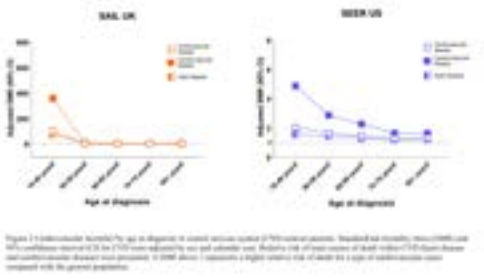


Figure 2 smr by age.jpg

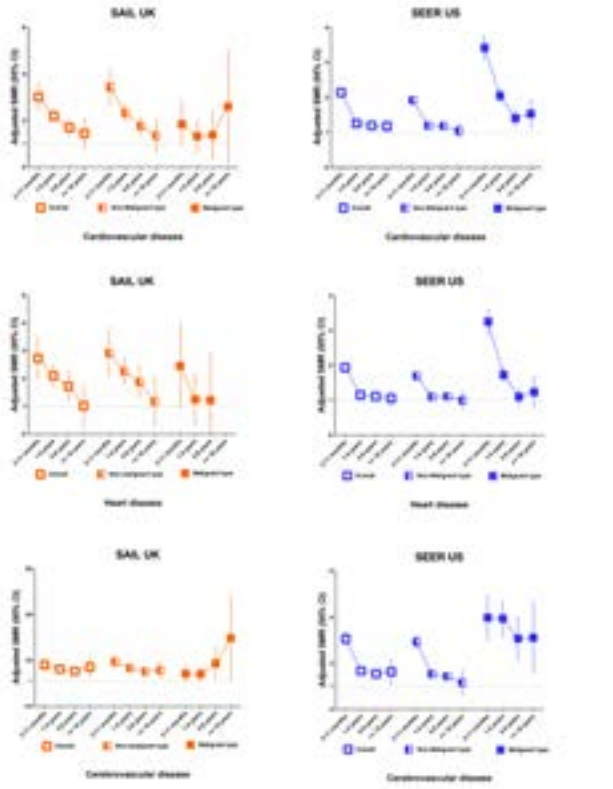


Figure 3 Cardiovascular mortality by follow up after cancer diagnosis. Standardized mortality ratios(SMRs) for cardiovascular disease adjusted by age, sex and calendar year in overall CNS tumours and by malignancy. SMRs for heart disease and cerebrovascular disease were presented. A SMR above 1 represents a higher relative risk of death for a type of cardiovascular cause compared with the general population.

Figure 3 smr by fot.jpg

Seizure Outcome after surgery for Insula High Grade Glioma

Oral Presentation - Video on demand (5 minutes)

Mr. Joshua Pepper [1], ***Ms. Konstantina Karabatsou*** [2], ***Mr. Pietro D'Urso*** [3], ***Mr. Ismail Ughratdar*** [4], ***Dr. Victoria Wykes*** [4], ***Prof. Colin Watts*** [4], ***Ms. erminia albanese*** [1]

1. *University Hospital North Midlands,* ***2.*** *Salford Royal Hospital,* ***3.*** *Salfrod Royal Hospital,* ***4.*** *Queen Elizabeth Hospital Birmingham*

Aims

The insula cortex is an eloquent island of mesocortex surrounded by vital structures making this region relatively challenging to the neurosurgeon. Historically, lesions in this region were considered too high risk to approach given the strong chance of poor surgical outcome. Advances over the last few decades have meant that surgeons can more safely access this eloquent region. Seizure outcome after excision of insular low grade gliomas is well reported but little is known about seizure outcomes after excision of insular high grade gliomas.

Method

We performed a retrospective analysis of all patients presenting with new onset seizures who underwent excision of insular high grade glioma at three regional neurosurgical centres in the United Kingdom.

Results

Thirty eight patients were identified with an average age of 45.7 years (stdev 15.3) with median follow up of 21 months. At long term follow up 23/38 were seizure free (Engel I), 2/38 had improved seizures (Engel II), 6/38 had poor seizure control (Engel III+IV) and 7/38 died.

Conclusion

In summary, excision of insular high grade glioma is safe and results in excellent post operative seizure control.

Survival in patients with radiological diagnoses of glioblastoma: a retrospective study of 115 patients on a best supportive care pathway.

Oral Presentation - Video on demand (5 minutes)

Mr. James Riley [1], ***Mr. James Hodson*** [2], ***Mr. Vladimir Petrik*** [3]

1. *University of Birmingham,* ***2.*** *Queen Elizabeth Hospital Birmingham,* ***3.*** *University Hospitals Birmingham NHS Foundation Trust*

Aims

Glioblastoma multiforme (GBM) is a devastating disease with notoriously poor survival. Studies examining survival in patients given best supportive care (BSC) are few and far between. All patients harbouring brain tumours referred to the Neuro-oncology service at the Queen Elizabeth Hospital in Birmingham are recorded in the Somerset Cancer Registry. We set out to analyse survival times and identify patient and tumour-related factors significantly affecting prognosis.

Method

We identified 126 patients from 2015 to 2019 in our Somerset Cancer Registry with radiological diagnoses of glioblastoma for whom the Neuro-oncology MDT recommended BSC. We performed a retrospective analysis of clinical records and radiological images. 11 patients were excluded (8 due to insufficient imaging data, 2 who underwent subsequent surgery, 1 patient with brain metastases). Survival was measured in completed weeks since the index MDT decision. Associations between survival time and both patient- and tumour-related factors were assessed using Kaplan-Meier curves and log-rank tests. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p<0.05$ deemed to be indicative of statistical significance throughout.

Results

Data were available for N=115 patients (69 males, 46 females), with a mean age of 79 ± 8 years. All patients died within 32 weeks of diagnosis, with a median survival time of 8 weeks. Only 8 patients survived for more than 20 weeks. Survival was significantly shorter in those with a greater number of main cerebral structures affected ($p=0.044$), with a median of 6 vs. 10 weeks for 3 or more vs. 1 structures affected (hazard ratio: 1.61, 95% CI: 0.99-2.62). Bilateral tumours involving the corpus callosum were also associated with shorter survival ($p=0.039$). None of the other factors considered were found to be significantly associated with survival, including age ($p=0.193$), gender ($p=0.371$), performance status ($p=0.300$) and tumour size ($p=0.331$).

Conclusion

With the exception of the number of main cerebral structures affected (frontal, parietal , temporal and occipital lobes, corpus callosum, insula, basal ganglia and brain stem) , patient- and tumour-factors traditionally used by the MDT to prognosticate do not correlate with survival time in patients receiving BSC for radiological diagnoses of GBM. With 50% of the cohort dying within 8 weeks it is clear that we must reconsider the timing of referrals to palliative and hospice care. Finally, the fact that some patients survived for more than half a year with no surgical or oncological treatment suggests that the process of selecting patients for BSC vs aggressive treatments needs refinement.

Telephone versus face-to-face neuro-oncology consultations: comparing patient satisfaction, convenience, family support and clinician attitude during the COVID-19 pandemic

Oral Presentation - Video on demand (5 minutes)

Ms. Emma Toman [1], ***Mrs. Claire Goddard*** [1], ***Mr. William Garratt*** [1], ***Mr. Frederick Berki*** [1], ***Ms. Zenab Sher*** [1], ***Ms. Teresa Scott*** [1], ***Mr. Andrew Stevens*** [1], ***Mr. Vladimir Petrik*** [1], ***Mr. Ismail Ughratdar*** [2], ***Mrs. Anwen White*** [1], ***Mr. Athanasios Zisakis*** [1], ***Prof. Colin Watts*** [3], ***Dr. Victoria Wykes*** [3]

1. *University Hospitals Birmingham NHS Foundation Trust,* ***2.*** *Queen Elizabeth Hospital Birmingham,* ***3.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

During the first wave of the COVID-19 pandemic, to limit the number of patients attending hospital, the neuro-oncology department selected a large number of appointments to be conducted via the telephone.

This project aimed to determine how patients and clinicians perceived telephone consultations in the neuro-oncology service compared to traditional face to face appointments.

Method

A 20-question patient satisfaction survey combined quantitative and qualitative questions and was distributed between June and August 2020. These were distributed by email to 88 patients who attended neuro-oncology clinic in person (“face-to-face”), or by telephone.

Concurrently, a 15-question survey was distributed to all clinicians conducting telephone and face-to-face consultations for the neuro-oncology service. Questions included in the clinician survey were designed to mirror the patient satisfaction questionnaire where possible.

Fisher’s exact test was used to determine significance, which was set at $p< 0.05$.

Results

51.1% (n=45) of patients returned the questionnaire.

Of those who received telephone appointments, 89.5% (n=17) felt the consultation was convenient, 94.7% (n=18) were satisfied and 80.0% (n=16) were able to have a family member/friend present.

Of those who attended face-to-face appointments, 96.0% (n=24) felt their consultation was convenient, 100% (n=25) were satisfied and 87.5% (n=21) were able to have a family member/friend present.

There was no significant difference in patient convenience, satisfaction or family/friend presence (p=0.395, p=0.432 and p=0.498 respectively) between face-to-face and telephone clinics.

Overall, the clinicians reported undertaking a mean of 9.5 telephone consultations per week. Only 42.8% (n=3) use telephone appointments for first-time neuro-oncology consultations, whereas 100.0% (n=7) use them for results and follow-up appointments. Only 51.7% (n=4) felt that undertaking telephone consultations is convenient and 42.8% (n=3) have experienced difficult situations with patients during telephone consultation.

Conclusion

This project suggests that neuro-oncology telephone consultations provide patients with the same level of satisfaction and convenience as face-to-face appointments. We have also demonstrated that using the telephone does not provide a significant barrier to having family or friends present to support the patient.

We have shown that clinicians are universally utilising neuro-oncology telephone appointments for follow-up and results whereas much fewer use the telephone for performing initial consultations. Given the high-level of satisfaction demonstrated in the patient questionnaires this reflects effective patient-selection for remote consultations.

The COVID-19 pandemic has forced oncology services to evolve and results of this project suggest that telephone neuro-oncology consultations are widely accepted by patients and clinicians. We therefore propose that remote consultations should continue beyond the pandemic in select cases.

Oral Presentation - Video on demand (7 minutes)

A Feasibility Study Evaluating the Use of Cell-free DNA Analysis in Laboratory Brain Cancer Investigations

Oral Presentation - Video on demand (7 minutes)

Dr. Ros Ganderton [1], ***Ms. Chantelle Monck*** [1], ***Dr. Tomasz Wojdacz*** [2], ***Prof. Mark Slevin*** [3], ***Ms. Nicola Meakin*** [1], ***Mr. Paul Grundy*** [1]

1. *University Hospital Southampton NHS Foundation Trust,* ***2.*** *MethylDetect ApS®,* ***3.*** *Manchester Metropolitan University*

Aims

Circulating tumour DNA (ctDNA), shed from solid cancers in to the plasma, represents an exciting analyte for diagnosis and monitoring of disease in cancer patients. However, its use in glioma brain cancer patients represents a challenge, due to reduced permeability of the blood brain barrier.

This pilot study sought to investigate the practical aspects and clinical utility of using cell-free DNA (cfDNA) in glioma tests in a NHS diagnostic laboratory. Firstly, we investigated the potential of ctDNA as a proxy for the brain cancer biopsy; where cfDNA analysis was compared to the paired FFPE brain specimen for relevant glioma genetic biomarkers. Secondly, ctDNA constitutes a portion of the overall cfDNA and there is evidence cfDNA metrics *per se* may also be of value as prognostic tools and surrogates of tumour burden. Additionally, we investigated a potential role for cfDNA metrics in prognostic impact; linking cfDNA concentrations to clinical outcome measures.

Method

10ml peripheral blood was collected in specialist preservative tubes and cfDNA isolated using an extraction kit (Qiagen MinElute ccfDNA kit). cfDNA concentration and purity was assessed using chip-based automated electrophoresis.

Where relevant (12/39 cases), cfDNA samples were run though laboratory tests of IDH variant detection, 1p19q co-deletion assessment and MGMT promoter methylation analysis. Results were compared with 'standard of care' brain biopsy tests.

A potential correlate of cfDNA concentration and clinical outcomes data were assessed in a sub-cohort of glioblastoma patients (n=32). The cohort was divided in to 2 groups – high cfDNA vs. low cfDNA - based on whether a subject's extracted sample cfDNA concentration fell above or below the mean. Comparison of overall survival in months between subjects was checked for normal distribution using the Shapiro-Wilk t-test. The test of equity of survival distributions for the high cfDNA *vs.* low cfDNA was then analysed as a Kaplan-Meier curve.

Results

The protocol delivered cfDNA of high purity, averaging 91%, within the plasma nucleic acid fraction, however the cfDNA concentrations (mean ≈1ng μl^{-1}) fell below the conventional limit of detection of the laboratory tests. In spite of the low concentration, cfDNA samples did generate test PCR amplicon; however results reflected the germline DNA profile rather than the new somatic changes of the tumour. The cfDNA analysis did not pick up the tumour biomarkers seen in the paired tumour biopsy sample.

In a second part of the study, cfDNA concentrations for the glioblastoma cohort were assessed in the context of their clinical outcomes data. The data showed a correlate where high cfDNA concentration in the extracted sample was independently associated with inferior outcome in terms of overall survival, with Log Rank significance p=0.014 (Figure 1).

Conclusion

The cfDNA yields from a 10ml blood sample were consistently too low to meet the limit of detection require-

ments of the standard laboratory neuropathology genetic tests and glioma tumour profile could not be picked up against the germline background. Thus, in spite of the considerable advantages to glioma plasma molecular testing, using cfDNA as a proxy for a brain biopsy would currently not be possible in our routine diagnostic environment.

However, within the limitations of the pilot project testing strategy, the data showed an interesting correlate where high cfDNA concentration was independently associated with inferior outcome in terms of overall survival for glioblastoma patients. Given the simplicity of obtaining this quantifiable metric, there are grounds for further investigations as to its utility; not only with survival outcomes, but also potential correlation with the clinical assessment of tumour burden, blood brain barrier integrity and disease pseudoprogression.

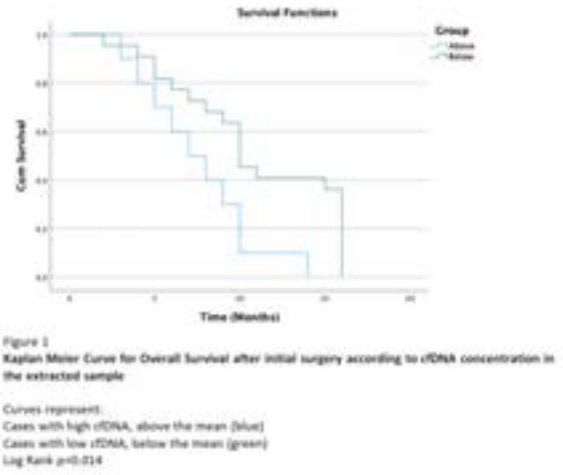


Figure 1
Kaplan Meier Curve for Overall Survival after initial surgery according to cfDNA concentration in the extracted sample

Curves represent:
Cases with high cfDNA, above the mean (blue)
Cases with low cfDNA, below the mean (green)
Log Rank p=0.014

Bnos abstract figure 1.png

A snapshot of “real world” current neuro-oncology practice in ten UK centres participating in the Tessa Jowell BRAIN MATRIX platform study

Oral Presentation - Video on demand (7 minutes)

Dr. Victoria Wykes [1], ***Dr. John R. Apps*** [2], ***Dr. Joshua Savage*** [3], ***Dr. Sara Meade*** [4], ***Dr. Ute Pohl*** [5], ***Mr. Amit Patel*** [2], ***Prof. Lucinda Billingham*** [2], ***Dr. Gerard Thompson*** [6], ***Prof. Adam Waldman*** [6], ***Prof. Olaf Ansorge*** [7], ***Prof. Colin Watts*** [8]

1. *Institute of Cancer and Genomic Sciences, University of Birmingham,* ***2.*** *Cancer Research UK Cancer Clinical Trials Unit, University of Birmingham,* ***3.*** *Cancer Research UK Clinical Trials Unit, University of Birmingham,* ***4.*** *Queen Elizabeth Hospital Birmingham,* ***5.*** *Queen Elizabeth Hospital, Birmingham,* ***6.*** *Centre for Clinical Brain Sciences, University of Edinburgh,* ***7.*** *Nuffield Department of Clinical Neurosciences, University of Oxford,* ***8.*** *Institute of Cancer and Genomic Science, University of Birmingham UK*

Aims

The TJBM Platform Study (https://www.birmingham.ac.uk/research/crctu/trials/brain-matrix) is a programme of work aimed at improving the knowledge of, and treatment for, glioma. The study will develop a backbone infrastructure for a molecular diagnostic pathway, particularly epigenetic classification and whole genome sequencing (WGS), and a data-repository of disease imaging, including real-time centralised Response Assessment in Neuro-Oncology (RANO) review, treatment and outcome data. Developed with the involvement of patients and relatives, patient reported outcome measures (PROMs), particularly quality of life assessment will be collected for patients.

We present the feasibility data collected from the initial ten UK centres selected to participate in the TJBM study. This presents an opportunity to understand current local neuro-oncology practice, identify differences between services and chances to optimise these, bearing in mind the heterogeneity in our patient populations, staff and hospital facilities.

Method

Ten UK centres were selected to participate in the TJBM platform study, and each centre completed a multidisciplinary feasibility questionnaire to facilitate participation and collaboration across the centres. Data were collected from hospital electronic MDT (Multi-Disciplinary Team) records, clinic letters, operative and imaging notes, MDT or personal experience. Continuous variables were reported using medians and ranges due to the non-normality of the data and categorical variables were reported as numbers and percentages. Tables and bar charts were generated to display relevant data. Analysis and plots were generated using Microsoft Excel sheets and SPSS (IBM) version 26.

Results

Work load

Between 2016-2018 service provision redistribution reflects a trend towards higher volume centres. Overall, glioma workload within ten TJBM centres has remained stable (Figure 1).

Imaging

All TJBM centres have good access to imaging techniques and neuroradiology expertise, including relevant ‘advanced’ imaging. All have RANO capability, although not widely used clinically.

Neurosurgery

All centres have access to 5 ALA, perform awake craniotomy for language assessment and motor/sensory mapping are typically performed asleep, with subtle variation in techniques.

Pathology

Despite molecular analysis advances, current practice is limited to the evaluation of formalin embedded tissue by traditional morphology/ immuno-histochemical staining, with limited targeted testing of specific genetic changes (Figure 2).

Clinical oncology

Oncology treatments for glioma were as per NICE guidance with some minor local variation.

The data has informed the development of the TJBM protocol, an overview of which will be presented (Figure 3).

Conclusion

Through systematic real-world data collection the TJBM platform study will provide a detailed understanding of practice within the UK, linked to molecular tumour genotype, treatment response outcome measures, and also regular quality of life assessments.

Use of the platform infrastructure, will facilitate trials and add-on observational and biological studies to obtain rapid, efficient, and cost-effective data collection, and integrate findings with comprehensive molecular biological profiling and radiological features, thereby reducing the time and administrative burdens in trial delivery.

This infrastructure will help establish a trial-competent network on which future research and collaborations can be based. Academic and industry partners will be able to use the TJBM platform through collaboration, overseen by a strong governance framework. This will maximise the opportunities and abilities to translate advances into trials and patient benefit.

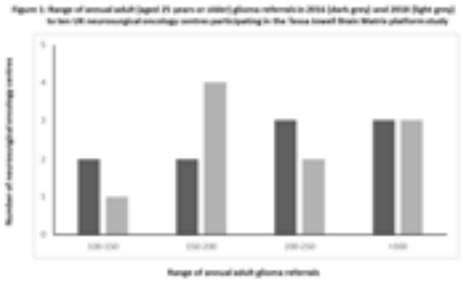


Figure 1.jpg

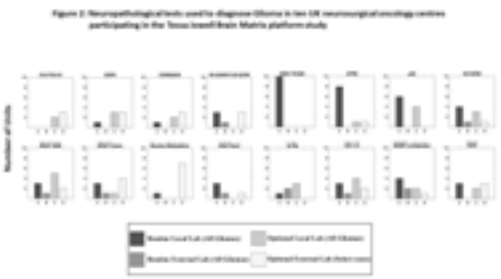


Figure 2.jpg

Activation of MAPK/ERK signalling in Merlin-null Schwann cells leads to increased and sustained immune cell infiltration in the peripheral nervous system

Oral Presentation - Video on demand (7 minutes)

Mx. Evyn Woodhouse [1], ***Dr. Liyam Laraba*** [2], ***Ms. Charlotte Lespade*** [1], ***Ms. Marie Srotyr*** [1], ***Prof. Alison C. Lloyd*** [3], ***Prof. David B. Parkinson*** [4]

1. *University of Plymouth, UK,* ***2.*** *Plymouth University,* ***3.*** *MRC Laboratory for Molecular Cell Biology, UCL, UK,* ***4.*** *Peninsula Medical School, Faculty of Health, University of Plymouth, Plymouth, UK*

Aims

Previous work has shown that increased numbers of macrophages are associated with more rapid schwannoma tumour growth and we are interested in signals that control entry of macrophages and other immune cells into these tumours. Activation of the Raf-kinase domain and the Raf/MEK/ERK pathway within Schwann cells has been observed to induce an inflammatory response in peripheral nerves in the absence of injury. Activation of an inducible Raf-kinase transgene in Schwann cells allows modelling of acute demyelination of peripheral nerves without nerve injury. This Raf-oestrogen receptor fusion protein (Raf-TR) is activated by the oestrogen analogue Tamoxifen and so allows targeted, controlled activation of the Raf/MEK/ERK pathway within the Schwann cells.

Here, in order to understand drivers of tumour formation, we assess the effect of MAPK activation in Merlin-null Schwann cells upon immune cell infiltration within the PNS.

Method

RafTR-P0CRE-NF2$^{fl/fl}$ mice of 4-6 weeks age were injected daily (IP) with 2mg of 4-hydroxy-tamoxifen or vehicle (corn oil) control for 5 consecutive days. RafTR was activated on either a Merlin (NF2) wild-type (NF2 fl/fl, P0-CRE-) or NF2 null (NF2 fl/fl, P0-CRE+) background and effects on immune cell infiltration studied in each condition.

Immunofluorescence was performed in the dorsal root ganglia (DRGs) and sciatic nerves of mice to identify various immune cell infiltrates at various timepoints. These will include neutrophils, mast cells, T-Cells and macrophages using the cell markers Csf3r, C-kit, CD3 and IBA1 respectively.

Results

At 21 days post treatment, a significantly increased infiltration of macrophages within the sciatic nerve and dorsal root ganglia was observed in mice treated with Tamoxifen when compared to vehicle controls. Loss of *NF2* led to a massive increase in the number of macrophages recruited to peripheral nerves in tamoxifen-treated mice compared to Cre- mice and Cre+ treated with vehicle alone. Further assessment of other immune cell infiltration including neutrophils, mast cells and T cells are ongoing.

Conclusion

Raf/MEK/ERK signalling, in the absence of tumour suppressor Merlin, significantly increases the infiltration of inflammatory cells such as macrophages into peripheral nerves even in the absence of injury. As this effect is enhanced in *NF2* null mice, this suggests that Merlin plays an important role in inhibiting the inflammatory response in peripheral nerves. It also suggests that Merlin could be involved in maintaining the blood nerve barrier (BNB), as in its absence the greater influx of immune cells into the nerves and DRGs suggests a more complete loss of BNB function than just activation of the Raf/MEK/ERK cascade alone.

An audit on the diagnosis of primary CNS lymphoma

Oral Presentation - Video on demand (7 minutes)

Dr. Dorothy Joe [1], ***Dr. Lucia Yin*** [1], ***Dr. Shireen Kassam*** [2], ***Dr. Katia Cikurel*** [1], ***Mr. Jose-Pedro Lavrador*** [3], ***Mr. Francesco Vergani*** [3], ***Mr. Richard Gullan*** [3], ***Mr. Ranjeev Bhangoo*** [3], ***Prof. Keyoumars Ashkan*** [3], ***Dr. Gerald Finnerty*** [4]

1. *Department of Neurology, King's College Hospital NHS Foundation Trust, London,* ***2.*** *Department of Haematology, King's College NHS Foundation Trust,* ***3.*** *Department of Neurosurgery, King's College Hospital NHS Foundation Trust, London,* ***4.*** *Department of Basic and Clinical Neuroscience, King's College London, London; Department of Neurology, King's College Hospital NHS Foundation Trust, London*

Aims

Primary central nervous system lymphoma (PCNSL) is a rare form of non–Hodgkin lymphoma with exclusive manifestations in the central nervous system, leptomeninges and eyes. It forms around 5% of all primary brain tumours. It is an aggressive tumour which has a poor prognosis if left untreated. It is imperative that diagnosis is made timely so treatment can be started promptly. Therefore, we performed an audit looking into the speed of diagnostic process of PCNSL in our tertiary Neuro–oncology Unit.

Method

Single-centre retrospective review of PCNSL cases referred to a tertiary Neuro–Oncology Unit over a six month period from June to November 2020.

Results

A total of 1309 cases were discussed in the Neuro–oncology MDT meeting over the study period. Fourteen cases (6 male, 8 female; median age [range] 66 [59–83] years) were identified as highly likely PCNSL. Neuroimaging suggested PCNSL as the likely diagnosis in twelve patients. Twelve patients were started on steroids after CT or MRI brain scans. Nine patients had a surgical target and proceeded to have diagnostic brain biopsy. Two patients had different working diagnoses and three patients were deemed unsuitable for brain surgery. One patient required repeat brain biopsy. A tissue diagnosis was made in twelve patients. One patient deteriorated rapidly and one patient had a brain lesion that was deemed too high risk for surgery. The median time between neuroimaging and biopsy was 25 days. The median time taken from first investigation to the pathological confirmation of PCNSL was 36 days (range 6–86 days).

Conclusion

The chief reason for delay in diagnosis of PCNSL was that patients were started on steroids before diagnostic investigations were completed. Steroids caused the brain lesions to become smaller or disappear. Accordingly, time was needed to allow withdrawal of steroids before diagnostic investigations could be repeated. Diagnostic delays may have been exacerbated by logistical issues associated with COVID–19. We propose that there needs to be greater awareness of how early introduction of steroids can markedly delay the diagnosis of PCNSL.

Arginine deprivation therapy induces apoptotic cell death in melanoma brain metastasis

Oral Presentation - Video on demand (7 minutes)

Ms. Aithne Atkinson [1], ***Dr. Nelofer Syed*** [1]

1. *John Fulcher Neuro-Oncology Laboratory, Brain Tumour Research Centre of Excellence, Imperial College London*

Aims

The development of melanoma brain metastasis (MBM) occurs in ~50% of metastatic melanoma cases, and significantly worsens prognosis to a median survival of 12.8 months. Melanoma is often reported as an arginine auxotroph due to transcriptional silencing of argininosuccinate synthase 1 (*ASS1*). Arginine deiminase (ADI) is a non-mammalian enzyme which depletes blood arginine by converting it to citrulline and ammonia, and in its pegylated form ADI shows clinical efficacy in the treatment of a number of cancers via exploiting tumour arginine auxotrophy, resulting in targeted arginine deprivation of tumour cells. While cutaneous melanoma is the prototype cancer for this therapy, studies to date have excluded central nervous system metastasis.
We have demonstrated that patient derived primary MBM models are sensitive to arginine deprivation *in vitro*, confirmed suitable clinical biomarkers of sensitivity, and established the mechanism of tumour cell specific cytotoxicity.

Method

Patient derived primary cultures of MBM were established and subject to treatment with arginine deprivation. Gene expression and methylation analysis was examined by RT-qPCR, western blot, Illumina mRNA sequencing and Illumina methylated DNA immunoprecipitation-sequencing (MeDIP-seq) on ADI treated and untreated samples. Cell death, cytotoxicity induction and caspase-3 and-7 recruitment was analysed using an Incucyte S3 live-cell imager, by fluorescently labelling cells with Incucyte Cytolight Red Rapid dye, Cytotox Green dye and Caspase-3/7 Green dye, and imaging cells every 2 hours over the course of 2 weeks. 3D spheroid growth and invasion was measured by culturing cells as tumour spheroids before treating with ADI, and imaging spheroids every 2 hours for 2 weeks using an Incucyte S3 live-cell imager. Nuclear leakage and mitochondrial morphology was observed by fluorescently staining treated and untreated cells with DAPI and MitoTracker Red, and imaging on a Leica DMi8 confocal microscope.

Results

Primary MBMs differentially express ASS1 at substantially lower levels than non-cancerous melanocytes, however some models are capable of upregulating *ASS1* following confrontation with arginine deprivation. Despite this, long-term sensitivity of primary MBMs to arginine deprivation was observed in both 2D and 3D models. In addition, arginine deprivation was seen to inhibit MBM invasion in a 3D model – an important feature in MBM pathogenesis. Initially, autophagy was induced in arginine deprived MBM, however in all models the induction of cytotoxicity correlated with recruitment of caspase-3 and -7, and intrinsic apoptotic cell death confirmed. Nuclear leakage, and eventually complete nuclear destruction was observed, in addition to mitochondrial fragmentation.

Conclusion

Arginine deprivation is highly effective in reducing 2D and 3D MBM growth, as well as limiting invasion. While apoptotic cell death was observed in all models, the initial induction of autophagy could pose threat of resistance development in a clinical setting, and so combinational therapies with autophagic inhibitors and/or additional apoptotic inducers should be investigated. It is unclear whether nuclear leakage and mitochondrial degradation are the cause or product of apoptosis. Considering the strong clinical evidence for the use of arginine depriva-

tion in non-CNS metastatic melanoma and the results of this study, arginine deprivation is a highly suitable treatment for pre-surgical MBM to limit invasion and increase resection, and for post-surgical continuation.

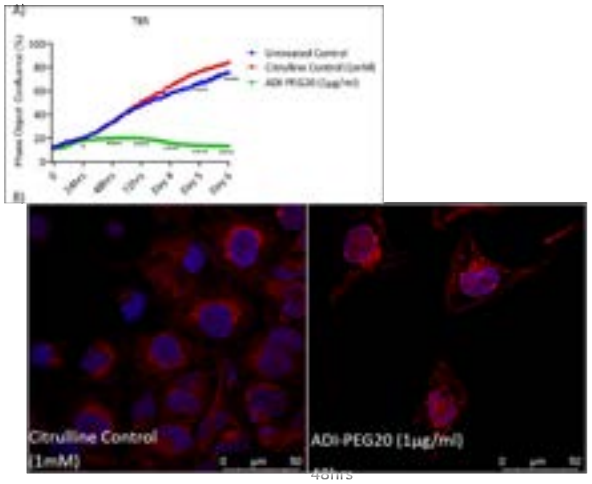


Figure 1: Arginine deprivation inhibits the growth of primary MBM and induces mitochondrial fragmentation. Primary MBM cell cultures (TB5 shown) were treated with media only (untreated control), vehicle control (citrulline control) or 1µg/ml ADI. **A)** Cells were imaged at 10X in bright-field using an Incucyte S3 every 2hrs for 6 days, and % confluence quantified using Incucyte Basic Analyser software*. **B)** After 48hrs treatment, cells were fixed in PFA and stained with MitoTracker Red and DAPI. Images were taken on a Leica DMi8 at 63X.

**Significance is shown to citrulline control. Data displayed as mean ± SEM (some error bars are shorter than data point symbol). n=3. Two-way ANOVA with Tukey's multiple comparisons test was performed to determine significant differences between groups (*P $<$ 0.05, **P $<$ 0.01, ***P $<$ 0.001, ****P $<$ 0.0001).*

Mbm abstract figure.png

BRAIN Surgical Tissue for Advanced Tumour models in Precision medicine: Developing the BRAIN-STAT pathway

Oral Presentation - Video on demand (7 minutes)

Dr. Victoria Wykes [1], ***Dr. Alina Finch*** [2], ***Dr. Daniel Blakeway*** [3], ***Dr. Chiara Bardella*** [2], ***Dr. Ute Pohl*** [4], ***Prof. Andrew Beggs*** [2], ***Prof. Colin Watts*** [5]

1. *aa,* ***2.*** *Institute of Cancer and Genomic Sciences, University of Birmingham,* ***3.*** *Institute of Immunology and Immunotherapy, University of Birmingham,* ***4.*** *Queen Elizabeth Hospital, Birmingham,* ***5.*** *Institute of Cancer and Genomic Science, University of Birmingham UK*

Aims

There are approximately four thousand neuro-oncology procedures in the UK per annum. Many of these result in tissue and biofluid specimens that are surplus to diagnostic requirement and can be collected as standard of clinical care. However, developing technologies and treatments for precision medicine require access to a range of individualised biospecimens paired with deep clinical phenotyping data. Here, we present Brain Surgical Tissue for Advanced Tumour Models (BRAINSTAT) programme, an infrastructure that has been established between Queen Elizabeth Hospital, Birmingham and the University of Birmingham, to collect, structure and store these resources and also maximise their value for research over the long-term. Using this approach our aim is to provide high-quality, annotated resources to help develop novel treatments for patients with brain tumours.

Method

BRAINSTAT infrastructure allows:

1. *Prospective consent*

Biospecimens, including tumour tissue (brain and other primary in the case of metastasis), cyst fluid, dura, skin, CSF, blood (matched “germ-line” and for circulating cell free tumour DNA analysis), urine and saliva can be collected. Consent for long term follow-up, is either via clinic or NHS digital. More limited consent for non-oncological neurosurgical cohorts (e.g. epilepsy or vascular) and healthy volunteers allow healthy access-tissue and biofluids to be collected.

B. Rapid transfer of fresh surgical tissue samples:

Strong collaborative links and close physical proximity between operating theatre and laboratory allows rapid transfer of biospecimens minimising transit time.

C. Standardised annotation across disciplines

The RedCAP database system allows granular control over data-access, and each specialist research team is provided access only to the sub-sections relevant to them. All users must have Good Clinical Practice certification and GDPR training, prior to access of the BRAINSTAT database.

Results

Between 25/11/2019-16/03/2020 and 27/07/2020-16/11/2020, 65 patients were consented for BRAINSTAT at the weekly neurosurgical oncology clinic. (Recruitment gaps due to the SARS-COVID 19 pandemic). Pathological diagnosis of surplus tissue collected included: 37 high grade glioma, 3 low grade glioma and 16 brain metastasis including: (6 lung, 6 breast, 2 colorectal, 1 oesophageal, 1 endometrial). Meningioma (5 WHO I; 1 WHO III) 1 patient undergoing anterior temporal lobectomy for hippocampal sclerosis contributed access tissue from the lateral neocortex. 1 patient had a non- neoplastic, non-diagnostic sample. All patients had matched “germ-line” blood samples.

Median time from resection to arrival in the laboratory was 10 minutes (range 4-31). Standardised operating protocols to optimise this have been developed.
Glioblastoma and breast-brain metastasis tumourspheres and cerebral organoids are currently being validated.

Conclusion

Despite the challenges of the pandemic we have established a viable tissue pipeline from neurosurgical operating theatre to our university laboratories. We are developing clinically annotated human brain tumour cell lines, stem cells and 3D organoid models, principally for commonly encountered brain tumours such as glioma and metastasis.
The research sets the foundation for a multitude of downstream applications including:
- Building more complex organoid cultures e.g. by including other cell types such as healthy brain cells and endothelial cells allowing future experiments to more accurately model tumour growth.
- Developing high-throughput, patient-specific drug screens of novel drugs and drug combinations using these 3D tumour models aiming to more effectively treat tumour proliferation and spread. These patient avatars will help inform and test more “stratified” personal medical treatments and will provide opportunities to allow earlier intervention with the aim of improving survival, coupled with a better quality of life.

Characteristics of glioblastoma long-term survivors

Oral Presentation - Video on demand (7 minutes)

Dr. Tamara Ali [1], ***Mr. Farouk Olubajo*** [1], ***Dr. Nitika Rathi*** [1], ***Dr. Piyali Pal*** [1], ***Prof. Michael Jenkisnon*** [1], ***Mr. Andrew Brodbelt*** [1]

1. *The Walton Centre, Liverpool*

Aims

Glioblastoma (GBM) is the commonest and most aggressive primary malignant brain tumour in adults. A small number of patients survive for >5 years and are referred to as long-term survivors (LTS). This study aimed to quantify and characterise GBM LTS in a single large UK centre.

Method

A retrospective observational cohort study was performed. Patients diagnosed with GBM in a single UK centre between 2000–2011 (inclusive) who survived >5 years from diagnosis were included. Histopathological samples were re-examined as per the WHO 2016 classification criteria and tested for molecular biomarkers including MGMT promoter methylation, IDH1/2 mutations, 1p19q codeletion and ATRX. Demographic, imaging, treatment and outcome data were collected.

Results

1130 patients diagnosed with GBM were identified, 30 of whom survived for >5 years. Twenty-three were re-confirmed as GBM histologically and seven were reclassified as anaplastic oligodendroglioma or anaplastic astroctyoma. Median overall survival for this cohort was 6.2 years. We report a 2% 5-year survival, and a 0.7% 7-year survival. LTS-associated factors were younger age (<65 years old), frontal unilateral tumours, maximal management (surgery and chemoradiotherapy), good post-operative performance status (WHO <2), MGMT promoter methylation and IDH1/2 mutation.

Conclusion

A small subset of GBM patients survive for >5 years. Most still succumb to the disease, implying 5-year survival is not indicative of a cure. On applying current molecular markers, a quarter of previously diagnosed glioblastoma in this LTS population were revised to be WHO grade III gliomas.

Clinical Features at Presentation for Glioblastoma Patients Impact Survival Predictions in a Machine Learning Model

Oral Presentation - Video on demand (7 minutes)

Dr. Alistair Lawrence [1], ***Mr. Rohit Sinha*** [1], ***Mr. Stefan Mitrasinovic*** [1], ***Mr. Stephen Price*** [1]

1. *Cambridge Brain Tumour Imaging Laboratory, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital*

Aims

To generate an accurate prediction model for greater than median survival using Random Forest machine learning analysis and to compare the model to a traditional logistic regression analysis model on the same Glioblastoma Dataset.

Method

In this single centre retrospective cohort study, all patients with histologically diagnosed primary GB from October 2014 to April 2019 were included (n=466). Machine learning algorithms encompassing multiple logistic regression and a Random Forest, Gini index-based decision tree model with 100,000 trees were used. 17 clinical, molecular and treatment specific binarily categorised variables were used. The dataset was split 70:30 into training and validating sets.

Results

The dataset contained 466 patients. 326 patients made up the training set and 140 the validation set.

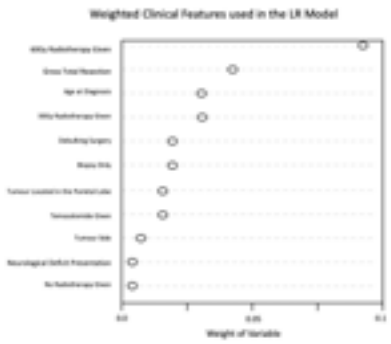
The Random Forest model's accuracy for predicting 18-month survival was 86.4% compared to the Logistic Regression model's accuracy of 85.7%.

The top 5 factors that the Random Forest model used to predict survival over 18 months were; mean MGMT status >10%, if the patient underwent gross total resection, whether the patient had adjuvant temozolomide, whether the patient had a neurological deficit on presentation, and the sex of the patient.

Conclusion

Machine learning can be applied in the context of GB prognostic modelling. The models show that as well as the known factors that affect GB survival, the presenting symptom may also have an impact on prognostication.

Gini rf model .jpg



Weightings lr.jpg

Cranial Meningiomas Requiring Cranioplasty

Oral Presentation - Video on demand (7 minutes)

Mr. Max Norrington [1], ***Mr. Christopher Millward*** [2], ***Dr. John Doherty*** [1], ***Mr. Mohammad Mustafa*** [1], ***Dr. Thomas Humphries*** [1], ***Mr. Conor Gillespie*** [1], ***Mr. George Richardson*** [1], ***Dr. Abdurrahman Islim*** [2], ***Prof. Michael Jenkisnon*** [2], ***Mr. Andrew Brodbelt*** [2]

1. *University of Liverpool,* ***2.*** *The Walton Centre, Liverpool*

Aims

Bone infiltration in association with intracranial meningioma (4.5% of cases) and primary intraosseous meningioma (2%) are rare. Management can be challenging, as cranial vault reconstruction may be required. This study aimed to examine the surgical techniques used and outcomes in this patient population.

Method

A single-centre, retrospective cohort study was conducted between January 2010 and September 2020. All adult patients who required cranial reconstruction due to bone involvement of their meningioma were included. Patient demographics, tumour characteristics, operative details, complications, and outcomes were examined. Statistical analyses were performed using SPSS v24.0.

Results

There were 30 patients (17 female; 56.7%), median age 54 yrs (range 28-86 yrs), of whom 25 (83.3%) had bone infiltration, and 5 (16.7%) had primary intraosseous meningioma. Only 10 patients had a Simpson I or II resection. Twenty-eight had 'on-table' primary cranioplasties. Materials used were titanium (n=13; 43.3%), acrylic (n=10; 33.3%), PMMA (n=5; 16.7%), and hydroxyapatite (n=2; 6.7%). There were 9 (mostly minor) surgical complications and only one wound infection. Twelve patients had WHO grade II tumours, and 14 required radiotherapy. Ten patients (33.3%) had re-operation for recurrent tumour, with a median time to progression of 41 months. At 6 months, 24 patients had a performance score less than 2.

Conclusion

On-table cranioplasty provides a lower risk surgical option for patients with high risk meningiomas.

Delayed contrast and multiparametric MRI for treatment response assessment in brain metastases following stereotactic radiosurgery

Oral Presentation - Video on demand (7 minutes)

Dr. Markand Patel [1], ***Dr. Dilina Rajapakse*** [2], ***Dr. Jian Ping Jen*** [2], ***Dr. Sara Meade*** [2], ***Dr. Helen Benghiat*** [3], ***Dr. Andrew Hartley*** [2], ***Mr. Vladimir Petrik*** [1], ***Mr. Ismail Ughratdar*** [2], ***Prof. Colin Watts*** [2], ***Dr. Paul Sanghera*** [2], ***Dr. Satheesh Ramalingam*** [2], ***Prof. Vijay Sawlani*** [2]

1. *University Hospitals Birmingham NHS Foundation Trust,* ***2.*** *Queen Elizabeth Hospital Birmingham,* ***3.*** *Department of Radiotherapy, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK*

Aims

Following stereotactic radiosurgery (SRS), brain metastases can increase in size in up to a third of cases. Conventional magnetic resonance imaging (MRI) has a limited role to distinguish between tumour recurrence and SRS-induced changes, which can impact patient management. Delayed contrast MRI treatment response assessment maps (TRAM) use the principle of contrast clearance seen in other tumours, where high vascularity shows a rapid rise in contrast as well as rapid clearance, whereas areas of damaged or low vascularity show accumulation of contrast. We aimed to assess the ability of delayed contrast MRI and multiparametric MRI techniques of diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and MR spectroscopy (MRS) to distinguish between radiation-related effects and tumour tissue, as these techniques assess tissue physiological and metabolic information.

Method

A retrospective review was performed on 23 patients who had delayed contrast and multiparametric MRI between October 2018 to April 2020. Studies were restricted to cases with brain metastases enlarging post-SRS with uncertainty at the MDT meeting regarding progression or treatment-related change, impacting the patient's management. MRI was performed at 3T including DWI, PWI, MRS with short and intermediate echo times, and 3D T1 MPRAGE at 3-5, 20-30 and 70-90 minutes after administration of intravenous contrast. Contrast clearance analysis was performed by selecting an enhancing region of interest (ROI), measuring signal intensities at the three different timepoints and taking apparent diffusion coefficient (ADC) and relative cerebral blood volume (rCBV) values from the ROI. Choline/Creatine values were calculated from a single-voxel (10 mm isotropic) encompassing the entire contrast-enhancing lesion. Outcome was established from MRI follow-up at 6 months, with a stable or responding lesion considered treatment-related changes and increase considered progression.

Results

Across 23 patients, 24 metastases were assessed. Two patients were excluded as appropriate follow-up was not available. Sites of primary tumours included breast (n=8), lung (n=6), melanoma (n=4), neuroendocrine tumour from the lung (n=2) and renal cell carcinoma (n=2). Mean age was 56 years and 50% were female. In this cohort, 59% (n=13) were classified as having radiation-related changes on follow-up. Delayed MRI contrast clearance between the 3-5 and 70-90 minute imaging was significantly higher in cases of progression (23.6% vs. 2.5% decrease, $p<0.05$), as were the rCBV and Cho/Cr ratio (rCBV 3.1 vs. 1.5 and Cho/Cr ratio 2.3 vs. 1.4, $p<0.05$). Accuracy, sensitivity and specificity of using TRAM alone (contrast clearance decrease of >0%) for progression was 63%/100%/38%, PWI alone (rCBV cut-off 2.0) yielded results of 77%/75%/79% and for both Cho/Cr ratio alone (cut-off 1.8) and combined with TRAM, it was 90%/88%/92%. Neuroradiologist assessment of all techniques was 95%/100%/92%.

Conclusion

This study shows the effectiveness of delayed contrast and multiparametric MRI for treatment response assessment in patients with brain metastases treated by SRS in clinical practice. Although a delayed contrast MRI study is a very sensitive tool for detecting tumour progression, it lacks specificity. The accuracy of differentiating between tumour and treatment-related effects increases when delayed contrast MRI is used in combination with other advanced techniques such as MRS. By combining all these techniques, neuroradiologists had the highest accuracy, sensitivity and specificity for detecting progression in post-SRS brain metastases.

Development of 'Core Outcome Sets' for meningioma in clinical studies: The COSMIC project.

Oral Presentation - Video on demand (7 minutes)

Mr. Christopher Millward [1], ***Mr. Sumirat Keshwara*** [1], ***Dr. Abdurrahman Islim*** [1], ***Mr. Nisaharan Srikandarajah*** [1], ***Prof. Tony Marson*** [1], ***Prof. Paula Williamson*** [2], ***Prof. Michael Jenkisnon*** [1]

1. *The Walton Centre, Liverpool,* ***2.*** *University of Liverpool*

Aims

To date, meningioma clinical trial activity has been limited, but a number of high-quality studies are underway, with more in development. There is heterogeneity in the outcomes reported in meningioma clinical trials. The COSMIC Project will develop two 'Core Outcome Sets' (COS) through comprehensive, transparent, consensus methodology; to ensure outcomes relevant to key stakeholders are reported within and across future meningioma clinical studies. The first will be for use in clinical effectiveness trials (COSMIC: Intervention), the second will be for use in clinical studies of incidental meningioma (COSMIC: Observation).

Method

Three systematic literature reviews will be performed to generate a long-list of outcomes potentially relevant to meningioma patients, healthcare professionals, researchers, and other stakeholder groups. The first systematic review will present the outcomes reported in published and ongoing meningioma clinical effectiveness trials. The second systematic review will present patient-reported outcomes (PRO) from the measurement tools utilised in meningioma PRO studies. The third systematic review will present the outcomes reported in published and ongoing clinical studies of untreated meningioma.

Outcomes will be deduplicated, unique outcomes categorised according to the taxonomy presented by COMET, and the lists combined. The long-list of outcomes will be prioritised through two, 2-round, modified eDelphi surveys including meningioma patients, healthcare professionals, researchers, and other stakeholder groups. Undecided outcomes from both eDelphi surveys will be ratified at two, one-day consensus meeting, with representation from all key stakeholder groups.

Results

We have formed a study advisory group with international representation from key organisations. The project already has confirmed support from the International Consortium on Meningioma (ICOM), the European Association of Neuro-Oncology (EANO), the Response Assessment in Neuro-Oncology Patient-Reported Outcome group (RANO-PRO), the Society for Neuro-Oncology (SNO), British Neuro-Oncology Society (BNOS), Society of British Neurological Surgeons (SBNS), The Brain Tumour Charity (TBTC), and Brainstrust.

Conclusion

Standardising minimum outcome reporting in meningioma clinical effectiveness trials and meningioma clinical studies, through the development of these two COS will ensure outcomes reported are relevant to key stakeholder groups, including patients, whilst reducing research waste for a disease with increasing clinical trial activity. We seek to raise awareness of this project and invite participation from a wide range of stakeholders to ensure that the final COS reflects the opinion of the neuro-oncology community. Registration will take place via the study website www.thecosmicproject.org between June-August 2021.

Effects of the tumour microenvironment on protoporphyrin IX accumulation in glioblastoma

Oral Presentation - Video on demand (7 minutes)

Dr. Paul Walker [1], ***Dr. Alina Finch*** [2], ***Dr. Victoria Wykes*** [2], ***Prof. Colin Watts*** [3], ***Dr. Dan Tennant*** [1]

1. *Institute of Metabolism and Systems Research, University of Birmingham,* ***2.*** *Institute of Cancer and Genomic Sciences, University of Birmingham,* ***3.*** *Institute of Cancer and Genomic Science, University of Birmingham*

Aims

Glioblastoma is the most common primary brain tumour and has a poor prognosis. Standard clinical intervention involves the resection of the tumour volume, chemotherapy and radiotherapy. However, achieving gross-total resection is challenging due to poorly defined boundaries as a result of tumour infiltration. Fluorescence-guided surgery (FGS) utilises an apparently selective accumulation of protoporphyrin IX (PPIX) that occurs in areas of glioblastoma after systemic administration of the metabolite 5-aminolevulinic acid (5-ALA). We have investigated the metabolic basis for the heterogeneity of the PPIX fluorescent signal, and its implications for glioma biology.

Method

Using glioblastoma cell lines and patient-derived primary cells, we have monitored the uptake of 5-ALA and conversion to the fluorescent molecule PPIX. Stable isotope tracing coupled with GCMS and LCMS was used to analyse intra- and extracellular metabolite levels arising from exogenous 5-ALA administration under both normoxic (21% O2) and hypoxic (1% O2) conditions.

Results

Uptake of exogenous 5-ALA from culture media and conversion to PPIX is observed in a time and dose-dependent manner in both normoxia and hypoxia. High levels of PPIX accumulation are associated with reduced cell proliferation despite the majority of the PPIX synthesised not being retained within the tumour cell, but exported into the medium. Under hypoxic conditions, reduced fluorescence is observed as a result of the decrease in oxygen availability likely affecting the oxygen-dependent enzymes. Stable isotope tracing experiments indicate an increase in the glutamine-derived succinate pool in response to exogenous 5-ALA, which is dependent on flux through the heme pathway.

Conclusion

Our data suggest that different microenvironments within the tumour alter the activity of the heme biosynthetic pathway, resulting in differential fluorescence in glioblastoma. It paves the way by which we could work to alter the glioblastoma microenvironment in order to further improve the use of FGS in guiding surgery across these devastating tumours.

Ependymomas: surgeon case volume and patient outcomes

Oral Presentation - Video on demand (7 minutes)

Ms. Rosa Sun [1], ***Ms. Naomi Slator*** [2], ***Mr. Andrew Kay*** [1]

1. *Queen Elizabeth Hospital Birmingham,* ***2.*** *North Bristol NHS Trust*

Aims

Ependymomas (tumours arising from ependymal cells) are rare in the adult population and therefore there is limited class 1 evidence on the treatment and management of these patients. We present our experience from a large single center.

We address whether management should be undertaken by sub-specialised surgeons with high volume experience.

Method

Retrospective comparative study.

Results

High volume surgeons operated on larger volume (16.14 mm3, 8.31mm3, p=0.10) and more complex tumours (multi-centric cases p=0.10). We find a non-significant improvement in complication rate (p=0.77), extent of gross total resection (70.8% against 65.7%) and a positive change in performance status for high volume surgeons (p=0.84). Length of hospital stay is significantly prolonged when complications occur (14.2 and 48.4 days, $p<0.05$).

Conclusion

Surgeons who have higher case load of ependymomas operate on more complex tumours. In addition, our results indicate there is a technical advantage of high volume surgeons compared to low volume surgeons, which translates into improved clinical outcomes for patients. We show that this has a significant impact on length of hospital stay, as well as the associated economical implications. For rare tumours such as ependymomas, super-specialisation and referral to surgeons with higher case volume will likely improve patient outcomes.

We call for a multi-centre, prospective studies to combine data in demonstrating statistical significance (power calculation for complication rate, N=150, p=0.05).

Estimating population-based incidence of brain metastases – a comprehensive incident cohort study

Oral Presentation - Video on demand (7 minutes)

Dr. Hamish Sinclair [1], ***Ms. Kerlann Le Calvez*** [2], ***Dr. Jiarong Chen*** [3], ***Ms. Lillie Pakzad-Shahabi*** [4], ***Dr. Luke Dixon*** [5], ***Dr. Waleed Mohammed*** [6], ***Dr. Waqar Saleem*** [6], ***Dr. Matthew Williams*** [6]

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Aims

Brain metastases are the most common intracranial tumour and affect approximately 20% of adult cancer patients, most commonly from lung, breast, melanoma, and kidney cancer. However, the true incidence of brain metastasis is unknown. England's cancer registration system only reliably captures brain metastases present at diagnosis (rather than those that develop later), and the same is true for US-based data. Although it is relatively easy to identify patients receiving some treatments for brain metastases (surgery, stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT)), identifying those receiving chemotherapy or no treatment is much harder. As a result, the existing literature is heavily biased towards reporting treated populations. This study attempts to find an unbiased estimate of the true number of patients developing brain metastases, based on data from a single centre.

Method

Cases of brain metastasis were retrospectively identified from the radiology information system database (SolitonTM). We performed a Boolean search for specific keywords in the radiology reports of all CT and MRI head scans performed at the trust between 1st January 2018 and 31st December 2019. The following keywords were searched for "metastases", "metastatic", "metastasis", "mets", "deposit", "deposits", "secondaries", "secondary" and "disseminated". Duplicate cases were then removed and the subsequent list was manually reviewed
We identified all patients who received any treatment for brain metastases who were diagnosed at our centre. We only included patients with newly diagnosed brain metastases (included: leptomeningeal; excluded: skull-based metastases). We excluded patients who were diagnosed in other centres and treated here or diagnosed outside the study period. We then extracted data on primary diagnosis, admissions, and survival.

Results

1192 patients had a CT or MRI of the head with a mention of "brain metastases" in the report; of these 305 were newly diagnosed with brain metastases during the study period (432 had metastases; 127 diagnosed earlier).
Of these 305 patients, 217 (71.1%) were treated locally (SRS = 88; WBRT = 74; surgery = 88; systemic therapy = 16; multiple treatments = 45) and 10 (3.3%) were referred elsewhere. 78 (25.6%) patients received no treatment.
Of the 217 treated patients, 124 were female, and the median age was 61. Of the 78 untreated patients, 38 were females, and the median age was 70 years old. The commonest primary diagnoses in both groups were lung (39%) and breast (21%) cancer. 16 (21%) of the untreated patients had an unbiopsied primary tumour.
Median survival for patients having (any) treatment was 52 weeks compared to 5 weeks for those not having treatment.

Conclusion

We have presented an unbiased single-centre estimate of brain metastases occurrence. Unlike previous work, we manually reviewed all imaging reports that suggested metastasis, and included all patients diagnosed with brain metastases at any timepoint. We reduced the bias associated with being a tertiary centre by only including patients who were diagnosed here, rather than referred from other centres.
25% of our cohort received no treatment, and survival in this group is poor. This is broadly in line with the only other study on this topic (Bentley, 2019) that reported a large minority (39%) of untreated patients.
Our key conclusions are:

1. When assessing the incidence of brain metastases, studies that do not account for untreated patients are likely to significantly underestimate incidence, and over-estimate survival
2. Improving outcomes in patients with brain metastases might be best achieved by addressing earlier identification and intervention in those who currently receive no treatment

Evaluation of health outcomes in patients aged 70 years and above with glioblastoma multiforme in NHS Tayside between 2017-2020.

Oral Presentation - Video on demand (7 minutes)

Dr. Caitlin Finnan [1], ***Dr. Hannah Lord*** [1]

1. *NHS Tayside*

Aims

The aim of this study is to evaluate health-related outcomes in patients aged 70 years and above diagnosed with glioblastoma multiforme (GBM) in NHS Tayside between 2017-2020.
Objectives include identification of factors which influence the oncological treatment modalities pursued; disease progression/recurrence and outcomes within each treatment modality category.

Method

Medical databases were reviewed retrospectively to identify patients aged 70 years and above diagnosed with GBM in NHS Tayside, between 2017-2020.
Analysed data identified patients' past medical history, symptoms and investigations preceding diagnosis; date of first brain imaging which demonstrated abnormality in-keeping with a likely diagnosis of GBM; factors influencing treatment modalities undertaken, molecular and genetic analysis of tumour samples; disease recurrence/progression, and date of death if applicable.

Results

54 patients diagnosed with GBM.
13 patients were aged over 70 years. 8 males, 5 females. Commonest co-morbid conditions were hypertension and gout.
2/13 received best supportive care only, based on poor performance status and extensive disease burden.

9/13 underwent neurosurgery; 7 debulked; 2 biopsy only.
7 isocitrate dehydrogenase (IDH1) wild-type; 2 IDH classification not known. 3 MGMT methylated; 4 unmethylated; 2 MGMT classification not known.

3/13 received temozolomide (TMZ) alone. 2 later received palliative radiotherapy (30Gy in 6 #) to control symptoms.
4/13 received 40Gy in 15 # with concurrent TMZ
4/13 received 60Gy in 30 # with concurrent TMZ.
5 received adjuvant TMZ following initial chemo-radiation: 3 after 40Gy and 2 after 60Gy
As of March 2021, 6/13 were alive, including all 4 who had received hypofractionated radiotherapy. 4 of these continue to demonstrate stable disease on most recent imaging.

Conclusion

Baseline fitness levels of patients were generally high, with few having significant co-morbidity pre-diagnosis.
Prognosis and morbidity was significantly poorer in patients who did not undergo any form of radiotherapy.
Patients who received hypofractionated radiotherapy demonstrated most favourable health-related outcomes, demonstrating longest survival and least evidence of disease recurrence/progression.
Although the sample size for this study is small, it highlights the potential benefits of radiotherapy on survival, particularly hypofractionated courses such as 40Gy in 15 fractions in a real-world population, even during a

global pandemic.
It would be useful to prospectively follow-up elderly patients with GBM to assess outcomes and quality of life.

Extent of resection in glioblastoma: a 10-year local survival analysis

Oral Presentation - Video on demand (7 minutes)

Mr. Theodore Hirst [1], ***Mr. Patrick McAleavey*** [2], ***Mr. Tom Flannery*** [1]

1. *Department of Neurosurgery, Royal Victoria Hospital, Belfast,* ***2.*** *School of Medicine, Queen's University Belfast, UK*

Aims

The impact on extent of resection (EOR) in glioblastoma has been well documented. It is clear that gross-total resection (GTR) confers best overall survival (OS), however the minimum EOR required to confer a survival benefit over biopsy is debated. Recent studies favour partial resection (PR) over biopsy for IDH-wildtype, MGMT-unmethylated tumours. We describe our experiences locally with these principles in mind.

Method

Retrospective evaluation of a single surgeon cohort. All patients over 18 years old, undergoing a surgical treatment for histologically confirmed GBM in the stated period were included. We collected information on demographics, tumour volume, EOR, complications, adjuvant therapies, molecular profile, and OS. We used log rank tests and Cox Proportional Hazards Models to identify factors associated with OS.

Results

The patient and tumour characteristics of our cohort were similar to those documented in the literature. The mean age was 56.6 years. 72 patients underwent biopsy and 202 had debulking surgery. Median OS was 11 months. Of those debulked, gross-total resection was achieved in 41 patients (20%); associated median OS was 29 months. Patients receiving partial resection (defined as EOR <80%) had no clear survival benefit over patients undergoing biopsy (median OS 6 vs 5 months) but had a higher rate of post-op neurological deficit (3% vs 12%). Tumour molecular profile appeared to influence survival outcome in a manner comparable to worldwide experience.

Conclusion

In our experience, partial resection is not a justifiable surgical aim in the typical glioblastoma cohort. The limited benefit that it may confer over biopsy appears to be outweighed by the risk of neurological deficit that affects quality and probably quantity of life. This finding applies to our glioblastoma population in general as well as those specifically with an MGM-unmethylated tumour.

Impact of surgical delays on pre-operative complications in primary GBM patients- a 5-year study

Oral Presentation - Video on demand (7 minutes)

Dr. thaaqib nazar [1], ***Mr. Stephen Price*** [2]

1. *Cambridge Brain Tumour Imaging Laboratory, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital,* ***2.*** *University of Cambridge*

Aims

Glioblastoma Multiforme (GBM) is one of the most aggressive primary brain tumors with poor prognosis (median survival 18 months) and no cure. Management strategies often involve maximum safe resection followed by chemoradiotherapy. There has been a move from managing such patients electively rather than the traditional model of treating them as an emergency. While this may have advantages, this can delay the time from presentation to operation. This delay has recently been further compounded by the current COVID-19 pandemic.

There is no data available as to whether the surgical delays that are currently occurring have an impact on patient care, and may outweigh the benefits of elective management on health services.

We aimed to conduct a single centre observational study to assess how long patients should be waiting prior to surgery. We hypothesised that the longer the wait, the higher the pre-operative complication rate and worse the outcomes.

Method

698 patients in a GBM database over a 5-year period (29/10/14- 8/11/19) were studied. All patient data was accessed via electronic patient records

Surgical delay was defined as the interval between date of being put on the waiting list (the date seen in the neuro-oncology clinic) to date of surgery.

Primary outcome measure was preoperative complications, which was categorised into transient neurological decline, stroke, seizures, diabetes/erratic blood sugars, emergency admission, others (e.g., cardiovascular compromise, steroid complications, blood disorders)

Inclusion criteria included: First presentation supratentorial WHO Grade 4 GBM confirmed on histology (this included histological variants such as Gliosarcoma and Epithelioid Glioblastoma), and all patients who had been seen in the neuro-oncology clinic prior to surgery.

Exclusion criteria included all patients who were not thought to have a GBM or high-grade glioma on initial imaging, those admitted as an emergency without being seen in a neuro-oncology clinic, recurrent or secondary GBMs.

Results

460 patients met the inclusion criteria in this study. There was a pre-operative complication rate of 14.6% (67/460). 55% of complications were due to a transient neurological decline (37/67) with 16.4 % (11/67) of patients presenting with seizures. For those with surgical delays ≤7 days pre-operative complication rates were 2.2 % vs 15.9% in those with delays >7 days, p value 0.012, Odds ratio 8.53 (95% CI 1.48- 88.09). Results were statistically significant in those with delays greater than 10 and 14 days (p values 0.0026 and 0.0004 respectively)

ROC Curve analysis revealed an AUC of 0.66 with sensitivities of 99%, 90% and 76% at surgical delays of 7,10 and 14 days respectively.

The median length of hospital admission in both groups of patients was 5 days (p= 0.2065)

All statistical analysis was carried out using Prism 9 and SPSS

Conclusion

In spite of unchanged length of hospital stay, we note a significant increase in pre-operative complication rates as a result of surgical delays greater than 7,10 and 14 days, which introduces an interesting debate in the merit of delaying operations for further assessment in clinic. Our objectives would be to minimize complication rate, therefore a high sensitivity i.e. true positive rate would be most desirable. The 99% levels achieved at 7 days In the ROC analysis lends weight to introducing policy to fast-track admissions for primary GBM patients.

Further directions could include assessing the impact reduced surgical services and redeployment might have had on complications rates and length of hospital stay on patients admitted over the COVID 19 pandemic.

Intracranial myxoid mesenchymal tumour with EWSR1-ATF1 fusion mimicking high grade glioma

Oral Presentation - Video on demand (7 minutes)

Dr. Santhosh Nagaraju [1], ***Dr. Ion Boiangiu*** [2], ***Prof. Ian Brown*** [2], ***Mr. Hussien El-Maghraby*** [3], ***Dr. U Pohl*** [1]

1. *Dept. of Cellular Pathology, University Hospitals Birmingham,* ***2.*** *Dept. of Clinical Oncology, University Hospital Coventry,* ***3.*** *Dept. of Neurosurgery, University Hospital Coventry*

Aims

Molecular profiling is increasingly used in the diagnosis of CNS and non-CNS neoplasms. More than a quarter of all soft tissue tumours are characterized by specific recurrent chromosomal translocations which can be used as molecular signatures. With increasing frequency, EWSR1 rearrangements are found on both mesenchymal tumours and primary glial/neuronal tumours.

Here we present a case of intracranial myxoid mesenchymal tumour (IMMT), a rare tumour which is becoming more recognised in recent years, affecting mainly children and young adults, and rarely older adults. It can be found in intraaxial and extraaxial location, with frequent dural connection. The tumour is defined by the genetic hallmark of EWSR1-CREB family gene fusion. Including our case, 16 intracranial tumours with this gene fusion have been reported to date. Our goal is to contribute further to the characterisation of the morphological spectrum, fusion partners and biological behaviour of rare EWSR1-CREB (non-ETS)-rearranged tumours of the CNS.

Method

Case: The patient is a 27 year old woman with a frontal lobe lesion, radiologically described as a tumour with dural attachment. She

underwent surgical debulking, and tumour tissue was histologically

examined with conventional immunohistochemistry. Additional genetic

testing included targeted mutation screening, FISH, EPIC (Illumina BeadChip) methylation array and next generation sequencing.

Histology showed a mitotically active neoplasm with relatively uniform

cells, round nuclei and oligodendroglioma-like clear cell change, but

no myxoid change. Glomeruloid microvascular proliferation and large

areas of tumour necrosis were present.

Immunohistochemistry was focally positive for GFAP, and negative or

normal for synaptophysin, IDH1 R132H mutation, ATRX and p53. The ki-67

index reached ~20%.

Sequencing of IDH1 and IDH2 did not reveal rare IDH mutations, and

FISH did not show 1p19q codeletion. Testing for BRAF V600 mutation was

negative.

Results

Although the histology initially suggested a diagnosis of oligodendroglioma, the integrated

diagnosis was compatible with glioblastoma, IDH wildtype.

Methylation array analysis by EPIC array did not result in classification of

currently known entities, neither confirming glioblastoma, nor providing a new diagnosis, when analysed on both brain tumour and sarcoma classifier.

This suggested a novel tumour entity not yet represented in the classifier algorithm.

Additional testing including next generation sequencing revealed EWSR1 gene

rearrangement with fusion partner ATF1 (EWSR1-ATF1 fusion).

Based on this, the diagnosis was revised to the emerging new entity of

‘intracranial myxoid mesenchymal tumor’ (IMMT) characterised by EWSR1

fusion with members of the cAMP response element binding protein (CREB) family (ATF1, CREB1 and CREM). Subsequent immunohistochemistry demonstrated positive staining for CD99 and EMA but not desmin. The patient underwent various oncological treatments and is recurrence-free 3 years after initial diagnosis.

Conclusion

Histologically, IMMT demonstrates a spectrum of features that overlaps with other tumours, but often displays circumscribed growth, uniform cellularity, cytoplasmic clearing and variable myxoid change. The clinical behaviour of these tumours is not fully understood, however provisionally considered intermediate grade.

EWSR1-CREB family fusion is not specific but shared with a diverse group of extracranial tumours including soft tissue, salivary gland, odontogenic and myoepithelial tumours.

Therefore, clinico-radiologico-pathological correlation is essential to achieve the final diagnosis, and ensure the absence of a primary tumour elsewhere.

Familiarisation with IMMT, its characteristic genetic profile and its as yet underreported natural course is crucial, as it can clinically mimic other intracranial tumours such as malignant meningioma or glioma but appears to behave less aggressively than high grade glioma.

It is also important to further our understanding of its optimal treatment through review of larger case series and global comparison of patient management.

Investigating mitochondrial SLC25A transporters involved in supporting glioma survival and metabolism under hypoxia

Oral Presentation - Video on demand (7 minutes)

Dr. Katherine Eales [1], ***Dr. Jennie Roberts*** [1], ***Dr. Alina Finch*** [2], ***Dr. Dan Tennant*** [1]

1. *Institute of Metabolism and Systems Research, University of Birmingham, UK,* ***2.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Advancements in cancer prevention, detection and treatment over the last 40 years have significantly transformed healthcare, however there are a few cancers, such as brain tumours, which are consistently lagging behind. The most common adult brain tumour is glioma; a highly aggressive cancer that invades deep into the surrounding brain consequently making treatment challenging. The severe hypoxic nature of glioma adds further complications to therapeutic efficacy as hypoxia limits efficient drug delivery as well as increasing treatment resistance. Therapies that therefore target both the hypoxic tumour microenvironment and metabolic pathways that sustain growth have significant potential to improve patient prognosis. Furthermore, it is well known that cancer cells demonstrate an abnormal metabolism, resulting in an altered requirement for amino acids to aid uncontrolled proliferation. We are therefore interested in a family of mitochondrial transporters, SLC25A, which translocate numerous solutes across the mitochondrial membrane and are crucial for many metabolic reactions.

Method

Computational analysis of data from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression project (GTEX) has shown that many of these SLC25A amino acid carriers are upregulated in glioma compared to normal tissue. Remarkably however, around 23 of the 53 mammalian SLC25A members lack defined substrate selectivity and so we are interested in identifying which transporters are particularly important in the metabolic adaptation to hypoxia. Using CRISPR and siRNA technologies, we have identified transporters that are functionally required for cell proliferation of glioma cell lines and patient tumour lines. Furthermore, qPCR and western blotting have been used to assess the regulation of these transporters under hypoxic conditions. Through the use of stable isotope-enriched nutrients and gas chromatography mass spectrometry (GC-MS) technologies, we have also investigated how these SLC25A transporters function metabolically in both knockout and knockdown cell models.

Results

Disruption of transporter expression in knockout cell models, glioma cell lines and patient tumour lines resulted in a reduced growth rate both under normoxic (21% O_2) and hypoxic (0.3% O_2) conditions. Assessing both the mRNA and protein expression of these transporters in glioma cell lines showed a significant and rapid upregulation under hypoxic conditions. Metabolic analysis of these knockout and knockdown models identified a series of tricarboxylic acid cycle (TCA) metabolites and amino acids which were significantly altered compared to control cells, thereby contributing to a dysregulated metabolic network under both normoxic and hypoxic conditions.

Conclusion

Metabolic analysis of these cell models has identified a novel means by which glioma metabolism can be perturbed through inhibition of these amino acid transporters. Characterising the function and identifying which SLC25A transporters are important for hypoxic tumour metabolism can therefore expose a potential way to exploit hypoxic areas in these tumours, subsequently making them more vulnerable to treatment and thus im-

pacting patient survival

Metabolomic profiling of ASS1+/- isogenic primary GBM cells reveal distinct metabolic responses to arginine deprivation

Oral Presentation - Video on demand (7 minutes)

Mr. Sajeenth Vishnu K [1], ***Dr. Elizabeth Want*** [1], ***Mr. Kevin O'Neill*** [1], ***Dr. Nelofer Syed*** [1]

1. *Imperial College London*

Aims

Glioblastoma Multiforme (GBM) is the most common grade IV primary central nervous system cancer for which there is no cure. Treatment is only palliative consisting of radical surgery followed by chemo/radiotherapy which extends survival by only a few months. There is clearly a need to identify novel and more successful therapeutic strategies. Targeting the altered metabolism of tumour cells is an approach currently being explored in the Syed laboratory, of which arginine deprivation is one. The argininosuccinate synthase 1 (ASS1) status of tumours is known to differentially affect its response to arginine deprivation. We aim to characterise the metabolic differences between isogeneic ASS- and ASS+ cells and their metabolic response to arginine deprivation using Ultrahigh Performance Liquid Chromatography tandem Mass Spectrometry (UPLC-MS/MS) specifically targeting amines. This analysis has the potential to identify additional novel therapeutic targets that can synergise with arginine deprivation and current standard of care.

Method

An ASS negative primary cell line, GBM31 (established from a fresh tumour), was transduced with the ASS1 gene using retroviral technology to generate an isogenic ASS positive cell line. qPCR was used to confirm expression of the gene. ADI-PEG20, an arginine degrading enzyme, was used to deplete the growth media of arginine and Sulforhodamine B Proliferation Assays were performed at various time points after addition of ADI-PEG20 (0,3,6,9,12 days).

UPLC-MS/MS was used for metabolomic profiling of cell pellets and spent media for a panel of 33 amino acids and biogenic amines in the presence and absence of ADI-PEG20 to allow Consumption and Release (CORE) analysis. Multivariate analysis of the amine panel was performed on SIMCA using unsupervised principle component analyses (PCA) followed by supervised Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA).

Results

We demonstrated that 0.2µg/ml ADI-PEG20 effectively depletes growth media of arginine within 24 hours and confirmed that no other amines were altered. 0.2µg/ml ADI-PEG20 also caused growth restriction of ASS- cells but not ASS+ cells.

Multivariate analysis revealed a comparable basal metabolic signature for both ASS- and ASS+ isogenic lines. Upon arginine depletion, internal metabolic differences were detected at 48 hours. We demonstrated that ASS+ cells rescue the detrimental effects of arginine depletion through upregulation of arginine biosynthesis, primarily through citrulline uptake and increased urea cycle activity. ASS- cells showed a diversion of Serine and Asparagine and an upregulation of fatty acid catabolism, all of which feed into the TCA cycle. Prolonged arginine depletion however induced cell death in ASS- cells. Further bioinformatic STRING pathway analysis revealed promotion of tumour invasion and proliferation in ASS- cells and preferential upregulation of energy homeostasis in ASS+ cells in response to arginine deprivation.

Conclusion

We have demonstrated that ADI-PEG20, is effective in concentrations as low as 0.2µg/ml and its effects are rapid.

A single genetic alteration of ASS1 status in isogenic primary GBM cells, was sufficient to alter the metabolic response to arginine deprivation, but had no impact on the basal metabolic profile of the cells. ASS+ cells were rescued through upregulation of energy homeostasis and the urea cycle whereas ASS- cells preferentially upregulated the TCA cycle and fatty acid catabolism, which momentarily promoted survival before induction of cell death. Our results provide some insight into the aggressive nature of ASS- tumours as observed in-vivo and demonstrate the adaptability of GBM in response to stressors. Targeting the entry points into the TCA cycle and fatty acid catabolism could enhance the therapeutic potential of arginine deprivation in GBM.

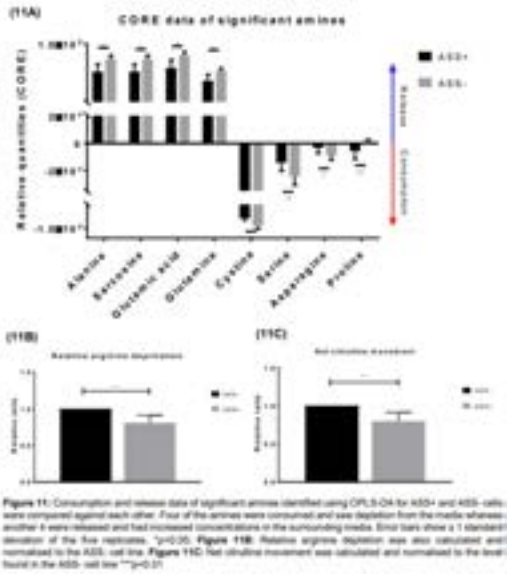
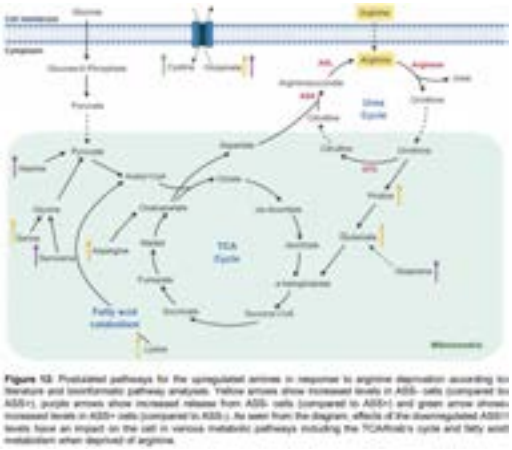


Figure 1.png



Summary figure.png

Amine	ASS+		ASS-		Postulated function – Reactome pathway analysis
	Cell	CORE	Cell	CORE	
Arginine	↓	-	↓↓	-	NO synthesis, amino acid response pathway
Citrulline	↑	C < ASS-	↑↑	Consumed	Arginine biosynthesis
Glutamic a/ glutamate	↑	R < ASS-	↑↑	Released	Maintenance and promotion of cell function, TCA cycle
Alanine	-	R < ASS-	-	Released	Metabolism and energy homeostasis
Glutamine	-	R < ASS-	-	Released	Converted into glutamate; TCA cycle
Sarcosine	-	R < ASS-	-	Released	Degraded into glycine; TCA cycle
Proline	↑	Released	↑↑	Consumed	Tumour stability; TCA cycle
Cystine	↑↑	C < ASS-	↑	Consumed	Energy homeostasis
Asparagine	↑	C < ASS-	↑↑	Consumed	Tumour invasion and cell proliferation
Serine	-	C < ASS-	-	Consumed	D-serine biosynthesis, glycine synthesis (precursor to pyruvate)
Lysine	↑	-	↑↑	-	Ketone body synthesis (fatty acid catabolism)

Table 1: Table summarising data from cell lysate samples and CORE calculations with postulated function of each amine from literature and Reactome pathway analysis. C = consumption; R = Release

Table 1.png

Metachronous oligodendroglial tumours with different IDH mutational profile in a young patient

Oral Presentation - Video on demand (7 minutes)

Dr. U Pohl [1], ***Dr. Santhosh Nagaraju*** [2]

1. *Dept. of Cellular Pathology, University Hospitals Birmingham,* ***2.*** *Dept of Cellular Pathology, University Hospitals Birmingham*

Aims

Oligodendroglioma is molecularly defined by mutation of isocitrate dehydrogenase (IDH) and 1p19q codeletion. IDH mutation is an early driver of tumorigenesis, via its oncometabolite 2-hydroxyglutarate, regardless of the exact mutational subtype in homologues IDH1 or IDH2. IDH mutant cells then acquire 1p19q codeletion, with haploinsufficiency likely to contribute to oncogenesis by reduced expression of genes on 1p and 19q, as well as mutations in TERT, FUBP1 (on 1p31.1) in ~30% and CIC (on 19q13.2) in ~>60% of 1p19q-codeleted gliomas.
We present a case of a young patient with metachronous oligodendroglial tumours, initially thought to represent contralateral recurrence of the same disease. However, IDH mutation analysis in each tumour revealed distinct types of mutations, involving both IDH1 and IDH2, indicating different cellular lineages of tumorigenesis. We aim to present this unusual combination by illustrating the histology and molecular profile, and review the literature with regards to multifocal but molecularly distinct glioma.

Method

Case: The patient is a 33 year old man initially presenting with seizures, who was found to have a frontal lobe lesion (hence called tumour 1) with focal radiological enhancement, followed by a contralateral lesion in the parietal lobe 6 months later (hence designated as tumour 2). He underwent separate surgical debulking, and each time, tumour tissue was histologically and genetically examined. Testing included targeted mutation screening by immunohistochemistry and PCR based methods, pyrosequencing for MGMT methylation analysis, FISH for chromosomal LOH analysis of 1p and 19q, immunohistochemistry for mismatch repair enzymes and next generation sequencing.

Results

Histology of tumour 1 revealed a neoplasm with uniform cells, round nuclei and oligodendroglioma-like clear cell change, without mitoses, microvascular proliferation or necrosis. Immunohistochemistry showed absence of IDH1 R132H mutation, retained expression of ATRX and no altered p53 staining. The ki-67 index reached 6%. Sequencing of IDH1/2 mutations revealed a rare IDH2 mutation (non-/R172K). FISH confirmed codeletion of 1p19q, and the integrated diagnosis was oligodendroglioma, IDH mutant and 1p19q codeleted, WHO grade II.
Histology of tumour 2 demonstrated oligodendroglioma morphology in areas, but more cellular and nuclear pleomorphism and focally brisk mitotic activity (7 mitoses in 10 hpf; ki67 index 20%), while both microvascular proliferation and necrosis were absent.
Immunohistochemistry showed IDH1 R132H mutation and retained ATRX, while p53 was not expressed. FISH studies confirmed codeletion of 1p19q, and the integrated diagnosis was anaplastic oligodendroglioma, IDH mutant and 1p19q codeleted, WHO-2016 grade III. NGS data and MMR results are compared.

Conclusion

We present a patient with two histologically similar, but molecularly distinct oligodendroglial tumours affecting both cerebral hemispheres. Apart from the grade, the important difference is the presence of different IDH mutations, 1) a rare IDH2 mutation (non-R172K) and 2) the common IDH1 (R132H) mutation.

While both types of IDH mutations identified are known to occur in oligodendroglioma, the difference clearly indicates two distinct lineages of tumorigenesis, especially as IDH mutation is considered an early event in gliomagenesis. IDH2 mutations are often associated with oligodendrogliomas, while IDH1 R132H is recognised to be frequent in both diffuse oligodendroglial and astroglial neoplasms.
Multifocal divergent gliomas have been described previously but oligodendrogliomas with differing IDH mutations in the same patient have not knowingly been reported yet. Importantly, though therapeutically irrelevant here, multicentric gliomas do not automatically imply relatedness. However, a common origin or predisposition (here, even predating IDH mutation) may not be ruled out.

Outcomes following Craniotomy for Brain Metastases

Oral Presentation - Video on demand (7 minutes)

Mr. Hadleigh Cuthbert [1], ***Ms. Ayesha Arshad*** [1], ***Mr. Sondos El-Adawi*** [1], ***Mr. Athanasios Zisakis*** [1], ***Mr. Georgios Tsermoulas*** [1], ***Dr. Victoria Wykes*** [2]

1. *University Hospitals Birmingham NHS Foundation Trust,* ***2.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Brain metastases account for more than 50% of all intracranial tumours, and are associated with universally poor outcome, significant morbidity, and diminished quality of life. Treatment decisions in this heterogenous patient cohort remain controversial, with a myriad of treatment options available (WBRT, surgery, SRS), but no clearly defined standard of care. Additionally, the prognosis for brain metastases varies widely with tumour type, and tailored decision-making is required. Surgical treatment decisions are made at a multi-disciplinary team level based on prognosis, tumour characteristics, and performance status.

The aim of this study was to assess the six-month mortality and overall survival of patients undergoing craniotomy for brain metastases at Queen Elizabeth Hospital Birmingham, in order to evaluate surgical decision-making and inform future treatment decisions through the neuro-oncology MDT.

Method

The present study is a single centre retrospective analysis of all patients with brain metastasis undergoing craniotomy from 15 April 2014 to 30 June 2018. Exclusion criteria included: patients with suspicious features for primary brain tumour on histology; patients managed without craniotomy; and patients who underwent surgery for biopsy only. The primary endpoint for these analyses was the survival time from the date of initial neurosurgical operation. Survival analysis was continued until 11 March 2021.

In those patients who passed away before 6 months, medical notes were reviewed to establish a cause of death as 'neurological' versus 'non-neurological'. 'Non-neurological' was defined as extracranial disease progression or intercurrent systemic illness (for example pneumonia, pulmonary embolus).

Results

A total of 322 patients were identified who met inclusion criteria. The median age was 60 years old, with a slight female preponderance. The cohort was highly heterogeneous with over twenty different primary tumour types identified; the most common primaries were lung (n=106), breast (n=83) and melanoma (n=46).

Median overall survival in this cohort was 8.1 months. Two-year survival was 19.3%. 39.4% of patients (n=127) survived for less than 6 months following their initial brain metastasis operation. Importantly, when considering cause of death in this cohort, the significant majority were non-neurological in nature.

Conclusion

Median overall survival in this study is lower than published literature. Strikingly, the majority of deaths within 6 months are non-neurological in nature. This suggests that improvement is required in the selection of surgical cases at an MDT level.

Careful patient selection in this cohort is crucial to avoid unnecessary morbidity and to preserve quality of life for patients who have a poor prognosis. There is marked heterogeneity in outcomes for brain metastases. Further, prognostic factors vary widely with primary diagnosis, and recent studies have highlighted benefits of using primary-specific prognostic systems to guide treatment decisions.

This study emphasises the need for treatment decisions to be individualised based on both patient and tumour characteristics. We are exploring the use of Diagnosis-Specific Graded Prognostic Assessments (GPAs) at this

Unit with the aim of improving prognostication of patients at MDT and better stratifying patients likely to benefit from surgery.

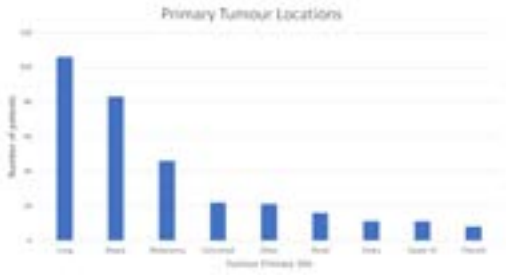


Figure 1 tumour location.png

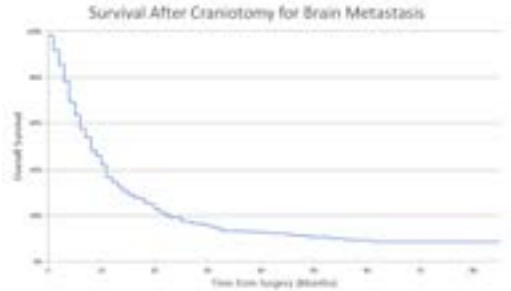


Figure 2 survival analysis.png

Study	Number of patients	Primary	Median OS (months)	Short term outcomes
Present study	**322**	**All**	**8.1**	**60.6% survival at 6 months**
Abrahams et al. (2001)	71	NSCLC	12.9	52.2% survival at 1 year
Rogne et al. (2011)	316	All	9.2	0.8% 30d mortality
Tabouret et al. (2013)	49	Breast	15.4	
D'Andrea et al. (2017)	71	Lung Renal Breast GI Melanoma	11	55% survival at 6 months
Vosoughi et al. (2018)	79	Melanoma	12.8	
Kawamata et al. (2019)	1015	All	15.4 (from time of diagnosis of metastasis)	

Table 1: comparing present study characteristics and outcomes to published outcomes following surgery in brain metastasis cohorts.

Table 1 literature comparison.png

Prevalence of BRAF V600 in primary gliomas: a systematic review

Oral Presentation - Video on demand (7 minutes)

Ms. Lily Andrews [1], ***Mr. Zak Thornton*** [1], ***Mr. Samir Saincher*** [1], ***Ms. Sarah Dawson*** [1], ***Dr. Vincent Cheng*** [1], ***Prof. Julian Higgins*** [1], ***Dr. Alexandra McAleenan*** [1], ***Dr. Kathreena Kurian*** [1]

1. *University of Bristol*

Aims

Glioma is a fatal disease that causes significant years of life lost to an individual. Mutations in the driver gene BRAF, such as the V600 alteration, may contribute to gliomagenesis in adults and children through abnormal signaling causing uncontrolled cell proliferation. The use of BRAF-inhibitor drugs including Vemurafenib and Dabrafenib have shown a favorable response in 48% and 50% of melanoma patients with BRAF V600 mutations respectively. BRAF inhibitors and MEK inhibitors have shown efficacy in certain paediatric gliomas in the recurrent setting.

Despite the potential benefit of BRAF inhibitors, the prevalence of BRAF V600 within primary gliomas is not fully discovered. Some studies identify the prevalence to be over 50%, while others find the prevalence to be around 1%. We performed a comprehensive systematic review to determine the prevalence of BRAF V600 within the adult and paediatric glioma population in different diagnostic groups.

Method

A systematic literature search was performed using Ovid MEDLINE and Embase from genesis to the 22nd October 2020. Studies were not restricted by language. Studies were eligible if patients were histologically diagnosed according to WHO guidelines as a primary glioma evaluating the prevalence of BRAF V600 and included ≥ 10 primary glioma patients. The review protocol was registered in PROSPERO (CRD42019127704). Search results were managed using Endnote. Two independent reviewers assessed the eligibility of the publications using Rayyan, conflicts were evaluated by a third reviewer. Included articles were extracted by one reviewer and confirmed by a second reviewer. Risk of bias assessments were conducted using Hoy et al's risk of bias tool. Results were synthesized using "metaprop" in R. The meta-analysis was carried out in R which produced forest plots.

Results

Our cohort included 182 studies with a total of 13669 adult and paediatric glioma patients classified diagnostically according to WHO guidelines. Among 48 glioma entities, BRAF V600 was identified most commonly in epithelioid glioblastoma with a prevalence of 69% (95% confidence interval (CI): 45-89%), followed by pleomorphic xanthoastrocytoma with a prevalence of 56% (95% CI: 48-64%), anaplastic pleomorphic xanthoastrocytoma with a prevalence of 38% (95% CI: 23-54%), ganglioglioma with a prevalence of 40% (95% CI: 33-46%), and anaplastic gangliogliomа with a prevalence of 46% (95% CI: 18-76%). Other glioma entities were found to have a prevalence of BRAF V600, these include astroblastoma (24%), desmoplastic infantile astrocytoma (16%), subependymal giant cell astrocytoma (8%), dysembryoplastic neuroepithelial tumour (3%), diffuse astrocytoma (3%), and pilocytic astrocytoma (3%).

Conclusion

To our knowledge, this is the largest systematic review examining the prevalence of BRAF V600 in adult and paediatric glioma classified according to diagnostic WHO criteria. However, there were some limitations in this review. The sample sizes of some studies were very small, and the method of mutational analysis for BRAF V600 varied between papers. We found BRAF V600 in a significant prevalence of epithelioid glioblastoma, pleo-

morphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma, ganglioglioma, and anaplastic ganglioglioma. Of interest, BRAF V600 mutation was found in a lower prevalence of astroblastoma, desmoplastic infantile astrocytoma, subependymal giant cell astrocytoma, dysembryoplastic neuroepithelial tumour, diffuse astrocytoma, and pilocytic astrocytoma. Consideration of assessment of BRAF V600 mutation may enable further treatment options with BRAF and/or MEK inhibitors in these particular diagnostic entities.

Re-operation for recurrent intracranial meningioma – is it worth it?

Oral Presentation - Video on demand (7 minutes)

Mr. george richardson [1], ***Mr. Conor Gillespie*** [1], ***Mr. Mohammad Mustafa*** [1], ***Mr. Basel Taweel*** [1], ***Mr. Christopher Millward*** [2], ***Dr. Abdurrahman Islim*** [3], ***Prof. Michael Jenkinson*** [2]

1. *University of Liverpool,* ***2.*** *The Walton Centre and University of Liverpool,* ***3.*** *The Walton Centre, Liverpool*

Aims

Meningioma is the commonest primary brain tumour. Despite surgery, meningiomas can recur. Surgery is usually the first line treatment for recurrent meningioma. The aim was to determine the risk factors associated with clinical outcomes (performance status, morbidity, mortality, recurrence) following re-operation for recurrence of intracranial meningioma.

Method

Retrospective cohort study (1998-2018). Eligible patients had re-operation for local recurrence of a previously operated meningioma. Collected data included baseline clinical and imaging characteristic. Primary outcome measure was performance status after each re-operation. Secondary outcome measures were medical and surgical morbidity, recurrence-free survival (RFS) and overall survival (OS).

Results

Fifty-eight patients were eligible (38 female, mean age at 1st re-operation 56 years (SD=11.4)). Eleven patients (18.9%) had 2 re-operations and 3 patients (3.4%) had 3 re-operations. Median follow up was 125.5 months (IQR 73-191.5). Median time to 1st recurrence and 1st re-operation were 36.5 (IQR 24.2–79.1) and 43.8 months (IQR 22.9–102.7), respectively. Fifteen patients (25.9%) had worse performance status after 1st re-operation, compared to 6.9% (n=4) after the primary operation (Figure 1). Complication rate was 32.8% (n=19) after the primary operation compared to 46.6% (n=27) after 1st re-operation. At primary operation, there were 29 (50%) grade 1, 26 (44.8%) grade 2, and 1 (1.7%) grade 3 tumours. Median RFS after first re-operation was 68 months (95% CI 45.5-90.5) (figure 2). Median OS was 312 months (95% CI 236.9-387.1) (Figure 3). Post-operative complications were a risk factor for worsened performance status following re-operation (OR 4.91, 95% CI 1.3-18.4).

Conclusion

Re-operation is associated with a worse performance status and increased risk of complications. Re-operating meningiomas for radiological recurrence without symptoms increases patient morbidity. Shared-care management decision should be made with patients when considering operating for radiological recurrence only.

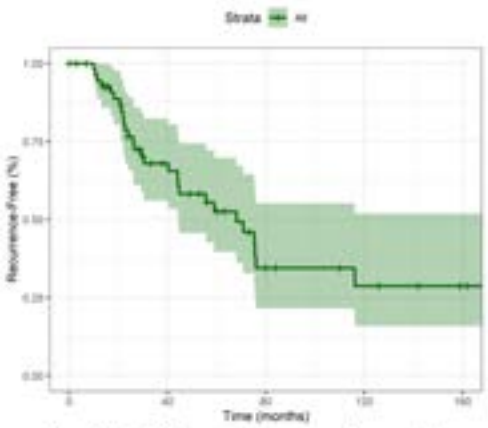


Figure 2. Kaplan Meier curve for recurrence free survival.

Figure-2-km-rfs.jpg

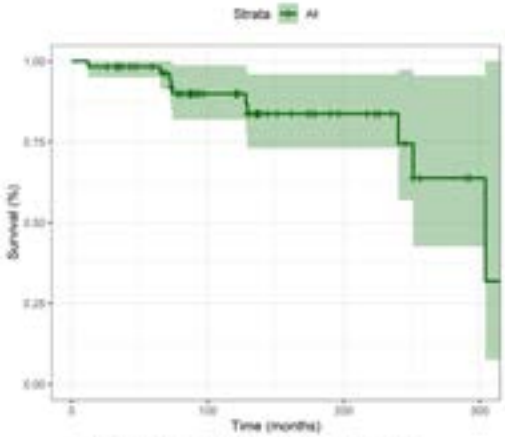


Figure 3. Kaplan Meier curve for overall survival.

Figure-3-km-os.jpg

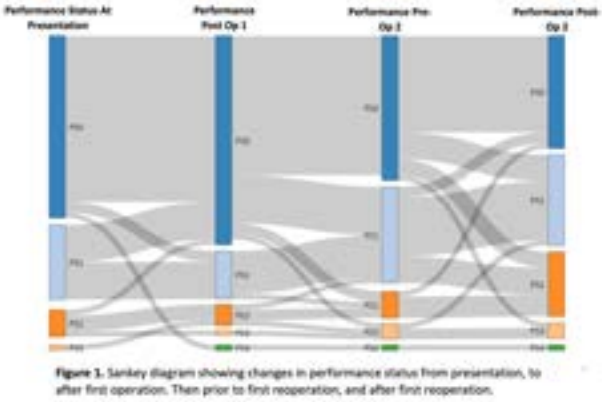


Figure 1. Sankey diagram showing changes in performance status from presentation, to after first operation. Then prior to first reoperation, and after first reoperation.

Figure-1-sankey.jpg

Role of treatments for diabetes and hyperlipidaemia in risk and mortality of primary and secondary brain tumours: a case control and cohort study

Oral Presentation - Video on demand (7 minutes)

Mr. Jamie Robinson [1], ***Prof. Richard Martin*** [1], ***Dr. Mio Ozawa*** [2], ***Dr. Martha Elwenspoek*** [1], ***Dr. Maria Theresa Redaniel*** [1], ***Dr. Kathreena Kurian*** [1], ***Prof. Yoav Ben-Shlomo*** [1]

1. *University of Bristol,* ***2.*** *University College London*

Aims

Studies suggest anti-hyperlipidaemic and -diabetic medications (fibrates and glitazones) may have a role in primary prevention and progression of brain tumours by targeting PPAR-α and -γ respectively.

Method

We conducted a case-control and clinical cohort study within the Clinical Practice Research Datalink and identified adults with primary or secondary brain tumours diagnosed between 2000-2016 prescribed either fibrates or glitazones. Multivariable logistic regression analysis and Cox's survival models estimated an association between drug exposure and brain tumour status and mortality.

Results

Our analyses showed little evidence of an association between fibrates exposure and either risk or mortality of brain tumours (adjusted odds ratio (aOR) = 0.98, 95% CI: 0.77, 1.23; adjusted hazard ratio (aHR) = 0.91; 95% CI: 0.76, 1.09). We observed a reduced risk for per-year increase in exposure duration for glitazones (aOR = 0.88, 95% CI: 0.81, 0.96, P=0.002) but no mortality benefit (aHR = 0.99, 95% CI: 0.80, 1.23).

Conclusion

We failed to find any strong evidence of a protective effect on risk or mortality for fibrate exposure. However, our results suggest longer duration exposure to glitazones is associated with reduced risk of primary and secondary brain tumours

Single-cell transcriptomics identifies a conserved brain tumour growth mechanism driven by HEATR1-dependent ribogenesis control

Oral Presentation - Video on demand (7 minutes)

Dr. Jon Gil-Ranedo [1], ***Ms. Laura Radriguez-Diaz*** [1], ***Dr. Karolina Jaworek*** [2], ***Mr. Nsikan Nsek*** [1], ***Mr. Joao Marques*** [3], ***Ms. Eleni Costa*** [4], ***Dr. Torsten Bossing*** [1], ***Dr. Claudia Barros*** [1]

1. *Peninsula Medical School, Faculty of Health, University of Plymouth, Plymouth, UK,* ***2.*** *University of Exeter,* ***3.*** *University of Bern,* ***4.*** *Queen Mary University of London*

Aims

It has been gradually accepted that several types of brain tumours, including low- and high-grade gliomas, are originated and sustained by a stem cell-like population named brain tumour-initiating cells (BTICs) (Gimple et al., 2019). There are growing evidence pointing to neural progenitors as cells of origin of BTICs, but the events driving the transformation remain unknown (Llaguno et al., 2019). In this work, we aim to identify and characterise processes driving or supporting transformation and immortalisation of BTICs, which could provide valuable insights on brain tumour initiation, progression and recurrence, allowing the design of more effective treatments.

Method

Loss of the *Drosophila* tumour suppressor *brat* or its human orthologue, *TRIM3*, promotes stem cell-like properties and brain tumour growth in *Drosophila* brains and human gliomas (Bowman et al., 2008; Chen et al., 2014). We performed a single-cell transcriptomics analysis comparing normal neural progenitors and transforming *brat* BTICs isolated directly from live larval brains. Differentially expressed genes were identified and validated, and overrepresented pathways potentially involved in tumour formation exposed. We are translating our findings by investigating expression and function of selected conserved human orthologues in glioma tissues and GBM-derived cell lines including BTICs.

Results

Our transcriptome analysis identified over 500 differentially expressed genes (FDR<0.15) in *Drosophila* BTICs, of which more than 85% have human orthologues. Overrepresentation analysis shows an enrichment in proteostasis processes including ribogenesis. We selected a ribogenesis-related gene, *HEATR1*, for further analysis. We found *HEATR1*[CB1] overexpressed in *Drosophila* BTICs and its human orthologue upregulated in both low- and high-grade gliomas, as well as in high grade glioblastoma (GBM)-derived BTICs. *HEATR1* inhibition in *brat* BTICs reduces ribosome ribogenesis, cell growth and proliferation, preventing brain tumour growth in vivo. Similarly, depletion of *HEATR1* in GBM cells impaired ribogenesis, decreasing RNA and protein synthesis and preventing proliferation.

Conclusion

The relevance of proteostasis in stemness control has been increasingly appreciated (Garcia-Prat et al., 2017). Our data points to changes in proteostasis upon neural progenitor transformation and tumour initiation, and demonstrate *HEATR1* as potential player in brain tumorigenesis through ribosome biogenesis regulation.

Static permeability assessment method to distinguish brain tumour recurrence from pseudoprogression

Oral Presentation - Video on demand (7 minutes)

Mr. kai tsang [1], ***Dr. Chun Pang*** [2], ***Dr. Sam Butler*** [1]

1. *University Hospital North Midlands,* ***2.*** *univ*

Aims

It is common to have adjuvant chemo-radiotherapy after primary brain tumour resection. It is a known side effect that enhancing lesion could be seen in radiation territory after treatment, termed as pseudoprogression. It has been a difficult task to distinguish brain between tumour recurrence from pseudoprogression after radiotherapy. Timing of occurrence of these can overlap. It is important to distinguish the two as management is completely different. Early intervention in recurrence could improve survival time while pseudoprogression could be self-limiting. Surgical resection of pseudoprogression could be counter-productive.

The radiological approach has been relying on multimodality investigation and close follow up. It has come to our institution notice that there is a new technique which could distinguish the two conditions efficiently. That's static permeability assessment method, also known as treatment response assessment maps (TRAMs).

Our experience with it so far has been beneficial.

Method

This is a retrospective case series review of primary brain tumour treatment in our neurosurgical institution in 2020.

Two high resolution 3D T1-weighted brain MRI images were acquired after a standard dose of gadolinium based contrast agent was injected. The first acquisition began five minutes after injection, and the second began 60 – 105 minutes post contrast injection. The TRAMs technique is based on image subtraction that is post processed after acquisition.

The resultant subtracted image set was mapped to grey scale values, where voxels showing contrast clearance were light grey/white, and those showing contrast accumulation were dark grey/black. The zero value (i.e. no clearance or accumulation) was therefore mid-grey. Those with contrast clearance is associated with tumour recurrence.

TRAMs images were compared to serial follow up imaging and histopathology results to determine the diagnostic accuracy of the technique.

Results

We have identified 21 patients in this period who had concern of either of pseudoprogression or tumour recurrence/progression. There were 6 females and 15 males, mean age 51. There were 14 glioblastoma multiforme (GBM), 5 astrocytoma, 1 oligodendroglioma and 1 post radiotherapy arteriovenous malformation.

17 cases were found to have clear cut recurrence, pseudoprogression or mixture of both in TRAMS. These foundings are backed up by histology or repeated follow up scan.

4 cases were considered as equivocal. In retrospect, these cases have challenging interpretation due to poor case selection.

TRAMs could distinguish high grade transformation as well as detecting recurrence. In some difficult cases, it is found that both pseudoprogression and recurrence could happen together.

Conclusion

TRAMs is a useful adjunct to the multimodalities of diagnostic techniques in tricky situation. This has provided an efficient and easy to use tool for radiologists to come up with the answer.

We are the first independent centre to report on this technique. This is still early days and fine-tuning of its use is still undergoing. It is clear this has saved precious resources and has given patients more suitable care.

We think it would be beneficial for us to share our experience with others and hope to get future collaboration with other centres.

T2-FLAIR mismatch sign for diagnosis of 1p19q non-codeleted or ATRX mutant astrocytoma

Oral Presentation - Video on demand (7 minutes)

Dr. Jian Ping Jen [1], ***Dr. Markand Patel*** [2], ***Dr. Michael Bowen*** [3], ***Dr. Ute Pohl*** [4], ***Dr. Santhosh Nagaraju*** [5], ***Dr. Victoria Wykes*** [3], ***Prof. Colin Watts*** [4], ***Prof. Vijay Sawlani*** [3]

1. *Department of Neuroradiology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust,,* ***2.*** *University Hospitals Birmingham NHS Foundation Trust,* ***3.*** *Queen Elizabeth Hospital Birmingham,* ***4.*** *Queen Elizabeth Hospital, Birmingham,* ***5.*** *University Hospital Birmingham*

Aims

The World Health Organisation (WHO) classification of adult gliomas has undergone significant revision in recent years, with current emphasis on the role of the molecular biomarkers IDH, 1p19q, ATRX, and p53 for classification of glioblastoma, astrocytoma, and oligodendroglioma. When correctly applied the T2-FLAIR mismatch sign is reported to have 100% specificity for WHO grade II or III IDH mutant 1p19q non-codeleted astrocytoma. We sought to verify this classic imaging-molecular correlate in our cohort at a single tertiary level neurosurgical referral centre in the United Kingdom.

Method

Data were gathered by searching the histopathology database for cases between 2014 and 2019 containing the keywords 'IDH Mutant' AND 'Astrocytoma' or 'Glioblastoma' or 'Oligodendroglioma' in the report. Inclusion criteria: Biopsy/resection proven IDH mutant tumours in adults (age >17). A strict application of the T2-FLAIR mismatch sign was used when evaluating MRI. Native T2 signal was required to be homogenous or near homogenous, with hypointense signal on T2 weighted FLAIR except for a hyperintense peripheral rim. In addition, the T2-FLAIR mismatch sign was not applied to tumours showing any unequivocal contrast enhancement or macrocystic change.

Results

66/185 cases were excluded for reasons of insufficient imaging, duplication, 1p19q partial deletion/unknown + ATRX wild type/unknown, IDH wild type/negative, Grade IV histology. 119 cases fit the inclusion criteria, all IDH positive. Group 1 comprised 49 (39%) 1p19q codeleted tumours, or oligodendrogliomas. ATRX was wild type (78%), unknown (18%), or mutated (<1%). Group 2 comprised 37 (29%) 1p19q non-codeleted tumours, or astrocytomas. ATRX was mutated (70%), unknown (22%), wild type (5%), or equivocal (3%). Group 3 comprised 41 (32%) 1p19q unknown tumours, all ATRX mutated, p53 expressed (83%). When p53 status was unaltered/equivocal, microscopy was convincingly astrocytic. Groups 2 and 3 comprised the astrocytomas (61%). T2-FLAIR mismatch was positive in 5 1p19q non-codeleted astrocytomas, 5 1p19q unknown ATRX mutant astrocytomas, and no 1p19q co-deleted oligodendrogliomas. Test sensitivity and specificity was 14% and 100% for 1p19q non-codeletion, 13% and 100% for ATRX mutation.

Conclusion

Although relatively uncommon, when present and correctly applied we confirm 100% specificity of the T2-FLAIR mismatch sign for IDH mutant 1p19q non-codeleted astrocytoma. However, if 1p19q status is unknown, clear astrocytic histology and ATRX mutation and/or p53 overexpression is also considered sufficient to diagnose astrocytoma. When 1p19q status is unavailable we also report 100% specificity of T2-FLAIR mismatch for ATRX mutated astrocytomas. T2-FLAIR mismatch was not observed in any 1p19q codeleted oligodendrogliomas or ATRX wild type tumours. More accurate methods of non-invasive glioma diagnosis will help improve neuro-histopathological correlation, prognostication, and guide the tempo of the pre-operative planning phase.

Temozolomide hypersensitivity – A story of success

Oral Presentation - Video on demand (7 minutes)

Dr. Lanka Alagiyawanna [1], ***Dr. Stephanie Prince*** [1], ***Dr. Debbie Wright*** [1], ***Dr. Enrico Clarke*** [1], ***Dr. Jeng Ching*** [1]

1. *University Hospital Southampton NHS Foundation Trust*

Aims

Background:

Temozolomide is an oral chemotherapy drug widely used in the treatment of glial tumours. This is generally well tolerated however, immediate and delayed hypersensitivity reactions have been described, necessitating treatment interruption that could significantly impact survival.

Method

Case description:

We report a case of a 39-year-old young woman with WHO grade 2 IDH1mutant diffuse astrocytoma (MGMT promoter methylated) of the left temporal lobe. She had tumour resection in 2012 followed by radical radiotherapy. Afterwards, she had close surveillance with regular brain imaging. The tumour started to progress in early 2020. We agreed to commence on temozolomide to control tumour growth.

She developed an itchy rash with easy bruising towards the end of the first cycle. It responded to a course of prednisolone. We proceeded with the second cycle and she developed a worsening rash on the third day. However she did not have signs or symptoms of anaphylaxis. This episode was again managed by a course of steroids and oral antibiotics. Since Temozolomide was the optimal treatment to control the disease progression at this stage, we agreed to persevere with temozolomide using a rapid desensitisation protocol.

Results

On the first day of third cycle, she was brought to the day chemotherapy unit and given prednisolone 30mg, fexofenadine 180mg and ondansetron 8mg, 30 minutes before the treatment. Our protocol was as follows; 5mg, 10mg, 20mg, 30mg, 50mg and 90mg of temozolomide at an interval of 30 minutes between the doses. She was advised to follow the same regime for the next four days of the third cycle. On days 6 -28, she has been advised to take fexofenadine 180mg once daily. Although there was a minor rash appeared on days 6/7, they subsided gradually. She tolerated the treatment without sinister symptoms or signs. We proceeded with the next 4 chemotherapy cycles adhering to the same protocol. The intensity of the rash gradually improved, and she became almost completely asymptomatic by the 7^{th} cycle. It was also encouraging to see the radiological response of the tumour with the treatment.

Conclusion

Although the published literature is minimal, rapid desensitisation is shown to be a safe and effective method to counteract temozolomide hypersensitivity. In an era where there is still a paucity of systemic treatment options for primary brain tumours, adopting rapid desensitisation to induce tolerability to temozolomide, a drug which has shown to improve survival, would be a valuable addition in managing our patients. Further, our experience suggests that this protocol is safe, effective, and does not necessitate inpatient admission.

The impact of the COVID-19 pandemic on paediatric glioma patients in low, middle, and high-income countries: a multicentre, international, observational cohort study

Oral Presentation - Video on demand (7 minutes)

Dr. Soham Bandyopadhyay [1], ***Dr. Global Children's NCDs Collaborative*** [2]

1. *Nuffield Department of Surgical Sciences, University of Oxford,* ***2.*** *University of Oxford*

Aims

Paediatric cancer is a leading cause of non-communicable disease deaths for children worldwide, with more than 90% of deaths occurring in low-and-middle-income countries (LMICs). The COVID-19 pandemic may have exacerbated disparities in paediatric cancer outcomes between LMICs and HICs. The World Health Organization (WHO) Global Initiative for Childhood Cancer has identified gliomas as a common cancer that can act as a benchmark for assessing global paediatric cancer care. This study aims to ascertain the short and medium-term outcome across 17 countries during the COVID-19 pandemic by determining 30- and 90-day all-cause mortality rates for paediatric glioma patients who underwent treatment.

Method

A multicentre, international, mixed- (retrospective and prospective), collaborative cohort study in 17 countries. Patients were recruited between March 12th 2020 and July 12th 2020.

Results

129 patients were recruited with the majority being histologically diagnosed as low-grade gliomas (n = 86/118, 72.9%). Seven children had a change to their planned chemotherapy treatment because of the COVID-19 pandemic. Similarly, seven children and eleven children had a change to their planned radiotherapy treatment and surgical treatment respectively because of the COVID-19 pandemic. Five patients died within the 30-day follow-up period, with all five patients being in LMICs. A sixth child, also in a LMIC, died within the 90-day follow-up period. This significant difference in mortality between LMICs and HICs was present when controlling for confounding for factors such as grade, ASA status, sex, weight, and age.

Conclusion

There has been relatively minimal change to the treatment of paediatric gliomas worldwide compared to their initial planned care. There was a significant difference in mortality for childhood gliomas between LMICS and high-income countries during the COVID-19 pandemic. There needs to be a concerted effort to improve equity in health outcomes globally.

The incidence of major subtypes of primary brain tumours in adults in England 1995-2017

Oral Presentation - Video on demand (7 minutes)

Ms. Hiba A Wanis [1]

1. *King's College London*

Aims

Primary brain tumours are a complex heterogenous group of benign and malignant tumours. Reports on their occurrence in the English population by sex, age, and morphological subtype and on their incidence are currently not available. Using data from the National Cancer Registration and Analysis Service (NCRAS), the incidence of adult primary brain tumour by major subtypes in England will be described. This is the first study to report the incidence of brain tumour subtypes in England. The information presented will enable us to better understand their burden in the population and, ultimately as registration data becomes more detailed, to use this data to improve cancer services for these patients.

Method

Data on all adult English patients diagnosed with primary brain tumour between 1995 and 2017, excluding spinal, endocrinal and other CNS tumours, were extracted from NCRAS. Incidence rates were standardised to the 2013 European Standard Population. Results are presented by sex, age, and morphological subtype.

Results

Between 1995 and 2017, a total of 133,669 cases of adult primary brain tumour were registered in England. Glioblastoma was the most frequent tumour subtype (31.8%), followed by meningioma (27.3%). The age-standardised incidence for glioblastoma increased from 3.27 per 100,000 population per year in 1995 to 7.34 in men in 2013 and from 2.00 to 4.45 in women. Meningioma incidence also increased from 1.89 to 3.41 per 100,000 in men and from 3.40 to 7.46 in women. The incidence of other astrocytic and unclassified brain tumours declined between 1995 and 2007 and remained stable thereafter.

Conclusion

Part of the increase in the incidence of major subtypes of brain tumours in England could be explained by advances in clinical practice including the adoption of new diagnostic tools, classifications and molecular testing, and improved cancer registration practices.

The ketogenic diet alters the expression of chromatin modifying enzymes in GBM to potentiate the effects of chemotherapy and radiotherapy

Oral Presentation - Video on demand (7 minutes)

Ms. Qingyu Zeng [1], ***Dr. Tzouliana Stylianou*** [1], ***Ms. Jessica Preston*** [1], ***Mr. Kevin O'Neill*** [2], ***Dr. Adrienne C. Scheck*** [3], ***Dr. Nelofer Syed*** [1]

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Aims

Glioblastoma Multiforme (GBM) is the most aggressive form of primary brain tumour, with a median survival of 12-14 months after diagnosis. Although GBM has been extensively characterised on the molecular level during the past decades, many targeted therapies have been proved ineffective due, in part, to high heterogeneity of GBM. Thus, novel therapies targeting the altered metabolism which is exhibited by all cancer cells have gained much attention. The therapeutic ketogenic diet (KD) is a high fat, low carbohydrate and adequate protein diet. It has been recognized as a treatment for refractory paediatric epilepsy for decades. Recent studies have shown that a KD reduced tumour growth and potentiated the effects of therapy in some glioma animal models. However, the underlying mechanism(s) is still unclear. Thus, the aim of this study was to understand the mechanism of action behind the KD's effects in inhibiting tumour growth and potentiating chemotherapy and radiotherapy.

Method

To unravel the mechanism of action, we analyzed the expression of genes encoding chromatin modifying enzymes in brain tumour samples from mice fed either a KD or standard diet (SD), using the Mouse Epigenetic Chromatin Modification Enzyme PCR Array (Qiagen, Germany). The expression of genes of interest selected from the array were validated by qRT-PCR. Human GBM cell lines and primary cells from GBMs were used to validate the results of the GBM mouse model. Beta-hydroxybutyrate, the main physiological ketone body found in the circulation of patients during KD, was used in *in vitro* experiments to mimic the *in vivo* physiological effect of a KD. The effect of protein arginine methyltransferase 8 (PRMT8) overexpression in GBM cells was studied using a lentiviral system. Cell proliferation was measured by Sulforhodamine B assay (Sigma, USA). Spheroid growth and invasion was measured in GBM spheroids cultured in Matrigel matrix (Corning, USA).

Results

Our results highlighted changes in the expression of a number of key chromatin modifying enzymes in mice fed a KD compared to those fed a SD. PRMT8, a gene highly downregulated in GBM, was upregulated in tumors from mice fed a KD, with corresponding downregulation of its target genes, dihydrofolate reductase (DHFR) and C-X-C chemokine receptor type 4 (CXCR4). Our results also showed that overexpression of PRMT8 in GBM cells reduced cell proliferation and invasiveness.

Conclusion

PRMT8, DHFR and CXCR4 have been shown to play key roles in tumour growth, invasion, migration and chemo/radio-resistance. Moreover, therapeutic strategies to downregulate these genes have been investigated in the form of methotrexate for DHFR inhibition and small molecule inhibitors of CXCR4. Thus, our results suggest that one mechanism through which the KD exerts its therapeutic effects may be through altering the expression of chromatin modifying enzymes. This provides additional support for the use of a KD as an adjuvant

in combination with existing therapeutic approaches.

The role of citrin in the mitochondrial adaptation to hypoxia in glioma cell metabolism

Oral Presentation - Video on demand (7 minutes)

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Aims

Glioma is a type of brain tumour arising from the glial cells within the central nervous system that occurs in both adults and children and can be divided into multiple subtypes. A significant characteristic of the tumour microenvironment in gliomas as well as most other tumours is low oxygen (hypoxia). Cancer cells adapt their metabolism to support proliferation in this environment, but this leads to metabolic compromise. Aspartate and glutamate availability is thought to be important in this adaptation hence, the efficient transport of these between the cytosol and mitochondria is important for cell viability and proliferation. The gene *SLC25A13* encodes Citrin, an aspartate/glutamate transporter which is localised to the inner mitochondrial membrane. The aim of this research is to understand the role of Citrin in glioma metabolism in both normoxia and hypoxia.

Method

SLC25A13 expression was determined in varying grades of glioma using UCSC Xena to analyse data from The Cancer Genome Atlas (TCGA), the Genotype-Tissue Expression project (GTEX) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET). *SLC25A13* knockdown U87 cell lines were created using a CRISPR-Cas9 approach. *SLC25A13* expression in these cell lines was confirmed using western blotting in both normoxia and hypoxia. Proliferation of the *SLC25A13* knockdown U87 cell lines was determined with sulforhodamine B assays. Metabolite analysis of these cells was performed using Gas chromatography–Mass spectrometry (GC-MS).

Results

*SLC25A13*expression was found to be higher in glioblastoma, compared to lower grade glioma and normal brain tissue. Contrastingly, *SLC25A13* expression was found to decrease in hypoxia in both control and *SLC25A13* knockdown glioma cell lines, and reduced expression in normoxia resulted in a decrease in proliferation. Metabolite analysis of these cells identified an increased amount of some TCA cycle intermediates and amino acids in the *SLC25A13* knockdown cells compared to the control cell line, suggestive of a dysregulated metabolic network. Overall, the data suggest lack of Citrin may result in an increased reliance on glutamate, rather than glucose, which may alter their ability to proliferate rapidly.

Conclusion

These findings suggest that Citrin may play an important role in cell metabolism. Further studies into the metabolic impact of reduced *SLC25A13* expression in hypoxia will better our understanding of Citrin in a tumour microenvironment-like system. This will determine whether Citrin may represent a novel therapeutic target to treat patients with glioma.

Three-staged stereotactic radiosurgery for brain metastases: a single institution experience

Oral Presentation - Video on demand (7 minutes)

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1. *London Gamma Knife Centre, Wellington Hospital,* ***2.*** *Medical Physics Limited*

Aims

Stereotactic radiosurgery (SRS) using the Leksell Gamma Knife system is a commonly used modality for the treatment of brain metastases (BMs). As the size of the target volume (TV) increases, so too does the dose of radiation delivered to surrounding healthy tissue. Large BMs are therefore a contraindication to the use of SRS. Critical organs adjacent to the TV may also be a contraindication to SRS. Staged SRS was proposed as a novel method of delivering three SRS treatments at a reduced radiation dose with a gap of two weeks between each session as a way of shrinking the TV . This allows treatment of TVs otherwise considered untreatable with standard, single-fraction SRS. Little data exists in the literature as to its efficacy. The objective of this study was to evaluate the efficacy of this novel approach and to identify factors which may predict treatment failure.

Method

A retrospective analysis was undertaken at a single, tertiary Gamma Knife centre. All patients who underwent treatment of their BMs with three-staged Gamma Knife SRS from January 2014 to December 2020 were identified and included. Patient demographics and primary cancer status was ascertained. SRS treatment details for each lesion were collected, including TV, dose and dosimetric data. The percentage reduction in volume of the TVs between the first and second stage, the second and third stage and the first and third stage were calculated. Follow-up data was collected to include follow-up imaging, further intracranial treatments received and survival status. The percentage reduction in volume between each stage was demonstrated on box-and-whisker plots. Statistical significance in reduction in TV between each stage was ascertained by paired samples T-tests. Correlation between initial TV size and percentage reduction post-SRS was determined by a correlation coefficient. Differences were deemed significant with p-values <0.05.

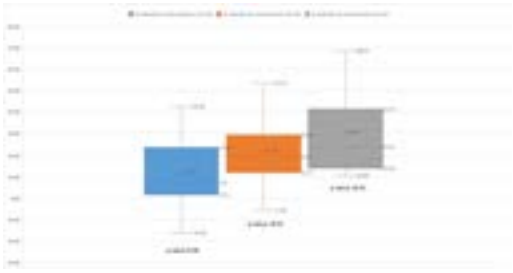
Results

12 patients with 14 staged BMs were identified and included. The median age was 61.5 (range 45-79). Seven had a primary malignancy of breast cancer, five non-small cell lung cancer, one melanoma and one colorectal. Median follow-up was 140.5 days (range 10-821). Median TV was 7.44cc (range 1.14-21.53). All TVs received 10Gy at each stage. The median percentage reduction in size of the TV was 7.41% between 1st-2nd stage (range -16.0-42.49%, p-value 0.06), 19.47% between 2nd-3rd stage (range -5.38-53.53%, p-value <0.01) and 24.25% between 1st-3rd stage (range 10.69-68.67%, p-value <0.01). The correlation coefficient between initial TV size and percentage reduction post-SRS was -0.41 (p-value 0.07). 13/14 lesions showed a partial response on first follow-up scan post-SRS, 1/14 lesions showed a mixed response. One patient died 184 days from completion of treatment but without intracranial progression. Two patients had salvage intracranial surgery, 154 and 536 days from completion of treatment respectively.

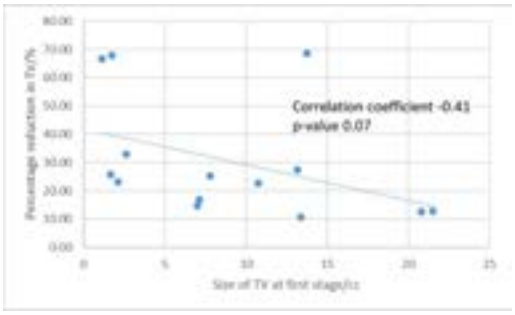
Conclusion

Three-staged Gamma Knife is shown to be effective at shrinking the TV and can therefore be used to treat lesions otherwise considered unsuitable for SRS. The presence of extra-cranial metastases did not predict for poor outcomes. Though local control with SRS is thought to diminish with increasing TV size, all staged lesions showed a reduction in size between first and last treatment, and no significant effect was seen between initial TV size and percentage reduction in TV. No patients experienced disease progression on first follow up scan,

with 13 of 14 lesions showing disease response. There were only two cases of intracranial progression, with one occurring 536 days post-SRS. Though limited by small numbers and short median follow up period, our data demonstrate encouraging results for three-stage SRS for lesions otherwise unsuitable for single fraction treatment, and should lead to further study.



Picture1.jpg



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Progression.jpg

Transcriptomic and methylome analysis of formalin fixed paraffin embedded craniopharyngioma tissue charcaterises differences between adamantinomatous and papillary types.

Oral Presentation - Video on demand (7 minutes)

Dr. John R. Apps [1], ***Dr. Jessica Pickles*** [1], ***Dr. Thomas Stone*** [1], ***Dr. Georg W Otto*** [1], ***Dr. Daniel Kelberman*** [1], ***Dr. Rosalind Davies*** [1], ***Ms. Magda Meier*** [1], ***Prof. Sergi Castellano*** [1], ***Prof. Thomas S Jacques*** [1], ***Dr. Timo Deutschbein*** [2], ***Prof. Juan Pedro Martinez-Barbera*** [1]

1. *UCL Great Ormond Street Institute of Child Health,* ***2.*** *University Hospital Würzburg*

Aims

Craniopharyngiomas are rare challenging tumours associated with significant morbidity, poor quality of life, and increased long term mortality. Around 25% of patients recur despite surgery and/or radiotherapy. There are two forms, adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). Transcriptomic and proteomic profiling of ACP has identified similarities with tooth development and identified pathways activated within tumours suitable for targeting with existing therapies. However, there remains a need to better understand the biological processes underlying tumour growth and recurrence/progression. To achieve this goal, further analyses on larger cohorts of archival formalin fixed paraffin embedded (FFPE) tissue are required. In this study we aimed to:

- Perform transcriptome sequencing on archival FFPE ACP and PCP tumours.
- Validate results by cross referencing with previously published cohorts.
- Further explore differences between ACP and PCP and between relapsing and non-relapsing tumours
- Explore the methylome and where possible correlate findings with transcriptome data

Method

Tumour samples were accessed from Children's Cancer and Leukaemia Group, Brain UK tissue banks, local pathology departments and international collaborators. Diagnosis and histological content were confirmed histologically. DNA and RNA were extracted from serial sections. In total, 13 cases of ACP and 4 cases of PCP underwent profiling. 16 samples from 10 ACP and 5 samples from 3 PCP underwent RNA sequencing. *CTNNB1* exon 3 and *BRAF*V600 loci were interrogated for mutations. Differential expression analysis was performed using DESeq2. Gene set enrichment analysis (GSEA) was used to compare results with previously published data sets. Methylation analysis was performed in 15 samples from 10 ACP and 4 samples of 3 PCP using the illuminaEPIC array. Samples underwent classification using the Heidelberg classifier. Differential methylation analysis was performed to assess each probe individually and to identify differentially methylated regions.

Results

Canonical exon 3 *CTNNB1* mutations were identified in all but one ACP samples, in the remaining ACP sample, and for all samples at the *BRAF*V600E locus, there was insufficient read depth to assess. Differential expression analysis identified 2942 genes upregulated in ACP and 2764 downregulated compared with PCP (adjusted p-value <0.1). Ontology analysis confirmed over representation of genes of the WNT pathway in ACP and MAPK pathway in PCP. GSEA validated the results, showing high concordance with previous frozen tissue derived datasets(NES=3.69 and -4.52 for genes upregulated in ACP or PCP, respectively (FDR<0.001)). Interrogating specific genes identified upregulation of tooth genes in ACP, but also keratins associated with hair development. For ACP, eight out of 15 samples successfully classified as ACP and three of four PCP samples classified as PCP. Differential methylation analysis identified differential methylation of WNT pathway targets, e.g., *AXIN2*and tooth related genes e.g. *MSX2*,*ENAM*.

Conclusion

Transcriptomic and methylome analyses of FFPE embedded tissue successfully reproduce results from frozen tissue. Differential expression analysis highlights the expression of genes related to hair development as well as those relating to tooth development in ACP. Differential methylation analysis revealed differential methylation of WNT pathway genes, and genes related to differentiation. Mining of the data generated in this project, and future FFPE derived datasets, will provide a further understanding of these genes and pathways in the genesis of craniopharyngioma and, in addition, will reveal the biological differences between relapsing and non-relapsing tumours.

Trial working groups for paediatric brain tumours

Oral Presentation - Video on demand (7 minutes)

Mr. Kristian Aquilina [1], ***Dr. Ruman Rahman*** [2], ***Prof. David Walker*** [2], ***Dr. Emma Campbell*** [2]

1. *Great Ormond Street Hospital,* ***2.*** *The Children's Brain Tumour Research Centre, University of Nottingham*

Aims

Children's brain tumours are the biggest cancer killer in children and young adults. Several recent developments have the potential to change the treatment of brain tumours in children. These include intra-CSF chemotherapy, ultrasound-mediated blood-brain barrier disruption, convection enhanced delivery, polymer delivery systems and electric field therapy, as well as intra-arterial and intra-nasal chemotherapy. To date, there have been very few clinical trials to evaluate any of these. The science and technology underlying these developments is not traditionally embedded within the standard paediatric neuro-oncology network. In addition, custom-built hardware, novel surgical procedures and, in some cases, the testing and licensing of implantable devices, add difficulty at the regulatory level.

Method

The authors participated in an international workshop funded by the charity Children with Cancer UK in 2016, where different experimental techniques aimed at optimising CNS drug delivery were discussed. Following this workshop and two subsequent workshops run by the CBTDDC (Children's Brain Tumour Drug Delivery Consortium) in 2018 and 2020, the CBTDDC and the recently developed ITCC (Innovative Therapies for Children with Cancer) brain tumour group started working together to set up a new initiative. Called the 'Clinical Trials Working Group for Central Nervous System Drug Delivery', this aims to accelerate clinical trials to assess the safety and effectiveness of drug delivery devices for the treatment of paediatric brain tumours. On March 1st, 2021, CBTDDC with guest chair, Mr Kristian Aquilina (Consultant Paediatric Neurosurgeon at Great Ormond Street Hospital), hosted the first virtual meeting of this group.

Results

We have assembled a prestigious steering group, comprising international researchers and clinicians with expertise in diverse aspects of translational and clinical research in CNS drug delivery. At our first group meeting on March 1st, 2021, 38 leading brain tumour research scientists and clinicians from the UK, EU and US tackled the challenges head-on, with commitment and a driving passion to identify and move forwards with the most effective ways of translating drug delivery modalities into clinical trials. Attendees were split into three break-out sessions based on distinct drug delivery systems, and lots of insightful comments were collated.

Conclusion

The ideas generated during the 1st

March meeting will help form the basis of a CBTDDC 'Clinical Trials' workshop in the autumn of 2021. In particular, there was an agreed consensus that a key objective will be the creation of a 'Roadmap' document for pre-clinical to clinical translation which would be shared with the paediatric neuro-oncology research community. CBTDDC look forward to working with steering group as we act on their recommendations to address the current challenges faced by translational drug delivery research. We present this abstract to the BNOS Annual 2021 Meeting to raise awareness of this initiative with the large number of relevant stakeholders who will be attending the event.

Tumour Treating Fields in Glioblastoma: Is the treatment tolerable, effective, and practical in UK Patients?

Oral Presentation - Video on demand (7 minutes)

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1. *The Walton Centre, Liverpool,* ***2.*** *Royal Preston Hospital,* ***3.*** *Queen Elizabeth Hospital, Birmingham,* ***4.*** *University of Cambridge*

Aims

Tumour Treating Fields (TTF) in combination with standard therapy, prolongs survival in patients with Glioblastoma (GBM). The aim of the current study was to assess the feasibility of integrating TTF into a standard UK neuro-oncology service with a focus on patient tolerability, compliance, and treatment delivery.

Method

A prospective study was performed of UK patients with IDH 1 Wild Type, MGMT Unmethylated GBM treated with TTF, in conjunction with conventional therapy. Patient compliance data, device-specific tolerability questions, and an evaluation of disease progression and survival were collected. Monthly quality of life (QoL) questionnaires (EORTC QLQ-C30 with BN-20) examined the trend of global health, psychosocial function and symptom progression.

Results

Nine patients were enrolled with a median age of 47 (7 males; 2 females). Overall, compliance with TTF was 89% (range 16% - 97%). Only one patient failed to comply with treatment. Patients tolerated the device with minimal side effects. Eight patients described mild to moderate skin irritation, whilst all patients were keen to recommend the device to other patients (100%). Most patients found the weight and size of the device to be its biggest drawback (72%). Progression-free survival was 5.5 months and median overall survival 14.9 months.

Conclusion

TTF was well tolerated amongst a small cohort of UK patients, who were able to comply with treatment without any significant complication. QoL questionnaires showed no sustained deterioration in global health, physical and emotional function until the final months of life, when disease burden was greatest.

Urgent elective pathway service reconfiguration facilitates increased use of surgical adjuncts, improvement in survival trends, and reduced hospital stay for glioblastoma patients

Oral Presentation - Video on demand (7 minutes)

Ms. Rosa Sun [1], ***Dr. Shivam Sharma*** [2], ***Mr. Vladimir Petrik*** [1], ***Mr. Ismail Ughratdar*** [3], ***Mrs. Anwen White*** [1], ***Mr. Athanasios Zisakis*** [1], ***Prof. Colin Watts*** [3], ***Dr. Victoria Wykes*** [3]

1. *University Hospitals Birmingham NHS Foundation Trust,* ***2.*** *Royal Wolverhampton trust,* ***3.*** *Queen Elizabeth Hospital Birmingham*

Aims

Glioblastomas (GB) are the most common and aggressive of intrinsic brain tumours. Median survival with maximal therapy is reported to be 14.6 months. Service reconfiguration at the Queen Elizabeth Hospital Birmingham (QEHB) has transformed the service for high grade brain cancer patients, including GB, from a predominantly emergency pathway based system to one of planned urgent-elective admissions consisting of: A. Patient-focused, consultant-led, research orientated "*one stop shop*" model of integrated outpatient neurosurgical oncology clinic B. Standardisation of urgent elective pathways C. Incorporation of neuro-surgical intra-operative adjuncts (neuro-monitoring, 5-ALA) into routine surgical practice for oncology. Using this model, we have reduced hospital length of stay (with associated financial savings), improved extent of resection and achieved a trend towards increased survival.

Method

We retrospectively identified patients with primary histological diagnoses of GB (WHO grade IV), who underwent surgery over a six year period, from 01/01/2014 to 31/12/2019, from the QEHB pathology database. Data was collected for demographics, surgical and oncological therapy, use of intra-operative adjuncts, emergency and elective admission status, year of admission, length of stay (LOS), and extent of resection (EOR) on first post-operative MRI scan from hospital databases.

Survival was analysed using the Kaplan-Meier method and independent-samples median testing for survival. Proportion of patients undergoing resective surgery and admission status was calculated by year. Overall median survival was calculated and subgroup comparisons made of patients by: age, admission status, year of admission, biopsy or resection, oncology treatment.

Hospital length of stay was calculated for patients by surgical procedure, admission pathways and compared across the year. Financial data taken from averages of inpatient episode costs were used to estimate cost savings.

Results

610 patients underwent primary procedures for GB, of which 64 were still alive at time of analysis (02/02/2021). Median overall survival time was 9.53 months, this was greatest in patients who underwent resection with completion of Stupp protocol: 28.67 months (n=114).

From 2014 to 2019, there has been an increase in elective admission rates (28.1% to 90.3%, $p<0.001$) and increased proportion of resective surgery (68.4% to 81.9%, $p<0.001$). There is a trend of improved survival from 2014 to 2019 (median 7.95 and 11.08 months, $\chi^2=9.249$, $p=0.002$).

Increasing use of intra-operative adjuvants improved EOR ($\chi^2 =31.064$, $p<0.001$). Through improved urgent-elective admission rates, hospital length of stay has decreased by five days for craniotomies and six days for biopsies. Cost analysis of three cases demonstrated that reducing the LOS by one night alone result in an average cost saving of approximately £750 per patient per night.

Conclusion

Switching to a system of planned and urgent elective based admission, with standardisation of neuro-oncology patient pathways, increased use of intra-operative adjuncts, earlier oncology multidisciplinary input and out-patient review, has improved the extent of GB resection, led to shorter length of hospital stay associated with significant financial savings and achieved a trend towards increased overall survival.

Use of a new mouse schwannoma tumour model to monitor changes in peripheral nerve morphology in Merlin null Schwann cells

Oral Presentation - Video on demand (7 minutes)

Ms. Marie Srotyr [1], ***Dr. Liyam Laraba*** [1], ***Mr. Glenn M. Harper*** [1], ***Ms. Charlotte Lespade*** [1], ***Mx. Evyn Woodhouse*** [1], ***Prof. Alison C. Lloyd*** [2], ***Prof. David B. Parkinson*** [1]

1. *Peninsula Medical School, Faculty of Health, University of Plymouth, Plymouth, UK,* ***2.*** *MRC Laboratory for Molecular Cell Biology, UCL, UK*

Aims

Our lab is interested in signals that trigger schwannoma tumour formation and we have previously shown that peripheral nerve injury triggers tumour formation in nerves with Schwann cell-specific loss of the Merlin (NF2) tumour suppressor. The Ras/Raf/MAPK/ERK pathway activity in myelinating Schwann cells is involved in nerve regeneration, causing demyelination and recruitment of inflammatory cells in areas of nerve damage, as well as dedifferentiation of myelinating Schwann cells into a repair-competent state. We have used a mouse model expressing a tamoxifen-inducible Raf-Kinase estrogen receptor fusion protein (Raf-TR) in myelinating Schwann cells of the PNS in either a control wild-type Merlin or Merlin-null background. This allows us to determine the effects of an injury-like signal in Schwann cells and its role in generating schwannoma tumour development. We present here a detailed analysis of the proliferation of Schwann cells within the nerve and morphological changes in PNS structure following Raf-TR activation.

Method

The P0-promotor driving the Raf-TR transgene is active in myelinating Schwann cells but inactive in the non-myelinating population, allowing specific targeting of the myelinating Schwann cell population. In addition to the Raf-TR gene, the mice exhibit a separate P0-promotor controlled Cre floxed NF2 gene which undergoes Cre-mediated recombinase at embryonic day 13.5 causing NF2 knockout in all developing Schwann cells. Mice aged between 4-6 weeks received intraperitoneal injections of either 2mg Tamoxifen or oil vehicle for 5 consecutive days and were then studied at either 10 or 21 days post-first injection. The peripheral nervous system of the mice was studied with fluorescent immuno-histochemistry staining, semithin sections and transmission electron microscopy (TEM) on sciatic nerves and dorsal root ganglia (DRG).

Results

Activation of the Ras/Raf/MAPK/ERK pathway in NF2 null Schwann cells led to higher rates of proliferation within sciatic nerves at 10d post-tamoxifen injections. At both 10d and 21d Raf-TR+ NF2-null mice sciatic nerve fascicles were visibly larger with significantly more cell bodies present than controls, however at 21d the rate of proliferation had reduced. In the DRG, proliferation was higher in Raf-TR+ NF2-null mice compared to controls, with proliferation remaining high at 21 days. Quantitative imaging of peripheral nerve semi-thins analysed to date showed no significant difference in the number of myelin rings present in the fascicles between different genotypes. Additionally, dual immuno-histochemistry staining with Myelin Basic Protein and EdU, markers for myelin and proliferation respectively, appeared to show proliferation in the non-myelinating Schwann cell population. Results from staining with other cell markers will also be presented, as well as a detailed analysis of nerve structure using TEM.

Conclusion

While developmental myelination of Merlin-null Schwann cells appears largely normal, the reaction of Merlin-null Schwann cells in the nerve to an injury signal (activation of the Raf-TR) is remarkably different from those

of control nerves. The high levels of proliferation in Merlin-null Schwann cells may be indicative of a higher tumorigenesis potential. While the proliferation of Merlin-null cells does reduce over time in the sciatic nerve, further experiments are now testing whether there may be ongoing tumour growth at other locations in the nervous system that are associated with NF2 tumours in human patients.

Power Poster Presentation (2 minutes)

A role of seizures in promoting progression of Glioblastoma Multifome

Power Poster Presentation (2 minutes)

Ms. Anam Anzak [1], ***Ms. Pratistha Panday*** [2], ***Ms. Glenda Scandura*** [1], ***Ms. Molly Hilling*** [1], ***Mr. Anand Pandit*** [3], ***Dr. Melissa De Gouveia*** [3], ***Ms. Catherine Zhang*** [4], ***Ms. Lauren Harris*** [4], ***Mr. Babar Vaqas*** [4], ***Mr. Edward McKintosh*** [1], ***Prof. Sebastian Brandner*** [5], ***Dr. Jeremy Rees*** [3], ***Dr. Britta Wandschneider*** [6], ***Prof. Silvia Marino*** [2]

1. *Royal London Hospital,* ***2.*** *Blizard Institute, Queen Mary University,* ***3.*** *National Hospital for Neurology & Neurosurgery,* ***4.*** *Queen's Hospital, Romford,* ***5.*** *Queen Square Institute of Neurology, University College London,* ***6.*** *Royal*

Aims

Emerging evidence suggests shared pathophysiological mechanisms and reciprocal effects of seizures and tumour growth in glioblastoma-multiforme (GBM). Recent work has shown both *local* hyper-excitability at the tumour-margin, and synaptic and gap-junction mediated integration into neural networks. Together with secreted factors and initiation of an inflammatory response, these mechanisms likely promote gliomagenesis. Moreover, use of the anti-epileptic drug (AED) levetiracetam has been associated with improved survival in patients with GBM receiving gold-standard therapy. This study sought to investigate deleterious effects of seizures on progression-free survival in patients with GBM.

Method

125 patients (76 Male, 49 Female, mean age 61.0 +/- 11.6 years, SD) with IDH-wild type (WT) GBM who completed both diagnostic brain biopsy and follow-up within Barts Health NHS Trust between 2014-19, were identified. Tumour biopsies were processed and diagnosed by the Neuropathology team at the National Hospital (NHNN), London. The primary end-point was progression-free-survival (PFS), defined as time from biopsy to date of the first report of radiological progression, or death, whichever occurred first. 71 patients met inclusion criteria of receipt of gold-standard treatment with temozolomide (+/- debulking surgery +/- radiotherapy; these therapeutic combinations exerted no effect on PFS in exploratory analyses, $p>0.05$). Patients were identified as being seizure-free, or with seizures on presentation. All patients with seizures on presentation had been commenced on a first-line AED. Patients with >1 seizure after commencement of AED were described as having uncontrolled seizures.

Results

Of all patients who received temozolamide, 67.6% were seizure-free and 32.3% had seizures. Of those, 74% were controlled on AED and 26% were uncontrolled. There was a significant difference in PFS in patients with uncontrolled seizures (median survival 3.2-months) versus those who were seizure-free (8.5-months, $p=0.037$, two-sample T-test), but no difference in PFS between patients with controlled-seizures and those who were seizure-free. We next explored the role of seizures on GBM progression by investigating delayed effects of seizures. Patients who had progressed or died at <3 months after biopsy were excluded. By 6 months a larger proportion of patients with seizures had progressed or died-compared to seizure-free patients (34% versus 12.5%, Relative Risk 2.8, Chi-square statistic $p=0.04$), indicating a higher risk of disease progression with seizures. Similar relationships between seizures and PFS were observed in a smaller series of patients at the NHNN (2014-15, n=18; age, biomarker, and treatment-matched).

Conclusion

We provide clinical evidence supporting a correlation between seizures and GBM progression, independent of

other prognostic factors. Silencing tumor-neuronal network interactions, through novel therapeutic strategies, may have the potential to improve survival in patients with GBM.

Can neurosurgical Twitter content help patients with brain tumours?

Power Poster Presentation (2 minutes)

Mr. Shumail Mahmood [1], ***Mr. Hasan Zeb*** [1], ***Mr. Yazan Hendi*** [1], ***Mr. Yasir A Chowdhury*** [2], ***Mr. Ismail Ughratdar*** [3]

1. *Birmingham Medical School, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom,* ***2.*** *University Hospitals Birmingham NHS Foundation Trust,* ***3.*** *Queen Elizabeth Hospital Birmingham*

Aims

The use of social media within healthcare is a growing phenomenon. Studies have shown that the use of Twitter by healthcare professionals can not only improve patient communication and understanding of their conditions but can also reduce costs due to a reduction in hospital visits. Social media can also help target younger patients and provide them with knowledge and guidance to allow them to better understand and live with their conditions. Despite this, the evidence supporting the use of social media in neuro-oncological or neurosurgical settings is limited. Recently, the neurosurgical department at the Queen Elizabeth Hospital in Birmingham have set up a Twitter account @UHBNeurosurgery, and following this, a service evaluation has been designed to determine the effectiveness of this at improving patient engagement, improving patient education, and improving patient awareness of neuro-oncological and neurosurgical conditions and treatments.

Method

A questionnaire was designed to obtain and collate patient understanding and awareness of the use of social media in healthcare, to try and determine whether or not it is beneficial and whether it can help improve their care. This consisted of twelve questions, all of which were aimed at identifying patients' own feelings about the benefits and drawbacks of social media in healthcare, and specifically in neuro-oncological and neurosurgical settings. This service evaluation was given local approval. Patients were selected from the post-treatment list of neuro-oncology patients at the hospital to ensure that only individuals who have had prolonged exposure to the department were selected. A total of 75 responses were obtained. This data was then analysed and summarised, and subsequently used to help determine whether the use of social media can improve care for patients suffering from brain tumours.

Results

43% of patients (n=32) use social media and had an average age of 45, whilst non-users had an average age of 59. 94% of social media users use Facebook, whilst 34% use Twitter. 14 individuals have previously used social media for neuro-oncology reasons: learning about diseases and prognoses (n=11), learning about their surgeries (n=12), finding support groups (n=6), and researching their doctors' profiles (n=5). 93% of these patients (n=13) found that social media helped improve their knowledge and their trust in the healthcare team. Twitter was mainly used for researching doctors and education purposes, whereas Facebook was used for support groups. Participants mentioned that they would most benefit from Q&As with doctors (n=15) and simplified videos/articles about their conditions (n=17), particularly when first diagnosed. 19% of patients (n=14) had concerns about using social media, including privacy/confidentiality (n=9), increased anxiety about conditions (n=4) and the possibility of reading incorrect/outdated information (n=5).

Conclusion

Social media may help improve the care of neuro-oncology patients by improving their access to reliable information. Younger patients are more likely to use social media, especially when first diagnosed, and the neuro-oncology MDT can use this to provide them the information and support they need as they come to terms with

their diagnosis. This may ease pressure on professionals, but by empowering and educating patients it may also improve outcomes. The potential drawbacks of social media must also be considered, however, and further research is needed to determine the presence and extent of these. Despite these drawbacks, the results suggest that by adopting social media and improving communication channels, healthcare professionals may better provide the well-rounded holistic care that patients with brain tumours require. Therefore, on the @UHBNeurosurgery account, we will produce simplified content, blogs from past patients, and support groups, followed by a re-audit to determine any improvements.

Describing the longitudinal journey to achieving integrated, team working at Velindre Cancer Centre, Cardiff

Power Poster Presentation (2 minutes)

Ms. Rachel Evans [1], ***Mrs. Rhian Burke*** [1], ***Dr. James Powell*** [1], ***Dr. Jillian MacLean*** [1], ***Dr. Najmus Iqbal*** [1], ***Dr. Owen Tilsley*** [1], ***Mrs. Lisa Love-Gould*** [1], ***Mrs. Kate Baker*** [1]

1. *Velindre Cancer Centre*

Aims

It is widely acknowledged that the complex and changing needs of neuro-oncology patients are best served by a holistic, coordinated multidisciplinary team. Without integrated working, there can be duplication, unmet need and fragmentation within the pathway which can be detrimental to patient experience and quality of life. This study describes the process towards achieving our unified vision of providing an integrated joint Clinical Nurse Specialist (CNS) and Allied Health Care Professional (AHP) clinic at Velindre Cancer Centre.

Method

The study provides rich qualitative and quantitative evidence of the holistic needs of patients attending Velindre Cancer Centre. It reflects on our three phrase journey from screening patients for AHP needs in outpatient clinic, the impact of having no proactive system in place for identifying holistic needs to our gold standard model of providing a joint CNS and AHP clinic available before, during and after oncology treatment.

Results

It is clear from the data that having a joint CNS and AHP clinic integrated into the patient pathway is optimal. The results show that there are clear patient, carer and wider team benefits to this innovative model of working.

Conclusion

Inherent within the joint CNS and AHP clinic is supported self-management, seamless communication and achieving a prudent model of care. Sustaining this model of care, ensuring adequate staffing and leading the way in sharing best practice is inherent and a priority for our future direction.

Development and characterisation of patient-derived glioblastoma 3D tumourspheres

Power Poster Presentation (2 minutes)

Dr. Alina Finch [1], ***Mr. Luke Reynoldson*** [1], ***Dr. Ute Pohl*** [2], ***Dr. Victoria Wykes*** [1], ***Prof. Colin Watts*** [1], ***Dr. Chiara Bardella*** [1]

1. *Institute of Cancer and Genomic Science, University of Birmingham UK,* ***2.*** *Queen Elizabeth Hospital, Birmingham*

Aims

Glioblastoma (GBM) treatment and survival have remained static in the last few decades, mainly because of the absence of novel therapies. This is in part due to the lack of relevant pre-clinical models available. For instance monolayer cell culture are frequently utilised in drug screening assays, even if they do not often represent an accurate system for these studies, mainly because of genotypic drift over time as they adapt to culture conditions. The main aim of this study was to generate a reliable preclinical model, such as 3D tumoursphere cultures from the surplus GBM tissue obtained following tumour resection. These patient-derived glioblastoma 3D tumourspheres will allow us to better understand glioma biology, and will be used as patient avatars *in vitro* to develop novel therapeutic strategies in a clinically relevant time scale.

Method

Patients consented pre-operatively to Brain Surgical Tissue for Advanced Tumour Models (BRAINSTAT) an infrastructure to collect, structure and store biospecimens including tumour, and long-term clinical annotation. Samples were transported from the Queen Elizabeth Hospital to the lab within 20minutes where they were divided into 3 pieces and used to: 1) extract DNA & RNA; 2) be formalin-fixed and paraffin-embedded; 3) be processed for tumoursphere culture.

To generate tumourspheres, tissue was enzyme-digested and minced through a 70µm filter before being centrifuged and re-suspended in stem cell media and plated in ultra-low attachment plates. Paraffin-embedded primary tissue was cut in 4µm section for H&E and IHC staining along with matched tumoursphere samples. Quantitative RT-PCR (qRT-PCR) was also used to assess the expression levels of a variety of stem cell markers. In parallel, DNA extracted from primary tissue and matched tumourspheres was used in the TruSight Oncology 500 gene panel and EPICMethylation arrays.

Results

Patient-derived tumourspheres formed and grew at varying rates, indicating a degree of inter-tumoural heterogeneity in their stem cell components. Tumourspheres demonstrated the capacity to self-renew in culture for at least 5 passages, and when embedded in Matrigel they demonstrated great invasive potential. To assess that the tumoursphere cultures were derived from the cancer stem cell component of the primary tumour, we stained both the human tumour samples and the derived 3D cultures with various stem cells markers by IHC. qRT-PCR was used to understand whether there was any variability in the expression of stem cell genes between different primary tumours and the matching 3D cultures. To understand whether the patient derived 3D tumoursphere recapitulate the genetic and epigenetic profiles of the corresponding primary tumour, the mutational status of 500 target genes as well as the methylation profile from matched primary tumour and tumourspheres was assayed.

Conclusion

This study shows BRAINSTAT delivers high quality viable tissue samples to the lab. We also show that GBM patient-derived 3D tumoursphere cultures have the potential to become a reliable preclinical model to study the biology of glioma formation and to assay novel therapeutic treatments.

Does the extent of resection has an impact on time to transformation: 10 years retrospective analysis of Low Grade Glioma treatment

Power Poster Presentation (2 minutes)

Dr. Bernadett Kovacs [1], ***Mr. Giles Critchley*** [2], ***Dr. Juliet Brock*** [2], ***Dr. Antonia Creak*** [2], ***Dr. Catriona Good*** [2], ***Mr. Sorin Bucur*** [2]

1. *Br,* ***2.*** *Brighton and Sussex University Hospital Trust*

Aims

Diagnosis and treatment of Diffuse Infiltrative Low Grade Glioma (LGG) pose a significant challenge to surgeons and neuro-oncologists due to lack of consensus on timing and treatment modality.

We have assessed the results of treated LGG patients for the past 10 years in our regional Neurosurgical-Neurooncology department to determine whether the extent of surgical resection has an impact on the time to transformation.

Method

We have assessed retrospectively all the patients (94) with the histological diagnosis of diffuse intrinsic low grade glioma. 72 were diffuse intrinsic grade 2 glial tumour, as diffuse astrocytoma, or oligo – astrocytoma and 22 were oligodendroglioma grade 2.

The extent of resection (EOR) was defined as: biopsy (15, 16 %), <50% (20, 21 %), 50-80% (10, 11 %) and >80% (49, 52 %).

Time to transformation was defined as the time from diagnosis to radiological transformation (for those without histological confirmation) or the time from diagnosis to surgery with histological confirmation of transformation.

Results

10.6 % (5 out of 49) of the patients from > 80 % resection group had transformed to a higher grade tumour after a median of 32 months.

60 % (6 out of 10) in the 50 – 80 % resection group after a median of 46 months, 30 % (6 out of 20) of the patients in the < 50 % resection group had transformed to higher grade tumour after a median of 50.5 months and 60 % (9 out of 15) of the patients who only had biopsies after a median of 32 months.

Conclusion

As only 10.2 % of patients in the > 80 % resection group transformed into higher grade, we can conclude that the extent of resection has an impact on whether the tumour will undergo malignant transformation. However if the tumour is to transform, the extent of resection does not seem to have impact on after how long that will happen.

Durable responses of leptomeningeal metastatic cancer to modern systemic therapy

Power Poster Presentation (2 minutes)

Dr. Emma Kenney-Herbert [1], ***Dr. Anant Krishnan*** [1], ***Dr. Rachel Lewis*** [1], ***Dr. Piers Plowman*** [1]

1. *St Bartholomew's Hospital*

Aims

The prognosis for patients with leptomeningeal disease is extremely poor with overall survival expected to be approximately 2-4 months from the time of diagnosis. It is notoriously difficult to treat. Neither intrathecal chemotherapy/targeted agents nor whole brain or partial spinal radiotherapy are able to provide a durable response. Systemic therapies often are not effective as they do not cross the blood-brain barrier. There is the added difficulty that patients often have poor performance status on diagnosis with leptomeningeal disease which often means they are not fit for treatment at all. We report treatment of two patients with leptomeningeal disease with modern systemic anticancer therapies with a durable response.

Method

Patients were verbally consented to have anonymised information included in this poster. Information was taken from patient records on CRS. Images were stored and then downloaded from the PACs system.

Results

We report treatment of two patients one with an anaplastic pleomorphic xanthoastrocytoma (APXA) and the other with metastatic melanoma.

The patient with APXA had the BRAF V600E mutation, she was initially managed with surgery, fractionated radiotherapy and temozolomide with progressive disease and development of leptomeningeal disease. She was then successfully treated with debrafenib and trametinib with resolution of leptomeningeal spread and remission for 18 months. Debrafenib and trametinib were provided under the compassionate use programme from Novartis.

The patient with metastatic melanoma was treated with gamma knife radiotherapy, pembrolizumab as well as surgery but then benefited from Ipilimumab and Nivolumab on development of leptomeningeal spread with resolution of symptoms and durable response on imaging for 6 months.

Conclusion

Several case reports have demonstrated BRAF targeted therapy's efficacy on central nervous system tumours however, rarely in patients with leptomeningeal disease. Our case of APXA shows a potentially significant development for patients with APXA with BRAFV600E mutation and leptomeningeal disease.

Immunotherapy has revolutionised the treatment of melanoma and transformed the prognostic landscape. There are isolated case reports of immunotherapy improving the prognosis of patients with leptomeningeal disease due to metastatic cutaneous melanoma, but it is not something which has as yet been well documented. Therefore, it remains important to share experience of successful treatment of these patients, given the rarity of leptomeningeal spread of cancer such that patient numbers are insufficient to enrol into meaningful clinical trials. Moreover, it will help to provide evidence to support the funding of targeted therapies for this rare and previously rapidly fatal complication of advanced cancer.

Effectiveness of BRAF Inhibitors in Patients with BRAF-V600 mutation-positive glioma: A Systematic Review

Power Poster Presentation (2 minutes)

Mr. Zak Thornton [1], ***Ms. Lily Andrews*** [1], ***Mr. Ian Yao*** [1], ***Ms. Sarah Dawson*** [1], ***Dr. Sarah Jefferies*** [2], ***Prof. Susan Short*** [3], ***Dr. Vincent Cheng*** [1], ***Prof. Julian Higgins*** [1], ***Dr. Alexandra McAleenan*** [1], ***Dr. Kathreena Kurian*** [1]

1. *University of Bristol,* ***2.*** *Cambridge University Hospitals NHS Foundation Trust,* ***3.*** *University of Leeds*

Aims

BRAF V600 is an oncogenic driver mutation found within a number of cancers, including melanoma, non-small cell lung carcinoma and glioma. This mutation results in constitutive activation of the MAPK pathway, which causes uncontrolled cell proliferation and survival. BRAF inhibitors (BRAFi) are used to selectively bind to mutated BRAF proteins and inhibit downstream activity. BRAFi have been found to extend median overall survival (OS), progression free survival (PFS) and result in better response rate in BRAF V600 melanoma. Around 2-5% of diffuse gliomas contain mutations of BRAF V600, with a high incidence in paediatric populations and both benign and malignant subtypes, such as gangliogloma and pleomorphic xanthoastrocytoma. Here, we performed a systematic review to evaluate the OS, PFS and best tumour response of BRAF V600 mutation-positive glioma patients treated with selective BRAFi, including but not limited to vemurafenib and dabrafenib, as monotherapy or in combination with MEK inhibitors.

Method

An electronic database search was performed on 12th October 2020 on MEDLINE and Embase without language or date restrictions to identify studies containing patients with BRAF V600 mutation-positive gliomas who had received BRAFi therapy. Abstracts from the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) were also considered if the full publication was not available. Our search retrieved 2,366 records. Records were de-duplicated within EndNote, removing 654 records. The remaining 1,732 records were then screened by titles and abstracts using Rayyan online software. We excluded 1,510 records, and the remaining 222 records were full-text screened against eligibility criteria by one reviewer, and checked by a second reviewer. 92 records failed to meet inclusion criteria. Data extraction was then completed and checked by the same reviewer. A total of 130 publications were used in this systematic review (PROSPERO Registration No. CRD42019127824).

Results

We studied 394 patients; 241 paediatric patients (<18 years) (median 9; range 0.08 to 17 years), 144 adults (34; 18 to 62 years) and 9 not reported (NR). Tumour response was categorised according to Response Assessment in Neuro-oncology (RANO) or Response Evaluation Criteria in Solid Tumours (RECIST) criteria. 154/241 (64%) paediatric patients had a recorded tumour response. Of these, 8 (5%) had a complete response (CR), 63 (41%) had a partial response (PR), 68 (44%) exhibited stable disease (SD) and 15 (10%) showed progressive disease (PD). Of the patients whose tumour progressed, median PFS was 9.0 months (n=35). Median OS was 4.5 months (n=10). 137/144 (95%) adult patients had a recorded tumour response. Of these, 10 (7%) had CR, 48 (35%) had PR, 43 (31%) had SD and 36 (26%) showed PD. Of the patients whose tumour progressed, median PFS was 3.8 months (n=90). Median OS was 8.2 months (n=34).

Conclusion

To our knowledge, our cohort is the largest systematic review examining use of BRAF inhibitors in adult and paediatric glioma patients. We describe the incidence of complete response, partial response, stable disease

and progressive disease with use of BRAF inhibitors in our cohort. A limitation of our study is that we do not have large comparable groups with and without BRAF inhibitor treatment to draw firm conclusions about the efficacy of treatment. In addition, our PFS and OS data are derived from a small cohort of patients, due to many patients still ongoing treatment at the time of publication or PFS and OS being not reported.

Elderly glioblastoma score to estimate the survival of 70+ year old patients with primary glioblastoma

Power Poster Presentation (2 minutes)

Mr. Mark Zorman [1], ***Dr. Philip Webb*** [1], ***Ms. Mickaela Nixon*** [1], ***Ms. Sanskrithi Sravanam*** [1], ***Ms. Susan Honeyman*** [1], ***Dr. Meera Nandhabalan*** [1], ***Mr. Richard Stacey*** [1], ***Mr. Vasileios Apostolopoulos*** [1], ***Dr. Claire Hobbs*** [1], ***Prof. Puneet Plaha*** [1]

1. *Oxford University Hospitals NHS Foundation Trust*

Aims

Glioblastoma is the commonest primary malignant brain tumour with particularly poor prognosis in the elderly. Most multivariate survival analyses to date have included relatively small numbers of 70+ year old patients and there is no consensus about the optimal management of elderly glioblastoma patients, additionally complicated by their considerable comorbidities and chemoradiation sensitivity. The aim of this study was to assess the independent contribution of different neurosurgical and neurooncological interventions, in combination with biological and histological prognostic factors, to the survival of elderly patients with glioblastoma. The data were used to devise and evaluate a two-stage scoring system to estimate the survival of elderly glioblastoma patients receiving different neurosurgical (Elderly Glioblastoma Surgical Score, EGSS) and neurooncological interventions (Elderly Glioblastoma Oncological Score, EGOS).

Method

This retrospective cohort study included 169 patients aged 70 and above with a new diagnosis of IDH-wild type glioblastoma who received neurosurgical management at the John Radcliffe Hospital in Oxford between 2013-2019. The data were extracted from the electronic patient records of the John Radcliffe Hospital and the associated district general hospitals that provided oncological therapy. The influence on survival was determined for the following variables: gender, age and WHO performance status (PS) at diagnosis, presence of comorbidities, extent of neurosurgical resection (biopsy alone, subtotal or gross total), intraoperative use of 5-aminolevulinic acid (5ALA), MGMT promoter methylation status and chemoradiotherapy regime. Variables with significant independent effect on survival were identified using Cox proportional hazards model and used to devise the EGSS and EGOS scores. The predictive accuracy of both scores was assessed in a randomly selected sample of 56 patients.

Results

The overall median survival (MS) of the cohort was 28.8 weeks. Significant effect on MS ($p<0.05$) was detected for age and PS at diagnosis, extent of resection, intraoperative use of 5ALA, MGMT methylation and aggressive chemoradiation regimes involving temozolomide. The effect of gender and comorbidities on MS was not significant ($p>0.05$). Adjusted for the effect of other study variables, age 75-80 and 80+ reduced MS with hazard ratios (HRs) of 3.9 and 7.8, respectively ($p<0.05$). Independent negative effect on MS was also detected for biopsy alone (HR=5.2), no chemoradiotherapy (HR=8.1) and PS=4, $p<0.05$. Direct positive effect on MS was demonstrated for PS=0-1 (HR=0.32), positive MGMT methylation status (HR=0.73), subtotal (HR=0.58) and gross-total resection (HR=0.36). Standard (60Gy in 30 fractions) and hypofractionated (40Gy in 15 fractions) radiotherapy with temozolomide directly improved survival with HRs of 0.114 and 0.133, respectively ($p<0.05$). EGSS and EGOS scores predicted MS with 65% and 73% accuracy.

Conclusion

Our results quantitatively demonstrate how the survival of elderly patients with glioblastoma is directly affected by age and performance status at diagnosis, the extent of neurosurgical resection, MGMT methylation

and different chemoradiation regimes. Collectively, our study suggests that that when appropriate and safe, 70 to 80-year-old patients with a new diagnosis of glioblastoma and good performance status (PS=0-1) may benefit from more aggressive neurosurgical and oncological management. The survival of elderly glioblastoma patients undergoing surgical and oncological management can be estimated using the EGSS and EGOS scores, respectively.

Establishing a link between commonly reported toxicities and tumour location in brain tumour patients treated with volumetric modulated arc radiation therapy (VMAT)

Power Poster Presentation (2 minutes)

Ms. Sharon Fernandez [1], ***Mr. Matthew Beasley*** [2], ***Mr. John Lilley*** [3], ***Dr. Louise Murray*** [1], ***Prof. Susan Short*** [4]

1. *University of Leeds and Leeds Teaching Hospitals NHS Trust,* ***2.*** *Leeds Teaching Hospitals NHS Trust,* ***3.*** *Leeds,* ***4.*** *University of Leeds*

Aims

In patients with brain tumours, treatment-related side effects can negatively impact quality of life (QOL). Whilst acute and late toxicities following brain irradiation are well understood, there is a lack of research linking specific toxicities to tumour locations.

The main aims of this project were to document the common toxicities in a brain tumour patient cohort, mainly focusing on glioblastoma (GBM), treated using volumetric modulated arc radiotherapy (VMAT) with doses of 60Gy and to investigate whether tumour location within the brain influences the side effect profile. The main outcome being that this work will allow us to better inform future patients of expected toxicities.

Method

This retrospective audit included 57 patients (34 men: 23 women) with varied tumour histology who received volumetric modulated arc therapy (VMAT). Reported toxicities and doses to target volumes and organs at risk (OARs) (brainstem, optic chiasm and lenses) were extracted from electronic clinical databases. Patients were classified by location of their tumour (temporal, frontal, parietal and occipital). Chi-squared tests were used to evaluate side effects by anatomical location of the tumour.

Results

Median follow-up (FU) was 7 months (range, 0-19 months). At the time of analysis, 40 patients (70%) were alive and without evidence of disease progression. Majority of the patient cohort had a diagnosis of GBM (82.5%).

During radiotherapy, common toxicities included fatigue (recorded in 68.4% of patients), headaches (28.1%), alopecia (24.6%), low mood (19.3%) and nausea (31.6%).

During radiotherapy treatment, there was an apparent increase in incidence of toxicities with time, as expected. Patients with temporal lobe tumours were reported to experience a statistically significant increase in tiredness, with 9% of patients with temporal lobe tumours experiencing this, compared to only 2% and 0% of patients with frontal and parietal location tumours respectively. Reductions in appetite (20%) in patients with temporal tumours were also significant compared to patients with tumours in other brain locations.

Conclusion

The purpose of this study was to explore potential links between commonly reported toxicities following VMAT and the anatomical location of the tumour. Patients with temporal lobe tumours appeared to experience increased tiredness and reduced appetite compared to patients with non-temporal lobe tumours. Further study is needed to validate this observation.

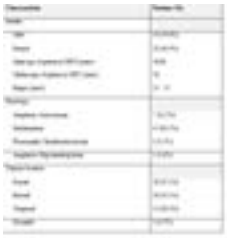

Table 1.jpg

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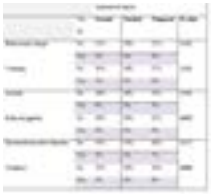

Table 3.jpg

Extent of MGMT promoter methylation modifies the effect of temozolomide on overall survival in patients with glioblastoma: a regional cohort study in Southeast Scotland

Power Poster Presentation (2 minutes)

Mr. Shivank Keni [1], ***Mr. Michael TC Poon*** [2], ***Dr. Sara Erridge*** [3], ***Dr. Paul M Brennan*** [4]

1. *Edinburgh Medical School, University of Edinburgh,* ***2.*** *Centre for Medical Informatics, Usher Institute, University of Edinburgh,* ***3.*** *Department for Clinical Neurosciences, Edinburgh Royal Infirmary,* ***4.*** *Centre for Clinical Brain Sciences, University of Edinburgh*

Aims

Dichotomy of *MGMT* methylation status in clinical practice and research may mask the prognostic value associated with the extent of *MGMT* methylation in patients with glioblastoma. This study aimed to evaluate the extent of *MGMT* methylation for its association with survival and its interaction with temozolomide.

Method

We included consecutive surgical patients with glioblastoma diagnosed in April 2012-May 2020 at a neuro-oncology centre where quantitative *MGMT* methylation assessment using pyrosequencing was routine. For patients reaching clinical threshold for *MGMT* methylation, we stratified them into high and low methylation groups using Youden index on 2-year survival. Survival analyses included extent of *MGMT* methylation, age at diagnosis, pre-operative Karnofsky performance score, extent of resection, temozolomide regimen and radiation therapy using accelerated failure time models.

Results

There were 342 glioblastoma patients in this study. The optimal cut-off point using Youden index was 25.5%. The number of patients in the unmethylated, low and high methylation groups was 190 (55%), 67 (20%) and 85 (25%), respectively. In the adjusted model, high (hazard ratio [HR] 0.63 0.47-0.84) but not low (HR 0.82, 95% CI 0.61-1.10) methylation group was associated with better overall survival compared to the unmethylated group. In the interaction model, there was evidence for better treatment response to less than standard temozolomide regimen associated with higher *MGMT* methylation (interaction term in low methylation p=0.027; high methylation p<0.001). There was no evidence for interaction between *MGMT* methylation and standard temozolomide regimen (interaction term for low methylation group p=0.329; high methylation group p=0.193).

Conclusion

Higher *MGMT* methylation was associated with better overall survival. The extent of *MGMT* methylation showed interaction with temozolomide depending on the chemotherapy regimen. Quantitative *MGMT* methylation may provide additional prognostic value and should be considered when assessing treatment effects of novel therapies.

Fibulin-2: A Novel Biomarker for Differentiating Grade II from Grade I Meningiomas

Power Poster Presentation (2 minutes)

Mr. Agbolahan Sofela [1], ***Prof. Oliver Hanemann*** [1]

1. *University of Plymouth*

Aims

There is an unmet need for the identification of biomarkers to aid in the diagnosis, clinical management, prognosis and follow-up of meningiomas. There is currently no consensus on the optimum management of WHO grade II meningiomas.

We aimed to assess Fibulin-2 as a molecular marker for differentiating between grade II and grade I meningiomas, by evaluating its expression in meningioma cells, tissue and blood plasma levels.

Method

In this study, we identified the calcium binding extracellular matrix glycoprotein, Fibulin-2, via mass-spectrometry-based proteomics, assessed its expression in grade I and II meningiomas and explored its potential as a grade II biomarker.

A total of 87 grade I and 91 grade II different meningioma cells, tissue and plasma samples were used for the various experimental techniques employed to assess Fibulin-2 expression. The tumours were reviewed and classified according to the 2016 edition of the Classification of the Tumours of the central nervous system (CNS). Mass spectrometry proteomic analysis identified Fibulin-2 as a differentially expressed protein between grade I and II meningioma cell cultures. Fibulin-2 levels were further evaluated in meningioma cells using Western blotting and Real-time Quantitative Polymerase Chain Reaction (RT-qPCR); in meningioma tissues via immunohistochemistry and RT-qPCR; and in plasma via Enzyme-Linked Immunosorbent Assay (ELISA).

Results

Proteomic analyses ($p < 0.05$), Western blotting ($p < 0.05$) and RT-qPCR ($p < 0.01$) confirmed significantly higher Fibulin-2 (FBLN2) expression levels in grade II meningiomas compared to grade I. Fibulin-2 blood plasma levels were also significantly higher in grade II meningioma patients compared to grade I patients.

Conclusion

This study suggests that elevated Fibulin-2 might be a novel grade II meningioma biomarker, when differentiating them from the grade I tumours. The trend of Fibulin-2 expression observed in plasma may serve as a useful non-invasive biomarker.

Finding the optimal skull-stripping method in MRI brain scans for deep learning segmentation of primary gliomas

Power Poster Presentation (2 minutes)

Dr. Andrew Ho [1], ***Dr. Matthew Williams*** [2]

1. *Norfolk and Norwich University Hospitals NHS Foundation Trust,* ***2.*** *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust*

Aims

The management of patients with primary brain tumours relies on cross-sectional imaging. Automated interrogation of imaging datasets at scale is challenging but increasingly possible using deep learning (DL). A key early step in automated analysis of MRI scans is tumour segmentation. Whilst manual segmentation is the gold standard, deep learning-based auto-segmentation algorithms, particularly using convolutional neural networks (CNNs), have achieved a high degree of accuracy.

An important pre-processing step for DL auto-segmentation is skull-stripping to exclude extra-axial structures. The skull-stripped images are then used both in training the CNN and when performing inference. For example, the annual BraTS challenge provides its dataset to the public and participants as skull-stripped images.

However, automated skull-stripping is potentially error-prone and may incorrectly include or exclude structures. A number of automated algorithms are available. In seeking to fully automate an MRI glioma segmentation pipeline, we assessed the performance of seven published automated skull-stripping algorithms.

Method

161 MRI scans from the TCGA-LGG and TCGA-GBM datasets were used, alongside the ground truth tumour segmentations provided by BraTS. The “silver-standard” brain mask was derived from the BraTS skull-stripped version of these scans; this had been generated using a semi-automated method with manual verification by the BraTS team. Seven automated skull-stripping algorithms were applied: BET; ROBEX; Deep MRI brain extraction; FreeSurfer; BrainMaGe; AFNI and BSE.

To investigate the effect of potentially-imperfect automated skull-stripping, DeepMedic (a 3D CNN) was trained on scans stripped by BraTS and that model was used for inference on scans skull-stripped using each of the automated algorithms. Dice coefficient for predicted whole tumour segmentation based on each model was calculated for all 161 scans by using 10-fold cross-validation. Finally, the CNN was re-trained using scans stripped with each of the automated skull-stripping algorithms to see if re-training improved model performance.

Results

All seven algorithms produced brain masks with a high degree of overlap with the silver-standard mask: mean Dice scores was highest for BrainMaGe (0.939) and lowest for BET (0.855).

In all seven cases, training the CNN with silver-standard stripped scans but providing automated-stripped scans for inference resulted in worse performance compared with inference using silver-standard stripped scans. Using silver-standard in training and inference provided a whole tumour mean Dice score of 0.881; mean Dice scores for the automated stripping algorithms ranged from 0.780 (Deep MRI brain extraction) to 0.875 (BET). Two-tailed Wilcoxon signed rank test showed this difference to be statistically significant in all cases ($p<0.05$).

Re-training the CNN using scans masked with an automated algorithm and performing inference with the same algorithm did not improve segmentation performance. Additionally, training inference using no brain mask resulted in a mean Dice of 0.853, higher than when using Deep MRI brain extraction.

Conclusion

Using an automated skull-stripping algorithm to remove extra-axial structures without manual verification pro-

vides a fully-automated pre-processing pipeline for auto-segmentation of brain tumours. However, this results in worse segmentation performance of the CNN compared with using a semi-manual brain mask. Re-training the CNN using automated stripped images does not improve performance. Thus, whilst manually performing skull-stripping when preparing images for auto-segmentation is time-consuming, it is nevertheless a key step in optimising segmentation performance.

Genetic Syndromes and Brain Tumours

Power Poster Presentation (2 minutes)

Dr. Vishal Manik [1], ***Dr. Omar Al-Salihi*** [1], ***Dr. Angela Swampillai*** [1], ***Dr. Lucy Brazil*** [1]

1. *Department of Clinical Oncology, Guys & St Thomas' Hospital, London*

Aims

Some genetic syndromes are known to increase an individual's lifetime risk of developing a malignancy. Few syndromes are associated with the risk of developing brain tumours such as Li-Fraumeni, Lynch syndrome and Turcot's syndrome. Few case series have demonstrated that brain tumours associated with genetic syndromes are diagnosed at a younger age, are aggressive in nature and could be associated with multi-organ cancer diagnosis. However, with the rarity of such cases along with sparsity of genetic units, there are no definite conclusions as to how we should manage these cases. Thus, we evaluated our cases over the last 5 years who presented to us with a brain tumour and also had a diagnosis of an associated genetic syndrome. The aim of this study was to review our genetic cases and see if an underlying genetic syndrome changes the way we manage these patients or changes their prognosis.

Method

We have looked at tumour related factors [histology, World Health Organisation (WHO) grade (low grade or high grade - Grade 3 {G3} Glioma or Glioblastoma Multiforme {GBM}), location, size, molecular profile (including methylation status and isocitrate dehydrogenase {IDH} mutations)], treatment related factors (date of diagnosis, surgical extent, adjuvant treatment, and second line treatment), other tumours diagnosed and time to progression and death.

Results

Total of 7 eligible patients were identified between November 2014 to April 2019 with median age at diagnosis of 34 (25-47). Syndromes were Lynch (n=3), Li-Fraumeni (n=3) and other(n=1). Supratentorial location was common (n= 4). All except one, had diagnosis of high grade glioma with IDH wild-type (n=5) and IDH positive (n=1). The median tumour volume at diagnosis was 41cc (2.6 – 112). Four patients underwent a debulking surgery. All 3 patients with Lynch had glioblastoma and received STUPP protocol. Two patients with Li-Fraumeni had G3 glioma, one received adjuvant temozolomide alone and other is on surveillance. Median time to progression was 5.9 months (3 – 12.3) and median time to death was 12.6 months (3.2 – 15.3) for 4 patients with IDH wild-type glioma. Notably the G3 glioma patient who did not have standard radiotherapy due to their risks with Li-Fraumeni syndrome did not have a shortened median survival.

Conclusion

Brain tumours associated with genetic syndromes are scarce, and the number of patients we have encountered are small and diverse. The median overall outcomes for unfavourable histology are as per reported standard. Data from a larger multi-centric collaboration to study the outcomes in these groups and where there could be a deviation from standard management due to competing risks is planned for the future.

Highly conformal IMRT to cavity for resected brain metastases; local control and toxicity outcomes from a single UK centre.

Power Poster Presentation (2 minutes)

Dr. Laura Coxon [1], ***Dr. Sara Meade*** [1], ***Dr. Paul Sanghera*** [1], ***Prof. Colin Watts*** [1], ***Dr. Victoria Wykes*** [1], ***Mrs. Anwen White*** [2], ***Mr. Vladimir Petrik*** [2], ***Mr. Athanasios Zisakis*** [2], ***Mr. Ismail Ughratdar*** [1], ***Dr. Helen Benghiat*** [3]

1. *Queen Elizabeth Hospital Birmingham,* ***2.*** *University Hospitals Birmingham NHS Foundation Trust,* ***3.*** *Department of Radiotherapy, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK*

Aims

After resection of a brain metastasis, recurrence is common, with >60% of patients experiencing local relapse within 1 year. Numerous trial data demonstrate reduction of relapse risk with adjuvant radiotherapy of varying modalities. Within the UK; NICE are clear that adjuvant whole brain radiotherapy (WBRT) should be avoided post resection of a single metastasis due to associated neurocognitive toxicity. Cavity stereotactic radiosurgery (SRS) is not currently commissioned by NHS England. The purpose of this study was to present a single centre experience in using highly conformal fractionated IMRT to the surgical cavity, reporting local control outcomes and toxicity.

Method

Sequential patients post resection of a brain metastasis who received fractionated cavity IMRT were recorded on a prospective database between July 2019 and November 2020. Baseline demographics including radiotherapy dose and treated volume were recorded. Outcome data were collected retrospectively and included local control, distant brain relapse and overall survival. Grade 3 or 4 toxicities (CTCAE v4.0) were recorded.

Results

Nineteen patients received post-operative IMRT to the surgical cavity with the following primary cancer diagnoses: breast (42%), lung (37%) and melanoma (21%). Median time from surgery to commencing radiotherapy was 40 days (range 23 – 110 days). The majority of patients were treated with 25Gy in 5 fractions (79%), with the remaining patients receiving 20Gy in 5 fractions. Median planning target volume (PTV) was 96.5cc (range 44.5 – 196.6cc).

At the time of analysis 8 patients have died. Median follow up in surviving patients was 5 months. Three patients (16%) have experienced local recurrence in the PTV. Time from completion of radiotherapy to local failure ranged from 4.5 – 12 months. Four patients (21%) developed distant brain failure at a median of 4.5 months post radiotherapy.

There were no episodes of grade 3 / 4 toxicity related to radiotherapy.

Conclusion

Although follow up in this cohort of patients is relatively short, this study confirms post-operative IMRT to the surgical cavity is well tolerated. Our local control rate of 84% is comparable to rates reported in a large randomised trial with both post-operative WBRT and SRS.

Five fraction IMRT is a cost effective adjunct to surgical resection with the potential to minimise toxicity and reduce risk of geographic miss associated with radiosurgery in difficult to define surgical cavities.

Hypothyroidism after craniospinal irradiation in children with medulloblastoma

Power Poster Presentation (2 minutes)

Ms. HELEN WOODMAN [1], ***Dr. Helen Benghiat*** [2], ***Dr. Miriam Pavon-Mengual*** [1], ***Dr. Jenny Adamski*** [1], ***Dr. Helen Jenkinson*** [1], ***Prof. Andrew Peet*** [1], ***Dr. Daniel Ford*** [2], ***Mr. Liam Herbert*** [2], ***Dr. Martin English*** [1]

1. *Department of Paediatric Oncology, Birmingham Womens and Childrens Hospital, UK,* ***2.*** *Department of Radiotherapy, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK*

Aims

Aim – Craniospinal irradiation (CSI) is an important part of paediatric medulloblastoma treatment. Long term endocrinopathies can develop including primary (PH) and secondary (SH) hypothyroidism. This study investigated PH and SH in a cohort of children from a single institution receiving CSI for medulloblastoma. We also investigated the relationship between radiotherapy technique and dosimetry on thyroid function.

Method

Method – Sequential patients < 16 years old diagnosed with medulloblastoma between January 2000 and December 2019 were identified. Patients were excluded if they had not received CSI, had received proton beam irradiation, died prior to developing endocrinopathies or had been lost to follow up. Baseline demographics were collected as well as thyroid function results and radiotherapy dosimetry. Time from completion of radiotherapy to first blood test demonstrating hypothyroidism was recorded. Statistical analysis was performed to investigate the relationship between dose to pituitary – thyroid axis and the development of hypothyroidism.

Results

Results – 56 eligible (F:M 23:33); median 8.5 (range 1-15) years; median follow up 81 (range 11 – 189) months. 38 received 3D conformal CSI (37 prone, 1 supine); 18 received CSI using helical TomoTherapy (HT) while supine. 20 received ≤ 23.4Gy CSI; 36 patients received >23.4Gy CSI (Range 31.2– 40Gy).

84% developed hypothyroidism after a median of 17 (range 3-51) months. 36 had PH, 11 had SH.

Prescribed CSI dose was not statistically different between PH, SH and Euthyroid groups, but with small numbers (36, 11 and 9) in each. Mean thyroid dose in the euthyroid group was 9.98 Gy vs 17.21 in the combined PH and SH groups (95% CI 2.57-11.89, p 0.005). This difference held for the PH group alone. 4 of 8 patients receiving HT with a CSI dose of 23.4 Gy remained euthyroid vs only one of 12 receiving the same dose at conformal RT.

Conclusion

Hypothyroidism is common after craniospinal radiotherapy for medulloblastoma. The thyroid should be contoured as an organ at risk and efforts made to reduce dose received in order to minimise risk of developing this complication of treatment.

Isocitrate Dehydrogenase-1 Wild Type is associated with increased expression of immunsuppressive immune checkpoints in newly diagnosed glioblastoma multiforme

Power Poster Presentation (2 minutes)

Dr. Alistair Paterson [1], ***Mr. Milo Hollingworth*** [2], ***Prof. Stuart Smith*** [3]

1. *Advanced Neuroimaging MSc, University College London, London,* ***2.*** *Department of Neurosurgery, Queen's Medical Centre, Nottingham,* ***3.*** *Department of Neurosurgery, Queen's Medical Centre, Nottingham, UK*

Aims

Isocitrate dehydrogenase -1 wild type (IDH-1 WT) glioblastoma multiforme (GBM) has a worse prognosis than IDH-1 Mutant. Expression of immunosuppressive immune check points (ICs) are associated with poorer prognosis in patients with solid tumours. We hypothesized that poorer prognosis in IDH-1 WT may be related to expression of immunosuppressive IC molecules in its tumour microenvironment. Expression of several ICs have already been described in GBM. We aimed to compare expression of these IC molecules between IDH-1WT and mutant tumours.

Method

ICs were identified from a literature search of studies with at least 10 patients with GBM that found significant differences in IC expression versus control using PubMed. mRNA expression data acquired from the Agilent-4502A Platform for each IC was analysed from The Cancer Genome Atlas (TCGA). Mean mRNA expression of each IC was compared between genotypes using independent sample T-tests. ICs with significant differences were used to dichotomise cases by median split in high and low IC expression. IC expression was compared between IDH-1 genotypes by binary logistic regression. Statistical significance was defined as p-value <0.05.

Results

We identified 124 eligible articles yielding 14 immune checkpoints in GBM: BTLA, CD160, CD200, PD-L1, B7/H3, CTLA4, IDO1, KIR, LAG3, PD1, TIGIT, TIM3, VISTA and 2B4.

302 patients with a new diagnosis of GBM from TCGA were studied (91% IDH-WT). Median survival was 11.3 and 23.5 months for IDH-1 WT and mutant respectively. Mutant GBM demonstrated lower immunosuppressive ICs BTLA, PDL-1, B7/H3, PD-1, TIM3 and VISTA but higher CD200 expression (p-value<0.05). High expression of immunosuppressive ICs, BTLA (OR 4.088 (95% CI 1.597-10.467; p-value=0.003) and PD-1(OR 3.710 (95% CI 1.447-9.510; p-value=0.006) was associated with IDH1-WT.

Conclusion

We have identified several immune checkpoints implicated in GBM. Differential expression of BTLA and PD-1 predict IDH-1 genotype and may play a role in the immune-tumour interactions in GBM and they could have a role in future treatment, potentially stratifying immunomodulation on the basis of IDH status.

Lipid levels and lipid associated genes as potential risk factors for glioma: a Mendelian randomisation study

Power Poster Presentation (2 minutes)

Ms. Katie Shea [1], ***Mr. Jamie Robinson*** [1], ***Dr. Kathreena Kurian*** [1]

1. *University of Bristol*

Aims

Glioma has an age adjusted incidence rate range from 4.67 to 5.73 per 100,000, with an overall 5-year survival rate of under 20%. Risk factors are not currently well understood. Mendelian Randomisation (MR) is a technique which can determine causal relationships between risk factors and disease. We have previously described a relationship between lipid associated genes and glioma using MR. We aimed to further investigate the effect of cholesterol and lipid associated genes on glioma risk.

Method

Our cohort comprised n= 12,496 cases (6191 glioblastoma (GBM), 5819 non-glioblastoma (non-GBM) including diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma and anaplastic oligodendroglioma) and 18,190 controls. Exposure data were obtained from n ~ 188,577 blood samples from the Global Lipids Genetics Consortium Genome Wide Association Study and mapped to lipid associated genes. Cholesterol was divided into high-density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and triglyceride (TG) subgroups. In addition, lipid associated genes were mapped to nearest single nucleotide variants. Two sample MR was run for overall cholesterol levels and for cholesterol levels mediated via lipid associated genes using outcome data from our cohort. Sensitivity analysis were performed to investigate the presence of heterogeneity and pleiotropic effects.

Results

The MR showed a 19% increase in glioma risk for non-glioblastoma subtypes (OR=1.19, 95% CI: 1.06 - 1.34, P=0.004) for each genetically proxied 1mmol/L increase in LDL-c level. There was no effect identified for HDL-c and TG. Genetic variants in the genes *PLA2G6* and *GCKR* were also implicated in reducing glioma risk across all glioma subtypes and GBM respectively through effects on triglyceride levels. *PLA2G6* (OR=0.02, 95% CI: 0.005 – 0.10, P=1.32×10^{-6}), *GCKR* (OR=0.53, 95% CI: 0.40 – 0.72, P=2.86×10^{-5}). MR implicated *PHLDB1*, a known lipid associated gene, with the increased risk of non-GBM via increasing total cholesterol levels.

Conclusion

This study provides initial evidence for a potential causal relationship between genetically predicted increased LDL-c levels and increased glioma risk. Further research is required to understand the potential biological mechanisms underpinning this potential relationship and implications for glioma patients.

Medium-term outcomes of Northern Ireland acoustic neuroma patients following Gamma knife radiosurgery.

Power Poster Presentation (2 minutes)

Mr. Colin Leonard [1], ***Mr. Tom Flannery*** [2], ***Mr. Stephen Cooke*** [2], ***Mr. Philip Weir*** [2], ***Ms. Susie Hampton*** [1], ***Dr. Neil Bailie*** [1], ***Dr. Gavin Wright*** [3]

1. *Department of Otolaryngology - Head and Neck Surgery, Royal Victoria Hospital, Belfast,* ***2.*** *Department of Neurosurgery, Royal Victoria Hospital, Belfast,* ***3.*** *. Leeds Gamma Knife Centre, Nova Healthcare, St. James's University Hospital, Leeds*

Aims

Acoustic neuromas are benign intracranial tumours arising from the myelin-forming Schwann cells of the vestibular nerve. Stereotactic radiosurgery is a useful therapeutic option for growing small-to-moderate sized tumours especially in patients who are felt to be high anaesthetic risk for surgery. Since 2010, the combined Otorhinolaryngology and Neurosurgery ("CON") clinic in the RVH has referred patients to Leeds Gamma Knife centre for treatment. The aim of this study was to review patient outcomes with a minimum of five years follow-up to establish the durability of treatment response, failure rates and any adverse effects of treatment.

Method

A retrospective review of 42 patients undergoing Gamma Knife treatment (GK) from August 2010 to December 2015 was conducted using local picture archiving and communication systems (NIPACS & iSite) as well as electronic health records (NIECR). All patients (21 M:21F) with an age range from 34-86 years, underwent treatment with a marginal dose of 12 Gy (at 50% isodose). GK was the primary treatment in 39 patients while three patients had undergone prior resection. Dose constraints used were mean cochlear dose of 4Gy and 12Gy brainstem volume < 10mm^3 and/or maximum point dose of 15 Gy. The tumour volume ranged from 261-10500 mm^3. Functional status following GK was assessed categorically by serviceability of hearing loss and method of hearing rehabilitation required.

Results

At the time of last imaging follow-up, 37 patients (88%) had evidence of local tumour control of whom four had died at two (n=2) and five (n=2) years following GK. One patient required surgery for progressive headaches within months of GK and two patients had evidence of tumour progression requiring surgery at 2 years post-GK. Two further patients have had evidence of slight tumour progression on their 5-year follow-up scan mandating closer surveillance. Two patients (4%) required shunt insertion for post-GK hydrocephalus. Audiological data was available for 37/42 (88%) of patients. At five years post treatment, 19/37 (51%) had no serviceable hearing. 18/37 (49%) had serviceable hearing of whom only 1 had a threshold of hearing that did not require conventional hearing aids.

Conclusion

GK is a safe and durable treatment for the vast majority of acoustic neuroma patients. However, even in patients with seemingly stable tumours for a number of years, longer follow-up is required in case of delayed relapse.

Metastasectomy in Multiple intracranial metastases: Analysis of survival and comparison of cases over a decade in a single unit.

Power Poster Presentation (2 minutes)

Ms. Sobiya Bilal Bilal [1], ***Ms. Andrea Perera*** [1], ***Mr. Giles Critchley*** [1]

1. *Brighton and Sussex University Hospital Trust*

Aims

To review trend in practice in a single unit over the last decade with regards to surgical management and outcome of patients with multiple intracranial metastases.

Method

Patients were retrospectively identified who had histology sent from 2007-2009 and 2017 -2019 consistent with diagnosis of intracranial metastatic disease. Patients were then identified who underwent metastasectomy for multiple intracranial metastatic lesions (defined as > 1 intracranial metastatic lesion identified on pre-operative MRI or CT post contrast). Online clinical notes and images were reviewed and data collected including post-operative survival, histology, primary oncological diagnosis, baseline demographic characteristics.

Results

From 2007-2009, 48 patients had histology from intracranial metastases and of those 5 patients had metastasectomy for multiple metastases (11%). From 2017 to 2019, 60 patients had histology from intracranial metastases of those 11 patients had metastasectomy for multiple intracranial metastases (18%). Of the 16 patients who had multiple intracranial metastases there were 7 females & 9 males (average age:59 years). (25-76). Lung (n=9) and breast (n=4) were the most common primary malignancies. Overall survival was 6.6 months after surgery. 1 patient remains alive in the cohort - current survival of 13 months. Between 2007-2009 average post-operative survival was 9.2 months (2-25 months). From 2017-2019 the average post-operative survival was 5.3 months (1-13 months). Most common metastasectomy site was the posterior fossa in 7 patients (44%). Only 8 patients had documentation available on their post-operative care of which only 50% of them made it to post-operative radiotherapy +/- adjuvant chemotherapy.

Conclusion

The trend towards palliative surgery in patients with multiple intra cranial metastases over past ten years had increased however; this did not have an impact over the outcome or the overall survival of these patients.

Molecular classification of paediatric CNS tumours – experience from a single neuropathology centre

Power Poster Presentation (2 minutes)

Dr. Zita Reisz [1], ***Mr. Ross Laxton*** [1], ***Ms. Leena Bhaw*** [1], ***Dr. Bassel Zebian*** [2], ***Dr. Cristina Bleil*** [2], ***Dr. Jozef Jarosz*** [3], ***Dr. Andrew King*** [1], ***Dr. Istvan Bodi*** [1], ***Prof. Safa Al-Sarraj*** [1]

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Aims

There is increasing evidence that molecular profiling of paediatric CNS tumours not only gives a deeper insight in their underlying genomic and epigenetic mechanisms but helps improve the diagnostic practices with more reliable prognostic stratification and identification of new therapeutic targets.

The aim of this research was to investigate the best practical approach for classification of paediatric brain tumours.

Method

A retrospective study was performed on 414 paediatric cases diagnosed between 2014 and 2020. Histology of all tumours were reviewed and selected cases were investigated further by methylation array and high-throughput sequencing techniques.

Results

Of 285 neuroepithelial paediatric tumours, 133 cases underwent methylation profiling and 47 cases were tested by NGS/RNA fusion panel. Methylation array successfully classified 36 embryonal tumours, 15 high-grade gliomas, 25 low-grade gliomas, 11 glioneuronal tumours and 15 ependymomas. The morphological diagnosis was confirmed in 70 cases (52%) and refined in 17 cases (13%). Molecular profiling resulted in clinically meaningful change in 13% of pathological diagnoses. NGS/RNA fusion panel detected pathogenic alterations in 63% of the samples. Histone H3-wildtype high-grade paediatric gliomas and embryonal tumours represented molecularly heterogeneous groups where molecular investigation was essential for reliable tumour classification. A subset of cases remained unsolved despite extensive investigation and these probably represent novel entities.

Conclusion

Implementation of molecular techniques in diagnostics of paediatric brain tumours is crucial to achieve a firm diagnosis and help the therapeutic decision, particularly in cases with unusual morphology or clinical behaviour. Nevertheless, even after using these techniques the diagnosis of some cases can still remain elusive.

Outcomes of children and adults with H3K27M mutant diffuse midline gliomas treated in a single centre.

Power Poster Presentation (2 minutes)

Mr. Pranjal Roy [1], ***Mr. Liam Herbert*** [2], ***Dr. Daniel Ford*** [2], ***Ms. Helen Woodman*** [3], ***Dr. Martin English*** [3], ***Dr. Jenny Adamski*** [3], ***Prof. Andrew Peet*** [3], ***Dr. Sara Meade*** [4], ***Dr. Paul Sanghera*** [4], ***Dr. Helen Benghiat*** [2]

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Aims

Diffuse midline gliomas (DMG) are a highly aggressive subset of brain tumours which develop in the thalamus, brainstem, and spinal cord and occur more frequently in children. Due to their location, biopsy carries risk and therefore radiological and clinical diagnosis remained the mainstay for years. Advances in neurosurgical technique and molecular analysis have identified a histone mutation (H3K27M), which now defines DMG, regardless of radiological / histological appearance. This study aimed to present outcomes of children and adults with DMG diagnosed both radiologically and after biopsy confirming H3K27M mutation.

Method

Consecutive children and adults with a radiological / pathological diagnosis of DMG were recorded on a database from January 2016 to November 2020. Using patient records we performed a retrospective analysis to determine baseline characteristics of this cohort, treatment received and survival outcomes.

Results

Nineteen patients were identified, 10 children, and 9 adults (>16 years at diagnosis). Eleven were female (58%) with median age 15 (range 6-36). Fifteen patients (79%) underwent biopsy with confirmed H3K27M mutation. Location of tumour varied: 10 (53%) brainstem, 8 (42%) thalamus and 1 (5%) spinal. Seventeen patients (89%) underwent radiotherapy (RT). Of the 2 patients (both adults) that did not have RT, 1 declined treatment, and the other died before RT. Of the 15 patients that were biopsied, all received radiotherapy with a median duration from biopsy to starting treatment of 23 days (range 11-132). Thirteen patients received 50-59.4Gy in 30-33 fractions, 2 patients received a hypofractionated schedule,1 patient received craniospinal radiotherapy and boost, and 1 patient an alternative regime due to requiring a general anaesthetic midway through treatment. At progression, 5 patients received repeat radiotherapy. Twelve patients have died (63%). Median overall survival is 12 months (range 1-58).

Conclusion

Median overall survival of 12 months in this cohort of patients is comparable to the literature. Further statistical analysis will be performed to allow comparison of paediatric and adult cohorts.

Outcomes of Patients with five or more Brain Metastases treated with Stereotactic Radiosurgery: a UK series.

Power Poster Presentation (2 minutes)

Dr. Helen Benghiat [1], ***Dr. Sameed Hussain*** [2], ***Dr. Sara Meade*** [2], ***Dr. Andrew Hartley*** [2], ***Mr. Mitchell Hickman*** [3], ***Ms. Hannah Augustus*** [2], ***Mrs. Ruth Stange*** [2], ***Dr. Geoffrey Heyes*** [2], ***Mr. Timothy Jackson*** [2], ***Prof. S Chavda*** [2], ***Prof. Vijay Sawlani*** [2], ***Dr. Michael Bowen*** [2], ***Dr. Peter Nightingale*** [2], ***Dr. Paul Sanghera*** [2]

1. *Department of Radiotherapy, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK,* ***2.*** *Queen Elizabeth Hospital Birmingham,* ***3.*** *University hosp*

Aims

Stereotactic radiosurgery (SRS) is accepted standard practice for good performance status patients with up to four brain metastases (BM). The role of SRS in patients with more than 4 brain metastases remains to be established. While randomised trials are ongoing, the purpose of this study was to present the experience of a single cancer centre in using SRS for patients with more than 4 brain metastases.

Method

Sequential patients with more than four brain metastases treated with SRS between March 2014 and August 2019 were prospectively recorded in a database. All patients satisfied current NHS commissioning criteria requiring a Karnofsky Performance Score greater or equal to 70, controllable systemic disease, total tumour volume less than or equal to 20cm^3
and a minimum estimated prognosis of greater than or equal to 6 months. Toxicity data collected included steroid dependence for greater than 4 weeks following treatment, new onset seizures and any Grade 3 or higher toxicity event as per CTCAE v5.0. Efficacy data collected included overall survival, local and distant brain failure.

Results

Ninety Five patients with more than 4 metastases received SRS to a total of 955 lesions. Six patients (6.3%) had received Whole brain radiotherapy prior to SRS. Eighty four patients (88.4%) received a single fraction of SRS (dose 15 to 24 Gy). The remaining 11 patients (11.6%) were treated with 3 fractions (dose 21 to 27 Gy). The median number of lesions treated was 7 (range 5 – 39), with a median volume of 2.6 cm^3 (range 0.2 – 15.5). Median overall survival for all patients was 9.9 months from the time of SRS (95% C.I. 6.5 – 13.3 months). There was no statistically significant difference in overall survival in patients with 5-10 versus greater than 10 brain metastases (median 9.9 versus 6.3 months p = 0.68). A significant trend for decreased overall survival was seen with increasing total volume of lesions (p=0.027).

Conclusion

Total volume rather number of metastases is prognostically important when treating more than 4 brain metastases.

Playing hide and seek with glioblastoma: Using epigenetic modulators to increase Cancer Testis Antigen and neoantigen expression

Power Poster Presentation (2 minutes)

Dr. Ruichong Ma [1], ***Dr. Margarida Rei*** [1], ***Ms. Katherine Ferris*** [1], ***Mr. Isaac Woodhouse*** [1], ***Dr. Sophie Kirschner*** [2], ***Dr. Anandhakumar Chandran*** [2], ***Dr. Skirmantas Kriaucionis*** [2], ***Prof. Olaf Ansorge*** [3], ***Dr. Hashem Koohy*** [1], ***Prof. Puneet Plaha*** [4], ***Prof. Vincenzo Cerundolo*** [1]

1. *Human Immunology Unit, University of Oxford,* ***2.*** *Ludwig Cancer Research, University of Oxford,* ***3.*** *Nuffield Department of Clinical Neurosciences, University of Oxford,* ***4.*** *Oxford University Hospitals NHS Foundation Trust*

Aims

Glioblastoma (GBM) is the most common and malignant primary brain tumour in adults with a median survival of only 14- 24 months despite treatment. The relentless and inevitable progression of GBM is thought to be facilitated by an immunosuppressive microenvironment, which weakens the ability of the central nervous system to mount an effective tumour-eradicating response. However, clinical response of GBM to immunotherapy, including checkpoint inhibitors, is modest. This is in part due to the low number of mutations seen in GBM. Epigenetic regulation of tumour cells is becoming increasingly recognised as an important factor in tumour immune escape with downregulation of chromatin modifying genes being shown to lead to increased sensitivity to checkpoint blockade and increased immune-mediated cell killing through increased expression of interferon stimulated genes. Here, we examine the effect of a decitabine (DAC), a DNA methyl-transferase inhibitor, on the expression of both cancer testis antigens (CTA) and neoantigens.

Method

Primary GBM cell lines were created through single cell suspension of fresh tumour specimens taken at the time of surgery and culturing on laminin coated plates using defined neural stem cell media. Neoantigens from Primary and U87MG cell lines were predicted using whole exome sequencing data. Differential expression of CTA and NAg caused by DAC treatment was determined using RNA sequencing data from the cell lines in the presence or absence of 1uM DAC. Peptide specific T cells were isolated from peripheral blood mononuclear cells (PBMC) of autologous donors and from healthy donors, using fluorescence labelled peptide-MHC class I tetramers. Autologous T cells were isolated either through mixed lymphocyte-tumour culture or *ex-vivo* single cell clonal expansion. T cell functionality was tested through intracellular cytokine staining and/or LDH release killing assay.

Results

Six out of nine potential neoantigen encoding mutations were significantly upregulated following DAC treatment in U87MG cell line and further 21 across the 4 primary patient cell lines. In addition, a wide range of CTA were consistently upregulated. Using neoantigen and CTA specific T cells obtained through an *in-vitro* priming technique, we show that co-culture with DAC treated cells compared to untreated cells leads to greater T cell activation and killing in a MHC:TCR dependent fashion. We also show that the same is true for a subset of autologous tumour specific T cells isolated from both patient tumour and peripheral blood samples.

Conclusion

Here we show for the first time that a large spectrum of CTAs as well as several neoantigens are upregulated following DAC treatment. We have optimised a protocol for isolation of a panel of peptide specific T cells, both from patients and healthy donors, for interrogation of increased neoantigen specific killing following treatment with DAC. We show these T cells show increased activation and killing following co-culture with cell lines

treated with DAC. Importantly, we also show that this is also true for autologous tumour specific T cells present within the tumour and peripheral blood. This provides exciting preclinical evidence for a novel combination immunotherapy for GBM.

Prediction of survival in paediatric brain tumours using multicentre perfusion MRI

Power Poster Presentation (2 minutes)

Dr. Steph Withey [1], ***Dr. Lesley MacPherson*** [2], ***Dr. Adam Oates*** [2], ***Mr. Stephen Powell*** [3], ***Dr. Jan Novak*** [4], ***Dr. Laurence Abernethy*** [5], ***Prof. Barry Pizer*** [6], ***Prof. Richard Grundy*** [7], ***Dr. Paul Morgan*** [7], ***Prof. Simon Bailey*** [8], ***Dr. Dipayan Mitra*** [9], ***Prof. Theodoros Arvanitis*** [10], ***Prof. Dorothee Auer*** [11], ***Dr. Shivaram Avula*** [5], ***Prof. Andrew Peet*** [3]

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Aims

Paediatric brain tumour survival rates vary between tumour types and with grade. Early identification of those at higher risk may allow better treatment decisions to be made. Dynamic susceptibility-contrast (DSC-) MRI involves rapid scanning following injection of a contrast agent providing estimates of perfusion parameters such as relative cerebral blood volume (rCBV). Leakage of contrast agent occurs in low-grade tumours resulting in underestimation of rCBV. We have previously shown that leakage correction is essential in this patient group. The aim of this work was to assess whether leakage-corrected DSC-MRI parameters could predict survival in paediatric brain tumour patients.

Method

85 patients underwent pre-treatment DSC-MRI scans at 4 centres on 6 different scanners. Scanning protocols were variable. Pixel-by-pixel contrast agent concentration time courses were analysed using the Boxerman model of leakage correction. Estimates of uncorrected and leakage-corrected rCBV ($rCBV_{uncorr}$ and $rCBV_{corr}$, respectively) and the leakage parameter, K_2, were obtained. Patients were followed up. Kaplan Meier survival analysis was performed on patient characteristics including sex, tumour type, grade and DSC-MRI parameters.

Results

Median follow-up time was 88 months (range = 45 – 183 months). At analysis, 24 patients had died, 61 were alive. Low $rCBV_{uncorr}$ and $rCBV_{corr}$ were associated with significantly better survival (p=0.003 and 0.040, respectively) using cut-offs of 2.5 and 2.1, respectively. A positive K_2, associated with leakage correction in low-grade tumours, was predictive of significantly better overall survival (p=0.020). Other prognostic factors were tumour type (p<0.01), tumour grade (p<0.01) and tumour volume (p=0.030).

Conclusion

In summary, perfusion MRI at diagnosis can aid in predicting which patients are likely to have better survival rates. Low perfusion was associated with better survival. This finding is robust across multiple centres, despite using multiple DSC-MRI protocols.

Rare Case of Intracranial Capillary Haemangioma with a Dural Tail Sign Mimicking Meningioma

Power Poster Presentation (2 minutes)

Mr. Hadleigh Cuthbert [1], ***Dr. Aimee Goel*** [2], ***Ms. erminia albanese*** [2]

1. *Queen Elizabeth Hospital Birmingham,* ***2.*** *University Hospital North Midlands*

Aims

Capillary haemangiomas are common cutaneous and soft tissue lesions which are often found at birth. Intracranial capillary haemangiomas are exceedingly rare, and are often mistaken for meningioma. We present a case presenting with a contrast-enhancing dural-based tumour thought pre-operatively to be meningioma, but subsequently confirmed histologically as capillary haemangioma. We conduct a literature review to identify the common presentations and characteristics of these lesions. We also discuss how capillary haemangiomas differ from other lesions of the CNS from a radiological and histological perspective.

Method

The present case report is based on surgical, radiological and pathological information gained from the neuro-oncology multidisciplinary team.

For the literature review, applicable publications from PubMed were identified using the search terms: “capillary haemangioma”; “capillary hemangioma”; “dural tail sign”; and “intracranial”. Only articles published in English were included for review. Serial reports involving the same patients were selected and one-time included. Data regarding clinical presentation, lesion location, diagnostic suspicion, and presence of dural tail sign were reported into a table for description and analysis.

Results

The literature review identified 49 other cases of intracranial capillary haemangioma. The median age at diagnosis was 16 years. Four cases presented with multiple lesions.

Capillary haemangiomas are commonly mistaken for other tumours, particularly meningiomas; of those studies that stated their presumed diagnosis, 12/22 considered meningioma in the differential. In all of the presented cases, the diagnosis was only made post-operatively based on histological findings.

Meningiomas share important radiological characteristics with capillary haemangiomas. These characteristics are: well-circumscribed, high intensity areas on T1- and T2-weighted MRI, and intense gadolinium enhancement. The absence of dural tail, and the presence of flow voids and intralesional haemorrhage on MRI, are important features for the diagnosis of capillary haemangioma. However, our case displayed a dural tail sign and was therefore thought to harbour a meningioma based on imaging. Only four other cases of intracranial capillary haemangioma with dural tail are reported.

Conclusion

Intracranial capillary haemangiomas are rare vascular hamartomas that are most common in young adults. These lesions most often presented with visual disturbance, cranial nerve deficits and headaches. They are rarely identified pre-operatively, and are commonly mistaken for meningioma or haemangiopericytoma. No imaging modality is diagnostic, nor has a pathognomonic sign been reported. The dural tail sign is commonly used to distinguish them from meningioma, but can rarely be present even in intracranial capillary haemangioma, and capillary haemangioma should therefore be in the differential diagnosis of meningioma.

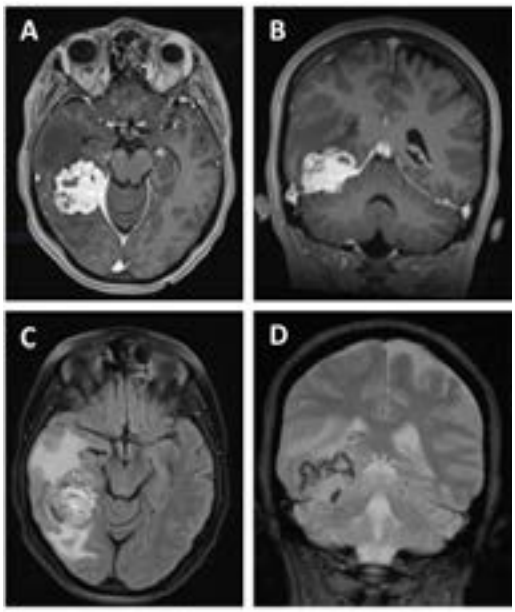

Figure 1: pre-operative MRI images showing an enhancing tentorial lesion with a wide dural base and dural tail sign. (A,B) T1 with gadolinium contrast; (C) T2 FLAIR; and (D) T2 gradient echo.

Figure 1.jpg

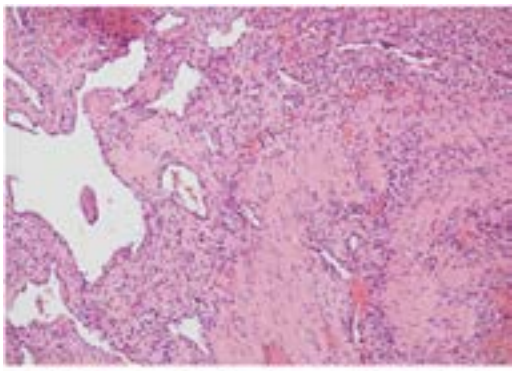

Figure 2: H&E staining showing thin-walled capillary-sized blood vessels. The stroma is rich in smooth muscle cells, with no mitotic or necrotic features.

Figure 2.jpg

Re-irradiation in Glioblastoma Multiforme: a single centre experience

Power Poster Presentation (2 minutes)

Dr. Hamish Sinclair [1], ***Dr. Seema Dadhania*** [1], ***Dr. Matthew Williams*** [1]

1. *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust, London*

Aims

Glioblastoma Multiforme (WHO grade IV glioma; GBM) is the most common malignant primary brain tumour in adults. Standard treatment involves maximal safe resection, chemoradiotherapy with concurrent temozolomide, followed by 6 cycles of adjuvant temozolomide. Despite treatment, the majority of patients will progress within 1 year, and 90% of recurrences occur in-field, close to the resection cavity. CCNU-based chemotherapy is standard of care at first progression, but treatment options include re-resection, systemic therapy, re-irradiation or best supportive care. There is minimal prospective or randomised data comparing these approaches. There are concerns regarding the risks of re-irradiation due to cumulative brain dose. We present outcomes of patients receiving re-irradiation for GBM at our institution.

Method

We retrospectively identified all adults (age ≥18 years) with a histological diagnosis of GBM (WHO grade IV) who underwent re-irradiation at a single UK based tertiary neuro-oncology centre between 1st May 2014 and 31st December 2020. Patients were included if they had previously received chemoradiation (either 45Gy in 15 fractions or 60Gy in 30 fractions) at either our centre or elsewhere. All patients were discussed at our neuro-oncology MDT prior to re-irradiation. Patient demographics and treatment details were obtained from the hospital records. Radiotherapy volumes were extracted from radiotherapy planning systems. Gross tumour volume (GTV) was defined as the area of T1 contrast enhancement on MRI, no CTV margin was used. Follow up data was completed up to 20th February 2021.

Results

In total 38 patients received re-irradiation within the defined period. Median age at diagnosis was 52 years (range 27 – 76 years). The majority had tumours that were unmethylated (71%) and IDH wild-type (92%). 17 patients (45%) underwent re-resection prior to re-irradiation. Median time from initial chemoradiotherapy to re-irradiation was 45.9 weeks (range 20.9 – 165.7 weeks).

12/38 (31.5%) patients underwent re-irradiation with a dose of 35Gy, 12/38 (31.5%) received 40Gy and 14/38 (37%) received 45Gy. All treatment was delivered in 10 fractions using inverse planning IMRT. Median progression free survival and overall survival from the start of re-irradiation was 10.7 weeks (95%CI 3.6-17.8) and 32.9 weeks (95% CI 25.0-40.8) respectively. Median overall survival from diagnosis was 92.9 weeks (95%CI 82.7–103.0). 2/38 (5%) patients did not complete re-irradiation. One patient developed a pulmonary embolism during treatment, one patient withdrew due to nausea and fatigue. There were no treatment related deaths.

Conclusion

Our observed outcomes for overall survival are consistent with comparable studies which have shown a median OS of between 4.9 – 12.5 months following re-irradiation. Care must be taken interpreting the data on progression due to the difficulty in determining true disease progression from radionecrosis. However, this is one of the largest UK series of re-irradiation in GBM, and shows that it is safe and feasible. The remaining challenge is to improve the efficacy, and to this end we and others are designing studies to attempt to improve the effectiveness of re-irradiation.

Screening novel Glycogen Synthase Kinase-3 Beta inhibitors for targeted glioma therapy in a blood brain barrier-glioma model

Power Poster Presentation (2 minutes)

Ms. Klaudia Rzepecka [1], ***Dr. Clare Lawrence*** [1], ***Dr. Lisa Shaw*** [1], ***Dr. Joseph Hayes*** [1], ***Dr. Jane Alder*** [1]

1. *University of Central Lancashire*

Aims

A substantial problem in finding novel treatments for central nervous system (CNS) is the blood brain barrier (BBB) which limits the disposition of drugs into the brain itself. Many BBB *in vitro*models have been developed, the most commonly used in pharmaceutical industry being monolayers of Caco-2 and ; however they do not accurately represent the neurovascular unit found *in vivo*, often using cells of different species, therefore the results cannot be translated.

We aim to validate our BBB model against the industry standards and test the effect of selected inhibitors on cell viability of patient derived glioblastoma cells. Their permeability through our dynamic, all-human, three-dimensional *in vitro*BBB model will also be tested to demonstrate if they will be able to reach the tumour inside the brain of patients.

Method

The BBB model has been validated through testing permeability of FITC-Dextrans over time and compared to same permeability testing on Caco-2 and hCMEC/d3 monolayers. TEER measurements were used to test barrier confluence in all cases.

*In silico*identification has led to selection of 5 novel, most promising naturally occurring GSK3β inhibitors with high selectivity. We aim to test the inhibitors on cell viability of firstly glioma cell lines and then patient derived glioma cells. Their permeability through our *in vitro*BBB model will also be tested. Addition of a tumour spheroid into the BBB model will be able to predict whether the inhibitors remain effective post transport through the BBB. To further investigate the mechanism of action of the GSK3β inhibitors on the tumour cells, apoptosis and necrosis assays will be carried out.

Results

Overall, the Caco-2 and hCMEC/d3 models show a lot of variability in the appearance of FITC-Dextran through the barrier, and therefore do not produce repeatable results. The results of the*in vitro* BBB model designed at UCLan using all human components to co-culture brain endothelial cells with astrocytes and pericytes has shown a greater level of exclusion of the FITC-Dextrans. This suggests that the barrier created is overall more intact than the industry models using cell lines, and results are more repeatable considering the small standard deviation values.

Results show that TEER is not entirely precise indicator of models' ability to exclude compounds. The BBB model showed the best ability to exclude compounds despite low mean TEER values. Caco-2 monolayers reaching the highest mean TEER showed higher permeability to compounds. Despite the mean TEER values for hCMEC/d3 monolayers and BBB trilayer model being similar, the permeability results were very different.

Conclusion

Metabolic function should also be considered when evaluating BBB pharmaceutical models. Although Caco-2

reached and surpassed the brain TEER *in vivo* values, it is a cell line formed from a different organ and therefore has different transporter activity. hCMEC/d3 monocultures did not have the cell-to-cell interactions with other cell types found in the NVU which has been shown to induce the specific BBB barrier phenotype. The BBB co-culture model formed of only primary cells, using cell types found in the NVU is the closest model to resemble the *in vivo* BBB, and therefore reflects the metabolic activity the most.

TEER should not be over relied on. TEER is a good indicator of confluence of the cultures providing one knows the top values the specified barrier can reach; this does not correlate directly to the compounds ability to permeate the barrier.

Speech and language therapy and survivorship: working with people with brain tumours

Power Poster Presentation (2 minutes)

Ms. Georgie Smith [1], ***Mr. William Garratt*** [2], ***Mr. Frederick Berki*** [2], ***Mrs. Claire Goddard*** [2], ***Dr. Paul Sanghera*** [1], ***Mr. Ismail Ughratdar*** [1], ***Prof. Colin Watts*** [1], ***Mr. Athanasios Zisakis*** [2], ***Dr. Victoria Wykes*** [1], ***Dr. Camilla Dawson*** [1]

1. *Queen Elizabeth Hospital Birmingham,* ***2.*** *University Hospitals Birmingham NHS Foundation Trust*

Aims

We undertook a service evaluation to explore how speech and language interventions may be optimally delivered for people undergoing awake craniotomy. Whilst the functional benefits of awake craniotomy have been determined [1], along with the importance of survivorship programmes for this cohort [2], there is little available research around how both facets may be delivered. We collected information from a single case study to improve our understanding of the practical and holistic elements of this complex intervention, to ensure we deliver best possible outcomes to people who undergo awake craniotomies, and to reflect on areas where improvement is required.

Method

We undertook a service evaluation of our speech and language therapy interventions, using clinical note audit, clinical reflections, and bench marking against survivorship guidelines set by the National Cancer Survivorship Initiative (NCSI). Our retrospective data collection was based on a case report of a patient diagnosed with a WHO Grade II oligodendroglioma. The clinical interventions provided pre- and post-operatively in both inpatient and outpatient settings were reviewed and analysed to establish how survivorship initiatives were applied and to consider how future interventions may be mapped more deliberately to improve patient experience.

Results

After post-operative intervention, scores on formal language assessment were near to or equal to baseline and language capability was effectively maintained. Despite effective preservation of functional ability, this patient reported a number of challenges often faced by cancer patients following primary treatment [3]. These included reduced confidence and social withdrawal, corresponding with avoidance behaviours, changes in relationships and delayed return to work. While survivorship initiatives were referenced and discussed during rehabilitation and therapeutic sessions, our analysis suggests that more deliberate and practical adaptations and solutions to navigating these complexities would have been of benefit. This reveals areas for development to improve patient management by integrating survivorship principles at an earlier juncture, and providing more robust opportunities for holistic and social model rehabilitation. We plan to devise a robust pathway involving all members of the MDT, covering inpatient and outpatient interventions, to promote independence and quality of life for the individual.

Conclusion

This case report enabled us to reflect on potential improvements to the service, with use of a robust survivorship programme. Specific learning included promotion of survivorship from the first consultation with the SLT and MDT. We have considered how data will be collected to audit our progress towards achieving these goals as a team, and will aim to present future collaborative experiences of the impact of this quality implementation project.

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Stereotactic Radiosurgery Brain Metastases Pathway at University Hospitals Birmingham NHS Trust

Power Poster Presentation (2 minutes)

Mr. Mitchell Hickman [1]

1. *University hosp*

Aims

University Hospitals Birmingham NHS Trust is a service provider for Tier 1 and Tier 2 clinical activity. The regional catchment area has a neuroscience population of 6.5 million. In the calendar year 2020 the dedicated Stereotactic Radiosurgery (SRS) service using CyberKnife treated 314 intracranial lesions, 219 were metastatic. In our centre metastatic cases are increasing exponentially; this is due to the increase in incidence and better systemic disease control. It is also now deemed favourable to treat the metastasis rather than the whole brain due to concerns of the resulting neurocognitive toxicity (O'Beirn, 2018)

Method

To educate other SRS services on how to adapt workflows and pathways to cope with increased demand. The presentation will highlight challenges we have faced, and what changes we have implemented to ensure we are adhering to NHS England service specifications. The presentation will ahighlight radiographer role developments to enhance patient experiences and expectations. This includes:

- Non-medical prescribing
- Non-medical imaging referrals
- Telephone consultations utilising patient reported outcome measures (PROMS)
- Radiographer-led clinics
- Future developments

Results

- 314 patients followed up by radiographer (January 2020 - December 2020)
- …… medications prescribed (requested)
- 240 imaging requests for metastatic cases, new patients and follow up/ (July 2020 - Dec 2020)
- target and organ and risk delineation
- adhering to NHS England specifications

Conclusion

Increasing patient numbers will eventually put strain on the system; therefore as a dedicated SRS service it is imperative that we adapt to ensure smooth workflow adhering to NHS England service specifications.

Steroid induced osteoporosis in glioblastoma multiforme patients

Power Poster Presentation (2 minutes)

Dr. Keisha Marchon [1], ***Mrs. Gill Walsh*** [2], ***Dr. Juliet Brock*** [1]

1. *Brighton and Sussex University Hospital Trust,* ***2.*** *BSUH*

Aims

The aim of this report is to highlight the risk of steroid-induced osteoporosis in Glioblastoma Multiforme (GBM) patients and to generate a guideline for management to prevent this outcome. This may become relevant to multiple other patient groups in whom long term steroid use is common.

Method

A retrospective review of patients attending neuro-oncology clinics over a three-year period (October 2016-October 2019) at one trust was carried out. Only patients with either GBM histology or a documented radiological diagnosis were included. Clinic letters for these patients were reviewed to assess whether they had required steroids and for how long. In-depth review of clinical letters and imaging was carried out to assess whether patients with confirmed GBM on steroids for any length of time had symptoms and/or radiological confirmation of osteoporosis/bone events.

Results

Over the three-year period, 211 new patients attended neuro-oncology clinics, 120 with a diagnosis of GBM either histologically or radiologically. 115 of these patients were started on steroids, usually at initial presentation, and the majority continued for several months. 12 GBM patients on steroids had radiological evidence of osteoporosis, of which 3 were symptomatic and significantly linked to steroid use. The effects of steroids on bone in these 3 patients were significant vertebral osteopenia with fractures, multilevel vertebral degeneration leading to cauda equine symptoms, and significant back pain with intraventricular spinal disc space narrowing respectively.

Conclusion

2.6% of GBM patients on steroids included in this retrospective analysis developed symptomatic osteoporosis. 9 other patients were also noted to have developed some bone degeneration however the exact co-relation with steroids could not be determined. The substantial side effects of steroids on bone suggest the need to consider a preventative rather than reactive approach. The cost benefit of a reduced number of hospital attendances and emergency scans would be in addition to the advantages of safer patient care, reduced symptom burden and better quality of life in patients living with a serious illness. The next step in this quality improvement project is to develop guidelines for prophylactic bisphosphonate prescribing in GBM patients likely to be on steroids long term.

Supportive care needs of TYA childhood brain tumour survivors and their caregivers: a mixed methods study

Power Poster Presentation (2 minutes)

Ms. Emma Nicklin [1], ***Prof. Galina Velikova*** [2], ***Prof. Adam Glaser*** [2], ***Dr. Michelle Kwok-Williams*** [3], ***Dr. Miguel Debono*** [4], ***Dr. Florien Boele*** [1]

1. *University of Leeds,* ***2.*** *University of Leeds and Leeds Teaching Hospitals NHS Trust,* ***3.*** *Leeds Teaching Hospitals NHS Trust,* ***4.*** *Sheffield Teaching Hospitals NHS Foundation Trust*

Aims

Childhood brain tumour survivors and their family caregivers can experience many late effects of treatment including social, cognitive and physical issues. Yet, the supportive care needs of survivors, now teenagers and young adults (TYAs), and their caregivers population are largely unknown. We aimed to gain an in-depth understanding of this populations' supportive care needs.

Method

This study used a convergent mixed methods design including quantitative (survey) and qualitative data (in-depth semi-structured interviews). Participants were recruited from long-term follow-up clinics (in three NHS Trusts in England) and online. Participants included childhood brain tumour survivors, at least five years from diagnosis, currently aged 13-30 and their primary caregivers. The results from quantitative and qualitative data were integrated using a Joint Display Table.

Results

136 eligible survivors and caregivers (78 survivors/58 caregivers) were approached to take part in the survey. In total, 112 participants (69 survivors/43 caregivers) completed the survey. A further 22 participants took part in face-to-face semi-structured interviews (11 survivors/11 caregivers). The integrated findings indicate that both survivors and caregivers have unmet needs many years after diagnosis. TYA survivors specifically had high unmet needs in relation to their psychological health, social lives (including romantic relationships), employment, and independence. Caregivers experienced even more unmet needs - including regarding their own psychological well-being and survivors' financial issues. Survivors further from diagnosis, unemployed survivors and single caregivers were more likely to report unmet needs. Barriers preventing survivors and caregivers accessing supportive services were highlighted, including (but not exclusive to) families not being aware of support available, location of services, and accessibility to information/support.

Conclusion

This research provides leads to improving supportive care and long-term follow-up services. Understanding unmet needs and recognising what services are required is critical to improving survivor and caregiver quality of long-term survival.

Surgical management of recurrent GBM- is it safe and does it improve survival? A single centre study.

Power Poster Presentation (2 minutes)

Dr. Shuvamay Chowdhury [1], ***Mr. Jungwoo Kang*** [1], ***Mr. Babar Vaqas*** [2]

1. *Queens,* ***2.*** *Queens Hospital, Romford*

Aims

Glioblastoma multiforme (GBM) is the most common primary brain tumour in adults. Recurrence following initial surgical resection is frequent and there is no widespread agreement on how this should be managed. The present study was aimed at determining if recurrent glioblastoma surgery is safe in our centre, and to explore if surgically-managed recurrence confers a survival advantage compared to non-surgically managed recurrence in comparable cases.

Method

Neuro-oncology multidisciplinary team (MDT) meeting notes from 01/01/2019 to 12/31/2019 were screened for recurrent GBM patients. Patients' data regarding their demographics, date of initial surgery, tumour size and performance status at time of MDT discussion, timing of surgery after recurrence and date of death or last clinical contact were retrospectively collected. For the surgical cohort data regarding surgical complications were collected. For the non-surgically managed patients, the reasons behind no surgical intervention were collected.

Results

37 consecutive patients with recurrent glioblastoma at MDT were examined. 15 patients underwent surgery (average age = 53.9), whilst 22 patients did not undergo surgery (average age = 57.8). There were no demographic related differences between the two groups. Surgical patients had focal recurrence (n=15/15) with good preoperative performance status. Adjuncts such as 5-ALA (n=7/15) and intraoperative ultrasound (n=5/15) were used and were helpful in guiding surgery. Reasons for declining re-do neurosurgery included low initial performance status (n=4/22), no surgical benefit or accessibility (n=17/22), and death prior to MDT discussion (n=1/22). The surgical cohort underwent safe surgery in terms of complications, such as wound infection (n=2/15), CSF collection (n=3/15), and temporary focal deficits (n=2/15). The Kaplan-Meier estimator demonstrated a significant improvement in survival (p=0.019) with median survival from initial surgery in the surgical cohort being 724 days, compared to 472 days in patients without surgery.

Conclusion

Our results suggest that surgical management of GBM patients with surgically accessible focal recurrence, good performance status and advanced surgical adjuncts as practiced in our unit is safe and increases survival. A randomised trial taking into account molecular diagnostic information may resolve the issue of selection bias in this group of patients but randomisation may be difficult. Standardisation of the approach for managing recurrent GBM across the UK may improve survival outcomes in this incurable condition.

The Impact of COVID-19 on the management of patients with high-grade gliomas: experience from a national tertiary centre

Power Poster Presentation (2 minutes)

Mr. Ciaran Hill [1], Dr. Jennifer Van Griethuysen [1], Dr. Zhangjie Su [1], Mr. Mehdi Khan [2], Mr. Abhiney Jain [1], Dr. Naomi Fersht [1], Dr. Michael Kosmin [1], Prof. David Choi [1]

1. *The National Hospital for Neurology and Neurosurgery,* ***2.*** *University College London*

Aims

COVID-19 has had a widespread effect on global health provision. The collateral effect on patient care has extended to all spheres of clinical care including neuro-oncology. High-grade glioma (HGG) is a rapidly progressive disease that requires prompt diagnosis, treatment and follow-up. We aim to review the practice in managing HGG patients in a specialist hospital in London during the first wave of COVID-19 pandemic, report our experience, and highlight the learning points that can be applied to future COVID-19 surges or other novel pandemics.

Method

A retrospective, observational cohort study was performed at a single tertiary dedicated neuroscience hospital in London (the National Hospital for Neurology and Neurosurgery). HGG cases were reviewed from electronic patient records, online referral system, as well as minutes from multidisciplinary team (MDT) meeting. Data about patient care for all referred HGG patients over a 2-month period between 16th March and 16th May 2020 (period of the first surge of COVID-19 and initial "lockdown" in the UK) were collected, focusing on MDT decision, interval from decision to treatment, and the numbers/reasons of delay as well as treatment and COVID related complications.

Results

35 HGG patients (mean age 61, range 22-81, male:female = 23:12) were referred to the neuro-oncology MDT or directly to the neurosurgical on-call service. 25 of them were recommended by MDT for operations (biopsy or debulking), in whom 20 underwent surgery as planned, 2 underwent altered operations, and 3 did not undergo surgery. The median interval between MDT decision and operation was 8 days (range 2-78 days), with the reasons of delay (over 2 weeks) being COVID positivity (n=1), initially suspicion of low-grade glioma (n=2), alternation in operation (n=2), or theatre capacity (n=1). 30 cases proved to be glioblastomas. 4 patients developed complications post-operatively, with 2 being surgical related and none COVID related.

Another 85 HGG patients under oncology service were due to receive chemotherapy (n=75) or radiotherapy (n=10). The majority of them received the recommended treatment without significant delay or complications. Adjustments on chemotherapy were necessary in 6 patients.

Conclusion

COVID-19 may impact the decision to operate but there were no substantial delays in care. It had little impact on final neuro-oncological decision making and surgical or chemotherapy/radiotherapy care delivery, with appropriate adjustments on chemotherapy as required. Surgical or COVID-19 related complications were uncommon. Our study showed that it was possible for patients with HGGs to continue to receive their usual standard of care without delay during the first wave of COVID-19 pandemic (with COVID-19 precautions as necessary), and this should be the goal in future COVID-19 surges.

The inflammatory environment in glioblastoma

Power Poster Presentation (2 minutes)

Ms. Jeannette Norman [1], Dr. Kastytis Sidlauskas [2], Mr. Sean Pellow [1], Mr. Reece Savage [1], Dr. David Chatelet [1], Dr. Mark Fabian [3], Dr. Jeng Ching [3], Mr. Paul Grundy [3], Prof. James Nicoll [1], Prof. Delphine Boche [1]

1. *university of southampton,* ***2.*** *Queen Mary University of London,* ***3.*** *University Hospital Southampton NHS Foundation Trust*

Aims

Glioblastoma (GBM) is the commonest primary brain tumour in adults. Approximately a third of the cells in GBM are microglia/macrophages rather than neoplastic cells, with evidence supporting a role for immune cells in GBM development. Here, we aim to characterise the complexity of the inflammatory environment.

Method

Tissue-microarrays were prepared from 59 GBM, IDH wildtype (WHO grade IV) biopsies from adult patients, representing the tumour core, infiltrating zone and relatively normal grey matter (leading edge of the tumour). Immunostaining for homeostatic microglia (Iba1, P2Y12), phagocytic microglia (CD68), microglial antigen-presentation (HLA-DR), Fcg receptors (CD64, CD16, CD32a), macrophages (CD163, CD206, TREM2), and T cells (CD3, CD4, CD8) has been performed. The analysis is currently ongoing and will include relevant clinical information.

Results

Iba1, HLA-DR, CD68, CD32a and CD16 showed a significantly higher expression in the core vs. leading edge ($p<0.001$) and in the infiltrating zone vs the leading edge ($p<0.003$). No difference was observed for CD64. Overall, HLA-DR expression was very low in all areas. CD163 expression was highest in the core, followed by the infiltrating zone ($p<0.002$). CD206 was significantly higher in the core vs leading edge ($p=0.008$). CD3 and CD4 show higher expression in the core and CD8 expression was not different between the areas. Within the different areas, correlations were observed between the microglial and T cell markers, with very few to no associations for CD64 and CD206.

Conclusion

Our initial findings confirm the presence of a substantial immune response to the neoplastic cells of a GBM both by resident microglia and potentially by macrophages with a haematogenous origin. CD206 identify a subpopulation of CD163+ macrophages within the tumour implying a different role of microglia and macrophages in the response to GBM. The low expression of HLA-DR and the absence of communication with CD64 might explain the impaired T-cell anti-tumour profile; whereas the association of T lymphocytes with CD68 but not CD206 suggests that the immune suppressive environment in GBM is triggered by microglia rather than recruited macrophages.

Poster

Assessment of molecular markers in Gliomas – adherence to NICE guidelines

Poster

Ms. Prisca Singh [1], ***Ms. Ananya Singh*** [1], ***Dr. Ute Pohl*** [2], ***Dr. Santhosh Nagaraju*** [3], ***Mr. Ismail Ughratdar*** [4], ***Mr. Yasir A Chowdhury*** [5]

1. *None,* ***2.*** *Queen Elizabeth Hospital, Birmingham,* ***3.*** *University Hospital Birmingham,* ***4.*** *Queen Elizabeth Hospital Birmingham,* ***5.*** *University Hospitals Birmingham NHS Foundation Trust*

Aims

The identification of molecular markers in gliomas can help prognosticate and predict treatment response (1, 2). The use of molecular markers varies considerably internationally (3) but in the UK we have standardised recommendations from NICE (1). This audit assessed the local adherence to NICE recommendations for molecular profiling of gliomas.

Method

A retrospective audit was carried out of all suspected glioma patients who had undergone biopsy or tumour resection. Patients were identified via the weekly Neuro-oncology MDT between August 2020 and February 2021. All patients whose histopathology assessments were complete were included in the study. Patients whose specimens were still under investigation were excluded. Subsequent histopathology and molecular reports were reviewed against the following NICE guidelines:

1. Glioma specimens were reported according to the 2016 World Health Organisation (WHO) classification of tumours of the central nervous system (4)
2. Molecular assessments included testing of:
    (a) IDH1 and IDH2 mutations
    (b) ATRX mutations to identify IDH mutant astrocytomas and glioblastomas
    (c) 1p/19q codeletion to identify oligodendrogliomas
    (d) Histone H3.3 K27M mutations in midline gliomas
    (e) BRAF fusion and gene mutation to identify pilocytic astrocytoma
3. Assess MGMT promoter methylation status in all high-grade gliomas
4. TERT promoter mutations were considered in IDH-wildtype gliomas

Results

100 patients with a suspected glioma were identified that underwent surgery providing a specimen in the study period and had completed pathology investigations. 63 glioblastomas were diagnosed, 20 astrocytomas, 6 oligodendrogliomas and 11 other tumours. A 100% of tumours were given a WHO classification diagnosis. IDH mutation status was also reported for every case. ATRX mutation was assessed in 100% of patients with astrocytomas and glioblastomas. All oligodendrogliomas (n=6) were identified with 1p/19q codeletion. 2 midline gliomas were diagnosed and both underwent assessment for histone H3.3 K27M mutation assessment. 2 pilocytic astrocytomas were identified and both were checked for BRAF fusion and mutation. MGMT status was checked in 100% of diagnosed high-grade gliomas. TERT promotor mutations were not check for any of the IDH-wild type gliomas.

Conclusion

All gliomas are reported in our unit are reported using the 2016 WHO classification of central nervous system tumours. NICE guidelines regarding assessment of specific molecular status and methylation status in gliomas are adhered to in 100% of cases.

Case Report: Brainstones – a rare interdisciplinary phenomenon

Poster

Mr. Patrick McAleavey [1]***, Mr. Tom Flannery*** [2]***, Dr. Brian Herron*** [3]***, Dr. Michael Hunter*** [4]

1. *School of Medicine, Queen's University Belfast, UK,* ***2.*** *Department of Neurosurgery, Royal Victoria Hospital, Belfast,* ***3.*** *Department of Neuropathology, Royal Victoria Hospital, Belfast, UK,* ***4.*** *Department of Infectious Diseases, Royal Victoria Hospital, Belfast*

Aims

Calcifying Pseudoneoplasm of the Neuraxis (CAPNON) are rare, non-malignant lesions of the central nervous system (CNS). Fewer than 100 cases have been reported in the literature since this entity was first described in 1978. Here we describe a case that involved extensive interdisciplinary investigations and discussions prior to her eventual neurosurgical management.

Method

A 39-year old right-handed teacher presented with episodes of facial paraesthesia and twitching radiating to her neck and right side of her body, over the previous year. There was associated intermittent drenching sweats, emotional lability, pain in her left buttock and leg, fatigue and generalised weakness. Her previous medical history was unremarkable other than anterior cervical discectomy for right-sided brachalgia one year prior. Peripheral power was 4/5 throughout and tone was normal.

Initial work-up by her local neurologist with brain CT /MR-imaging showed a 17mm calcified lesion in the left external capsule with a similar tiny right parietal entity. Her urine tested positive for Acid-Fast Bacilli suggesting possible tuberculosis (TB) granuloma. All other microbiological and immunological investigations were normal. Further investigations for TB by the regional Infectious Diseases (ID) team however proved negative. Her case was subsequently discussed with the supraregional ID centre who felt that intracranial TB was unlikely.

Results

The patient underwent surgical resection of the lesion to obtain histological diagnosis. Histology indicated CAPNON - a fibro-osseous, densely calcific lesion with portions of palisading spindle epithelioid cells, and chondromyxoid-like matrix. Post-operative MRI confirmed complete excision and apart from mild right facial / arm sensori-motor disturbance which subsequently recovered the patient made an excellent recovery. It was felt that the previous positive urine AFB was likely a false positive.

Conclusion

CAPNON presents as a heavily calcified lesion with favourable prognosis after resection. Long-term follow-up will be required to ensure no growth occurs in the tiny right parietal lesion.

Cerebellar liponeurocytoma – a rare case report

Poster

Mr. Omar Shawki [1], ***Mr. Salman Shaikh*** [2], ***Mr. Manoj Kumar*** [1], ***Mr. Ronan Dardis*** [1]

1. *University Hospital Coventry and Warwickshire,* ***2.*** *university hospital*

Aims

Cerebellar liponeurocytoma were first described in 1978 as a 'lipomatous medulloblastoma'. Since then, approximately 70 cases have been documented in literature. They were officially recognized as a distinct entity in 2000 as a WHO grade I neuronal tumour. Subsequenly, the 2007 classification of CNS tumours categorized them as grade II lesions. We describe the classical clinical and radiological presentation of this rare lesion.

Method

A 50 year hypertensive male with hypertriglyceridemia presented with 2 week history of gait imbalance alongwith intermittent headaches worse in the morning. Plain CT showed a posterior fossa lesion with marked hypodensity within. MRI was suggestive of a solitary lesion in the right cerebellum showing T1 and T2 hyperintensity, irregular diffusion restriction and heterogenous contrast enhancement. These features were suggestive of a fat containing neoplasm with differentials of dermoid, medulloblastoma or a liponeurocytoma. He underwent a suboccipital craniectomy and gross resection of the lesion. Intraoperatively, there was no definite plane around the mass which was soft and greyish in nature. Histopathological examination showed gross mucoid fragments with microscopy suggestive of a cellular neoplasm comprising of sheets of uniform round cells and prominent lipidised neuroepithelial tumour cells. Focal Homer Wright rosettes were seen. Immunohistochemistry was positive for synaptophysin, MAP2 and GFAP with ki-67 score of 1-2%.

Results

Imaging has showed no residue or recurrence at 2 years since surgery and the patient is fit and well on radiological surveillance. Cerebellar liponeurocytoma stand distinct from the commonly occurring medulloblastomas in showing no necrosis and low MIB index showcasing its benign nature. Although it has been mentioned that recurrence rate might be high in cases not undergoing radiation, there is no strong evidence to back this postulation yet.

Conclusion

Cerebellar liponeurocytoma is an infrequently occurring posterior fossa neuronal tumour. It is a WHO grade II lesion with a slow propensity for regrowth. Complete surgical excision must be the goal and evidence for adjuvant radiation is still lacking. Long term radiological surveillance is a must with recurrence reported as long as 18 years after primary surgery.

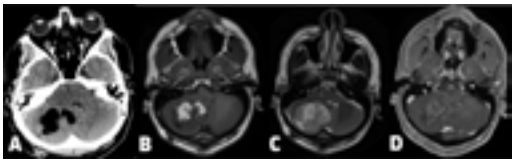
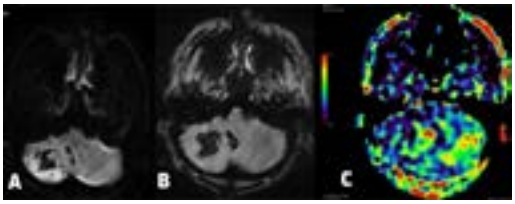


Figure 1.jpg



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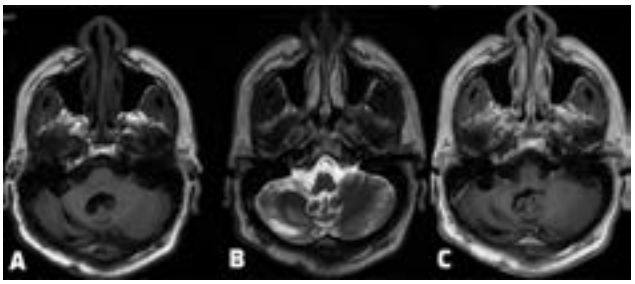


Figure 3.jpg

Circumventing Resistance to EGFR-Targeted Therapy in Glioblastoma

Poster

Ms. Demi Wiskerke [1], ***Prof. Richard Grose*** [1]

1. *Barts Cancer Institute*

Aims

With over 50% of glioblastoma (GBM) showing amplification of Epidermal Growth Factor Receptor (EGFR) at diagnosis, EGFR is an attractive target for therapy. However, EGFR-targeted therapies do not show efficacy against GBM in the clinic, reflecting a poor response *in vitro.*This project aims to understand resistance to EGFR targeted therapy in GBM. First, EGFR expression in treatment naïve and Temozolomide (TMZ) treated GBM cell lines was characterised. EGFR expression in response to TMZ was investigated to take into account any TMZ induced changes in GBM cells. By modulating EGFR expression using inducible overexpression constructs and shRNA constructs, the importance of EGFR in cell proliferation was elucidated. Cells with modulated EGFR expression were treated with TMZ and the tyrosine kinase inhibitor afatinib to explore the potential role EGFR plays in TMZ resistance and to understand the lack of response to inhibition of the tyrosine kinase function of EGFR.

Method

Cell lines used were U-87 MG, U-251 MG, U-118 MG and A172.

To determine EGFR expression in treatment naïve or TMZ treated GBM cells, two antibodies were used, one with an epitope in the cytoplasmic domain and one with an epitope in the extracellular domain. Several primer pairs binding in the extracellular and tyrosine kinase domain were designed to investigate EGFR mRNA expression. Cells were treated daily with GI10, GI50, and GI90 concentrations of TMZ for 7 days before RNA or protein extraction.

EGFR WT was cloned into a pINDUCER20 construct and transduced into U-87 MG and U-251 MG cells. Two inducible shRNA constructs against EGFR were established and transduced into U-87 MG and U-251 MG cells. Cells were treated with doxycycline to induce expression of either construct. For dose response curves, cells were treated daily with TMZ (10nM - 1mM) or every 2-3 days with afatinib (100pM - 10μM).

Results

EGFR was expressed at high levels in all cell lines investigated. TMZ treatment for 7 days resulted in downregulation of EGFR at GI50 and GI90 concentrations in 3 out of 4 cell lines. EGFR mRNA levels remained the same after TMZ treatment compared to DMSO treated cells.

Knockdown (KD) of EGFR resulted in decreased cell growth in at least 3 out of 4 cell lines whereas overexpression of EGFR did not lead to a growth advantage.

Interestingly, cells with EGFR KD showed increased sensitivity to TMZ.

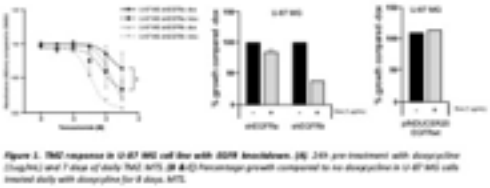
Cells treated with afatinib did not show altered response when EGFR was knocked down or overexpressed.

Conclusion

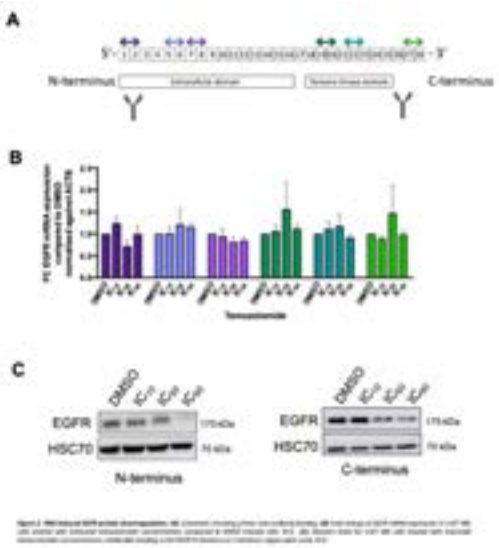
EGFR is being downregulated at protein level after TMZ treatment, most likely through a post-transcriptional mechanism, as EGFR mRNA levels remain unchanged. The downregulation of EGFR upon treatment, coupled with its re-expression in established resistant clones suggests a potential role for EGFR in TMZ resistance.

GBM cells rely on EGFR for proliferation and survival but do not respond to EGFR tyrosine kinase inhibition. This points towards involvement of an EGFR tyrosine kinase independent function in GBM which is crucial for cell survival but is unaffected by abrogation of tyrosine kinase function.

Future work will include elucidation of the mechanism of EGFR protein downregulation by looking at miRNA regulation of EGFR and exploring tyrosine kinase independent functions of EGFR in GBM.



Tmz response in u-87 mg cells with egfr kd.jpg



Tmz induced egfr downregulation.jpg

Coexistent two distinct pathologies masquerading as a single multicentric lesion

Poster

Mr. Salman Shaikh [1], ***Mr. Ronan Dardis*** [1], ***Mr. Aly Ahmed*** [1], ***Mr. Shabin Joshi*** [1], ***Dr. Santhosh Nagaraju*** [2]

1. *University Hospital Coventry and Warwickshire,* ***2.*** *University Hospital Birmingham*

Aims

The authors would like to present this case report of a patient with respiratory aspergillosis and an evolving multifocal Nocardia farcinica brain abscess which was in close conjunction with a coexistent temporal glioblastoma.

Method

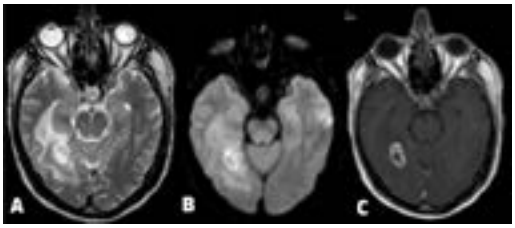
A 65 year-old male, left-handed, bricklayer by profession, was referred to us with multiple collapses and seizures. Imaging was suggestive of a right posterior temporal ring enhancing lesion. He was on antifungals for lung aspergillosis. MRI within 2 months revealed cerebellar, bifrontal and right temporal cystic lesions overlying the earlier ring enhancing mass. For diagnostic purpose, biopsy of the cerebellar lesion was performed which showed Nocardia farcinica abscess. He was started on appropriate antibiotics. Further surgery of the temporal cystic lesion was performed in view of deteriorating sensorium which showed abscess superficially and glioblastoma in the deeper component. He tolerated adjuvant radiation well while chemotherapy was withheld. Sadly, he passsed away within a year of his initial presentation.

Results

Review of literature tells us that concomitant abscess with neoplasms are a rare occurrence and are more frequently seen in the sellar tumours as they are in close proximity with the sinuses.

Conclusion

This report stands distinct in highlighting the need to thoroughly evaluate each foci of a multicentric cranial lesion on its own merit. A remote possibility does exist of intra-tumoural or peri-tumoural abscess occurrence which can be missed on radiology if appropriate sequences viz. diffusion and spectroscopy are not performed.



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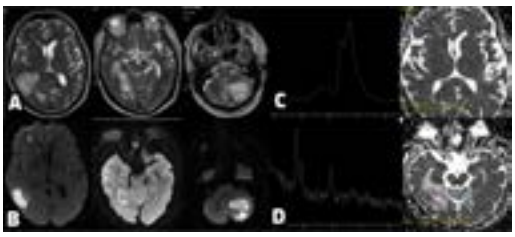

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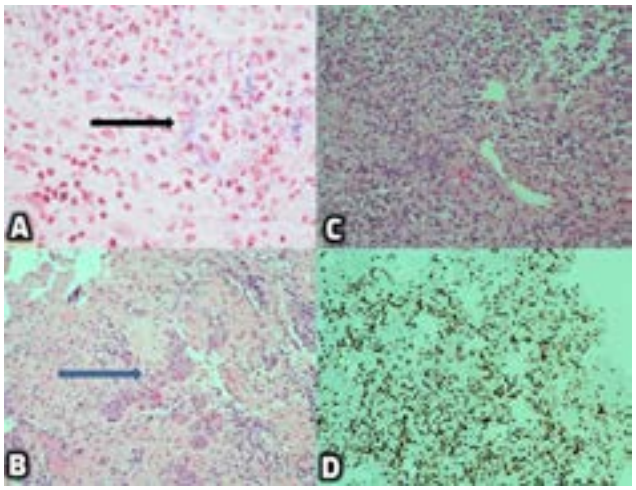

Figure 3.jpg

Double Trouble: A rare case of synchronous glioblastoma multiforme & anaplastic oligodendroglioma

Poster

Ms. Niloufar Farahani [1], ***Ms. Zeluleko Sibanda*** [1], ***Ms. Elizabeth Attia*** [1], ***Ms. erminia albanese*** [2], ***Dr. Shibu Joseph*** [3], ***Dr. Ute Pohl*** [4]

1. *Keele University Medical School,* ***2.*** *University Hospital North Midlands,* ***3.*** *University Hospitals of North Midlands,* ***4.*** *Queen Elizabeth Hospital Birmingham*

Aims

We report the first known case of synchronous glioblastoma multiforme (GBM) World Health Organisation (WHO) Grade IV and anaplastic oligodendroglioma WHO Grade III, arising without prior radiotherapy or underlying genetic predisposition syndromes (e.g., phakomatoses or mismatch repair deficiency syndromes). Our case is that of a 55-year-old woman who was referred to our service following a 3-week history of headaches, photophobia, confusion and dysphasia.

Method

Computed tomography (CT) and magnetic resonance imaging (MRI) were performed. Subsequent biopsy and immunohistochemical profiling were undertaken to further characterise the lesions.

Results

CT and MRI revealed two space-occupying lesions; a cystic left temporal lobe lesion and a heterogenous right frontal lobe lesion. Biopsy and immunohistochemical profiling confirmed that the two synchronous tumours arose from genetically distinct cell lineages: GBM (IDH-1 wildtype, loss of heterozygosity (LOH) at 19q locus only) and anaplastic oligodendroglioma (IDH-1 mutant, LOH at 1p/19q). Following resection of both tumours, the patient was commenced on a standard regimen of radiotherapy and temozolomide. Radiotherapy was delivered to both tumours with volumetric modulated arc therapy technique and simultaneous integrated boost with concurrent and adjuvant temozolomide chemotherapy.

Conclusion

This case highlights the importance of undertaking biopsies and extensive immunohistochemical profiling of distinct lesions to exclude the possibilities of metastases or multifocal tumours. This case raises challenges in regards to the treatment options due to the coexisting distinct tumours. Therefore, temozolomide was chosen instead of Procarbazine, CCNU (lomustine) and vincristine in adjuvant treatment targeting the aggressive histology and is more marrow friendly with less haematological side effects. Furthermore, much remains to be understood regarding the pathogenesis of synchronous but genetically distinct multifocal gliomas, and future genetic studies could further explore any shared molecular mechanisms.

Gliolan for Fluorescence-Guided Resection of High Grade Gliomas – Our Experience.

Poster

Ms. Zenab Sher [1], ***Dr. Suhaib Abualsaud*** [1], ***Mr. Yasir A Chowdhury*** [1], ***Dr. Yeajoon Cho*** [1], ***Mr. Athanasios Zisakis*** [1], ***Mr. Vladimir Petrik*** [1], ***Mr. Ismail Ughratdar*** [2], ***Mrs. Anwen White*** [1], ***Prof. Colin Watts*** [3], ***Dr. Victoria Wykes*** [3]

1. *University Hospitals Birmingham NHS Foundation Trust,* ***2.*** *Queen Elizabeth Hospital Birmingham,* ***3.*** *Institute of Cancer and Genomic Sciences, University of Birmingham*

Aims

Gliolan (5-aminolevulinic acid, 5-ALA) is a naturally occurring metabolite of the haem pathway which is taken up by malignant glioma cells, and then broken down into protoporphyrin IX, which fluoresces violet/red under the microscope. NICE guidelines recommend fluorescence-guided surgery to achieve maximal resection of high grade gliomas. However, maximal resection is determined by a number of factors, such as avoidance of eloquent brain. There is no clear consensus that stronger fluorescence equals a higher dose of gliolan bioavailability, but it has been proposed that stronger fluorescence indicates solidly proliferating tumour with higher cell densities. Our aim was to analyse the use of gliolan in our unit, with a focus on dosing, administration and degree of fluorescence noted intraoperatively. We also looked at whether sensitivity to sunlight causing a skin rash occurred.

Method

Prospective observational study into use of gliolan in resection of high grade gliomas. Data was collected on dose and timing of gliolan administration in our unit, timing of surgery, as well as the degree of fluorescence seen under blue light microscope intraoperatively. This was described on a scale of 1 – 5 with 1 for no fluorescence, 2 for 'patchy' fluorescence, 3 <50% , 4 for > 50% fluorescence, and 5 for florid fluorescence. We also noted whether operators recorded any skin-protection measures taken in the operation notes, and if any skin reaction occurred.

Results

1. n=20 patients operated on between 31st July 2020- 14th December 2020. 8 male, 12 females, mean age 60.5. 16 GBMs, 2 Gliosarcoma, 1 Anaplastic Oligodendroglioma, 1 diffuse glioma grade II.
2. In 17 operations, operators classified degree of fluorescence as '4. greater than 50%'. 3 were documented as '2. patchy' fluorescence. None were described as '5. Florid fluorescence' or '3. Less than 50% florescence'.
3. There was no correlation with degree of fluorescence reported by operators if gliolan was given earlier/closer to time of surgery. This ranged from 1 hour 43 minutes to 8 hours 24 minutes.
4. No patient experienced a skin reaction. In 8 cases, skin precautions were documented in operation note.
5. Dose of gliolan in mg/kg ranged from 12.1 mg/kg to 28mg/ kg. 16 were given '1 vial' of gliolan containing 1.5g. 3 patients had 1g and 1 patient had 1.1g of the gliolan

Conclusion

1) Fluorescence was less commonly reported as 'florid'; rather it was perceived as lighting up 'greater than 50%' in n=17 cases. This can be explained by the metabolic properties of malignant cells and their uptake of gliolan, confirming that gliolan does indeed make tumour tissue fluoresce.

2) Whilst skin protection measures may routinely be carried out peri-operatively, and mentioned in peri-operative checklists, these should be recorded in operation notes for patients undergoing gliolan-guided tumour resection.

3) There is a large variance in dose availability with most patients given ‘1 vial’ of 1.5g gliolan to ingest. Dose should actually be based on actual body weight with a maximum of 1.5g administered. Nevertheless, dose in mg/kg does not appear to correlate with degree of perceived fluorescence, nor did timing of gliolan administration (which is also largely variable, this may be attributed to operating on emergency and limited lists during the Covid-19 pandemic.

How far has glioblastoma prognosis come since 2005?

Poster

Ms. Jessica La [1], ***Ms. Victoria Hurwitz*** [1], ***Ms. Laura Mullens*** [1], ***Ms. Eleanor Kostick*** [1], ***Mr. Aeron Suarez*** [1], ***Mr. Ranjeev Bhangoo*** [2], ***Prof. Keyoumars Ashkan*** [2], ***Mr. Richard Gullan*** [2], ***Mr. Francesco Vergani*** [2], ***Mr. Jose-Pedro Lavrador*** [2], ***Dr. Katia Cikurel*** [3], ***Dr. Omar Al-Salihi*** [4], ***Dr. Angela Swampillai*** [4], ***Dr. Kazumi Chia*** [4], ***Dr. Lucy Brazil*** [4]

1. *King's College London,* ***2.*** *Department of Neurosurgery, King's College Hospital NHS Foundation Trust, London,* ***3.*** *Department of Neurology, King's College Hospital NHS Foundation Trust, London,* ***4.*** *Department of Clinical Oncology, Guys & St Thomas' Hospital, London*

Aims

The most common aggressive brain tumour diagnosis is glioblastoma multiform (GBM). Though we have a better understanding through the years of the underlying pathophysiology, this sadly remains incurable.
The purpose of this study is to ascertain whether the current prognosis for patients diagnosed with a GBM has extended since the average prognostic figures were published in 2005 following Stupp trial.
This found the median survival from the Stupp trial in the intervention arm was 14.6 months.
We are currently aware the information available to patients report the average statistic for prognosis of a GBM is 18- 24 months with aggressive treatment.
16 years on we look to find out if there has been significant progress in the prognosis of a patient with a gbm.

Method

Patients were identified from the bi-monthly Neuro oncology clinic along with the Neuro oncology database. Inclusion criteria included surgical intervention beyond a biopsy; adjuvant treatment with STUPP protocol and survival beyond 4 years. All patients molecular markers were included for analysis alongside all subsequent lines of treatment.

Results

At present, of the 30 patients currently included in this study, 27.6% of the patients life expectancy were between 8-13 years, of which 63% are still alive and under follow up. The remaining 72.4% of patients are within the 4-6 year survival with 62% currently alive and under follow up.
Unsurprisingly 83% of these patients were methylated, which corresponds to the positive prognostic factors.
38% of the patients were participated in a clinical trial, with one of the patients on their fourth line treatment under trial having had 3 craniotomies from 2013.

We noted, 34% of patients had second chemotherapy, with 24% going into third kind chemotherapy. 14% of the patients who are still currently under follow up are taking a form of alternative complimentary therapy sourced independently.

Conclusion

The data abstracted was from 2016, but sadly hundreds of patients listed did not have a date of death entered which made filtering correct patients difficult.
The small numbers included in this study offers a glimmer of hope for GBM patients, though we understand that the majority of the patients had prognostic factors in their favour which we know improve overall outcome. We note, the few unmethylated patients remain under follow up.

With highlighted GBM patients exceeding the average prognosis by more than double, at what value does quantity of life have over quality of life after possibly multiple craniotomies and oncology treatments? It would be prudent to measure the quality of life for these long-term patients.

We acknowledge we are identifying numerous long term GBM survivors, but the volume of patients included is too small to be reflected to adjust the currently published prognostic figure people are exposed to.

Hypofractionated Radiotherapy and Simultaneous Boost in radically inoperable cases with Glioblastoma

Poster

Dr. Fabiana Gregucci [1], ***Dr. Ilaria Bonaparte*** [1], ***Dr. Alessia Surgo*** [1], ***Dr. Roberta Carbonara*** [1], ***Dr. Maria Paola Ciliberti*** [1], ***Dr. Giulia Masiello*** [1], ***Dr. Raffaele Tucciariello*** [1], ***Dr. Morena Caliandro*** [1], ***Dr. Vincenzo Fanelli*** [2], ***Dr. Salvatore D'Oria*** [2], ***Dr. David Giraldi*** [2], ***Dr. Carlo Somma*** [2], ***Dr. Vincenzo D'Angelo*** [2], ***Dr. Alba Fiorentino*** [1]

1. *Department of Radiation Oncology, Miulli General Regional Hospital, Acquaviva delle Fonti-Bari, Italy,* ***2.*** *Department of Neurosurgery, Miulli General Regional Hospital, Acquaviva delle Fonti-Bari, Italy*

Aims

Aim of this study was to evaluate efficacy and toxicity of hypofractionated radiotherapy (hypoRT) with simultaneous integrated boost (SIB) associated with concomitant and adjuvant temozolamide (TMZ) in radically inoperable patients affected by Glioblastoma (GBM).

Method

Patients with a newly diagnosis of GBM not eligible for maximal safe surgical resection were evaluated in this retrospective study. If possible, a subtotal resection was performed or alternatively an open biopsy followed by hypoRT with SIB and concomitant plus adjuvant TMZ . The prescription dose for hypoRT was 40.05Gy in 15fractions on planning target volume (PTV) with a SIB of 52.5Gy on residual/macroscopic disease identified as gross tumor volume(GTV). The clinical target volume(CTV) was defined adding to GTV an isotropic margin of 1-1.5 cm, respecting the anatomical barriers and organs at risk(OaRs). Margin CTV-PTV was 3mm. In each case, the contouring of target and OaRs was performed using a rigid fusion between MRI and planningCT. FFF and VMAT technique with 2 or more coplanar or non-coplanar arcs were generated for each treatment plan. The primary endpoints were overall survival (OS) and progression free survival (PFS). Secondary endpoint was toxicity.

Results

From 09/2019 to 01/2021, 20patients (8female-12male) were treated, according to study criteria. The median age was 64years(range37-82) and median ECOG 2(range1-3). All patients have histological diagnosis of GBM IDH1wild-type and 30% showed MGMT methylation, 15%were not methylated and in 55%MGMT status was unknown. Subtotal resection was performed in 14patients(70%) while biopsy in 6(30%). The median time occurred between surgical procedure and RT was 56 days (range 15-103). The median GTV_52.5Gy was 45cc (range 13-208). The median PTV_40.05Gy was 208cc (range 84-330). At median follow-up time of 10 months (range 2-18), the median OS was not achieved (95%CI 6.06-na) and 1-year OS was 75.8% (95%CI 47.2-90.3); the median PFS was 9.8 months (95%CI 5.63-na) and 1-year PFS was 24.1% (95%CI 1.62-61.2). Regarding toxicity no acute or late neurological side effect grade ≥ 2 were reported. In all cases, prophylactic steroid therapy was administrated. Grade 3-4 hematologic toxicity occurred in 3 cases.

Conclusion

FFF-VMAT Hypofractionated Radiotherapy with SIB associated with concomitant/adjuvant TMZ in not eligible for maximal safe surgical resection patients affected by GBM is an effective and safe treatment compared with the current literature. To confirm these results, prospective study could be warranted.

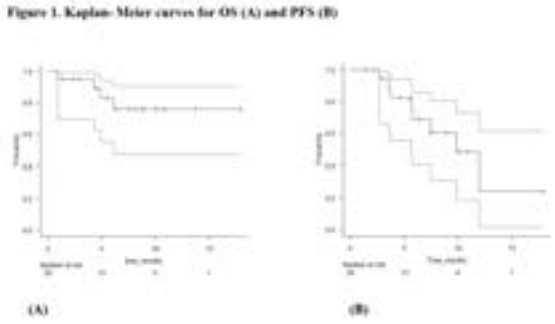

Figure 1.jpg

In or out? A review of GBM recurrence post radiotherapy in NHS Tayside.

Poster

Dr. Hannah Lord [1]

1. *NHS Tayside*

Aims

To review 24 months of data in NHS Tayside to assess if in patients treated with radiotherapy for Glioblastoma Multiforme, the tumour relapses within or without the radiotherapy the field.

Method

Patients identified on departmental database, and MRI scans pre-radiotherapy and post radiotherapy reviewed. When recurrence of tumour described on MRI report, radiotherapy plan assessed, and location of enhancing tumour recurrence identified to be within field; in low dose area of field; or outside of field.

Results

- 34 patients with newly diagnosed Glioblastoma Multiforme identified in 2018 and 2019.
- 22 male, and 12 female.
- 31/34 had pathology; 30 IDH1 wild type, one IDH1 mutated.
- 3/34 patients had no pathology.
- 13/34 received chemotherapy alone or best supportive care and were not further reviewed
- 21/34 received radiotherapy. All 21 received concurrent temozolomide
- 18 received 60Gy in 30#, and 3 received 40Gy in 15#.
- 18/21 of the radiotherapy treated patients have relapsed; three have not.
- All 18 relapses are in field
- 14 in high dose region; four in the low dose area, near the brain stem and optic chiasm.
- Three relapsed outside the field, and all 3 of these had relapse in the low dose area in field as well
- 12 patients remain alive. 10 of which have relapsed in field, and 2 of these also out of field. Two have no recurrence.

Conclusion

In NHS Tayside there is a male preponderance of patients with GBM, the majority IDH 1 wt. Two thirds of our cohort were of sufficient performance status to receive radiation treatment. 100% of relapses occurred in the radiation field and a small proportion also relapsed beyond the radiation field. The low dose area of radiation near critical structures needs to be minimised, as these patients are at risk of relapsing both within and beyond the radiotherapy field. However, distant relapse does not, per se, seem to predict for poorer survival, as 2/4 remain alive. Further prospective collection of data will be useful.

Nanoparticles in the Treatment of Brain Tumours: Translation of Nanoparticles into Clinic.

Poster

Ms. Bodunde Ajibade [1], ***Dr. Victoria Wykes*** [2], ***Dr. Chris McConville*** [1]

1. *School of Pharmacy, University of Birmingham,* ***2.*** *Institute of CAn*

Aims

Glioblastoma Multiforme (GBM) is a Grade 4 astrocytoma, and the most common type of brain tumor, diagnosed in adults. In the UK, GBM was stated to have a 5-year survival rate of just 12% in the year 2015-2017. GBM does not currently have an effective treatment. The Blood-Brain Barrier (BBB) acts as a biological barrier to the systemic delivery of chemotherapeutics, and overcoming this barrier is essential to GBM treatment. Nanoparticles have certain advantages as delivery systems for brain tumors. They use tuneable materials and can be easily adapted to suit the drug or target organ. This review shows the advancement of nanoparticles as delivery systems from lab to clinic and explains the gaps in translation.

Method

The Scopus database was used to find recent pre-clinical studies on nanoparticles used for systemic delivery of chemotherapeutics to the brain. All studies discussed were from high-credibility journals, using the Cite-Score as a credibility quantifier. The nanoparticles were tested against both in-vitro and in-vivo BBB models. The clinicaltrials.gov website was used to obtain clinical trial data on nanoparticles.

Results

The main nanoparticles found pre-clinically were lipid-based, polymeric, inorganic, protein-based, and hybrid nanoparticles. Liposomes, Gold, and polymeric nanocarriers were the only nanoparticles that made it to clinical trials from pre-clinical studies. Currently, no nanoparticle has been commercialized or approved for brain tumors.

Conclusion

The quantitative gap observed between pre-clinical and clinical studies is due to the technical issues of translation. Nanoparticles can be functionally categorized into; conventional, PEGylated, Ligand-targeted, and theragnostic. All approved nanoparticles are either conventional or PEGylated, however, the nanoparticles discussed in brain delivery are ligand-targeted and theragnostic. Conventional and PEGylated nanoparticles are easier to manufacture and tend to be less complicated than the other 2 categories, however, cannot effectively overcome the BBB.

The newer the generation of nanoparticles, the more complicated and difficult to manufacture. More research into technical issues with GMP manufacturing is required for advancement in nanotechnology.

Ajibade bodunde.jpg

Novel Local Delivery techniques to bypass the Blood Brain Barrier in the treatment of Glioblastoma

Poster

Mr. Rhys Llewellyn [1], ***Dr. Chris McConville*** [1], ***Dr. Victoria Wykes*** [2]

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Aims

Our aims are to:

Review various local delivery techniques and identify which show promise as viable treatment options for CNS tumours including glioblastoma. We consider what the current challenges are and how these may be overcome, paying particular attention to permeating the Blood Brain Barrier (BBB).

Present the BBB, exploring its role in glioblastoma treatment, and how and why its structure is currently a barrier to effective therapy. Consider structural barriers as well as genetic factors which contribute to the impermeability.

Evaluate several local delivery techniques, discussing current evidence as well as challenges in research and practical application. We also consider the opportunities for development of technology to add to the armamentarium of treatments, and the role of multidisciplinary teams in bridging the gap between the laboratory and operating theatre.

Method

A literature review to evaluate existing and ongoing local delivery methods was performed, following desired criteria and supplementing with relevant contextual information. Evidence was largely collected through Google Scholar, with searches refined by key terms such as: the technology or technique in question, impact of the publication and a preference for more recent publications. Clinical trials data was also searched and considered, from the database clinicaltrials.gov.

Results

Hydrogels, Convection Enhanced Delivery (CED), and Implantable devices have received the closest attention despite the collective failure to consistently demonstrate clinical benefit. Other novel techniques considered include Focused Ultrasound, Optogenetics and Viral Vectors.

Of the three main techniques explored, hydrogels demonstrated promise as a mechanism whereby the BBB and brain tumour barrier could be modelled, providing an opportunity to better understand markers and targets for molecular therapy. Both CED and Implants face challenges in application, from leaking and catheter placement in CED to poor bioadhesion of implants. Developments in implantable devices such as improved bioadhesion have begun to be investigated. Optogenetics and Viral Vectors are two novel techniques which offer the possibility of combining local as well as systemic techniques.

There is currently very limited evidence to support the use of local delivery techniques however future developments may optimise these systems.

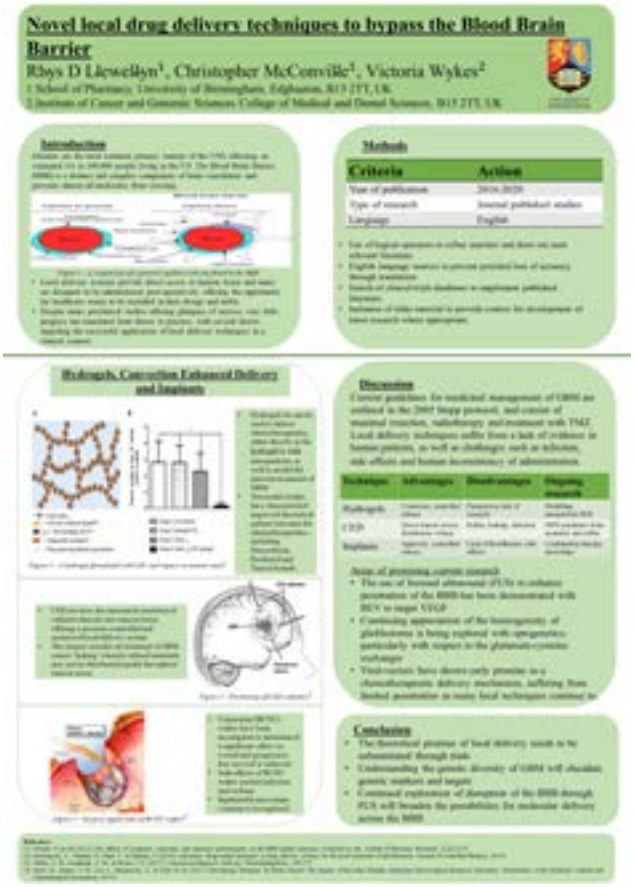
Conclusion

Stereotactic insertion of local delivery systems can be utilised to bypass the BBB for long-term drug delivery to a specific tumour area. Future research should address the following:

- Utilise hydrogel technology to develop increasingly accurate models of the BBB, taking into consideration

the microenvironment specificities of GBM.

- Encourage greater collaboration between research of nanoparticles and delivery systems, drawing on the learning and experience of the two technologies to continue to seek novel and impactful developments in viral delivery and FUS.
- Evaluate existing drug molecules that are unlicensed for use in brain cancers and investigate if they may confer pharmacological benefit in GBM, delivered using modulatory techniques direct to brain and tumour tissue.
- Collaborate with basic scientists and neurosurgeons to determine the challenges and successes of local delivery systems, as well as patients to optimise techniques.



Llewellyn rhys copy 3.jpg

PYCRL is a targetable vulnerability in hypoxic glioblastoma

Poster

Ms. Lisa Vettore [1], ***Ms. Cristina Escribano-Gonzalez*** [1], ***Dr. Jennie Roberts*** [1], ***Ms. Federica Cuozzo*** [1], ***Prof. David J Hodson*** [1], ***Dr. Colin Nixon*** [2], ***Dr. Richard Jones*** [3], ***Prof. Colin Watts*** [4], ***Dr. Dan Tennant*** [1]

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Aims

- To investigate the role of PYCRL in hypoxic glioblastoma

Method

A previous study has highlighted PYCRL as an enzyme that might contribute to survival in hypoxia. To better understand this, we used ^{13}C-tracing to monitor PYCRL activity in normoxia and hypoxia and the consequences for glioblastoma survival when we inhibit this enzyme. In addition, we used mass spectrometry-based proteomics to unravel unknown interactions between PYCRL and other enzymes essential to cancer survival. Finally, we validated our findings with a 3D spheroid model to better simulate what happens *in vivo*.

Results

1) PYCRL expression increases in hypoxic glioblastoma via TGF-b signalling
2) Inhibition of PYCRL may cause cell death via AIFM1 in hypoxia
3) PYCRL-mediated proline biosynthesis promotes glioblastoma proliferation by modulating redox balance

Conclusion

-PYCRL expression increases hypoxic glioblastoma
-PYCRL promotes survival in hypoxia via protein-protein interaction with Apoptosis-inducing factor 1
-PYCRL metabolic activity is required for maintaining redox control during glioblastoma proliferation

Radiosurgery for benignant Central Nervous System Disease: data collection of preliminary experience

Poster

Dr. Fabiana Gregucci [1], ***Dr. Ilaria Bonaparte*** [2], ***Dr. Alessia Surgo*** [2], ***Dr. Roberta Carbonara*** [2], ***Dr. Maria Paola Ciliberti*** [2], ***Dr. Giulia Masiello*** [2], ***Dr. Raffaele Tucciariello*** [2], ***Dr. Morena Caliandro*** [2], ***Dr. Vincenzo Fanelli*** [3], ***Dr. Salvatore D'Oria*** [3], ***Dr. David Giraldi*** [3], ***Dr. Carlo Somma*** [3], ***Dr. Vincenzo D'Angelo*** [3], ***Dr. Alba Fiorentino*** [2]

1. *General Regional Hospital "F. Miulli", Acquaviva delle Fonti-Bari, Italy,* ***2.*** *Department of Radiation Oncology, Miulli General Regional Hospital, Acquaviva delle Fonti-Bari, Italy,* ***3.*** *Department of Neurosurgery, Miulli General Regional Hospital, Acquaviva delle Fonti-Bari, Italy*

Aims

To evaluate acute/late side effects and early response of Linac-based Radiosurgery (SRS) for benignant Central Nervous System (CNS) Disease.

Method

Patients with benignant CNS disease suitable of SRS according to international guidelines were evaluated. In all cases, open-face masks dedicated for SRS were used for simulation and treatment. To correctly identify target, a fusion study of 1 mm-thickness CT simulation and diagnostic MRI was realized. PTV was defined by 1mm isotropic margin. FFF VMAT plans with 4 non-coplanar arcs were generated for each lesion. Prescription dose (Dp) was chosen based on pathology. Dp, normalization, optimization and Organs at Risk constrains were according to ICRU91 and in all cases they were respected. During treatment, 3CBCT were performed (2before-1after SRS): first to revise setup treatment, second to confirm shifts and third to verify position at the end of SRS. For each treatment session, SGRT was applied to evaluate intrafraction variations, acquiring data in 3 different time points: before, end and during SRS, respectively.

Results

Between 10/2019-04/2020, 10 patients(6 female/4 male) underwent to SRS. Median age was 64 years(range 32-87). Seven were brain meningiomas(5 inoperable for location, including 2cases of clivus disease, and 2underwent surgery with histology of grade III), 2were cavernomas in brainstem and 1was inoperable MAV located in frontal-parietal area. For meningioma, Dp was 25 Gy in 5 fractions with isodose optimization of 80%; for cavernomas, Dp was 12 Gy in 1 fraction with isodose optimization of 75%; for MAV, Dp was 20 Gy in 1 fraction with isodose optimization of 75%. Median PTV was 8.25cc (range 2-68). Mean overall treatment time was 2 minutes. At the end of treatment, no acute side effects were reported. At a median follow up (fu) of 10 months(range 7-14) any late toxicities were described. During fu, MRI showed for meningiomas stable disease, for vascular disease partial thrombosis of lesions in absent of signs of recent bleeding.

Conclusion

The present findings in this preliminary experience highlight the feasibility, safety, and effectiveness of Linac-based SRS for benignant CNS disease, in line with the literature results mainly based on Gamma Knife experience. Future more large evaluation with long follow up are warranted.

Staged Stereotactic Radiotherapy – Case Report and Literature Review

Poster

Dr. James Wang [1], ***Dr. Jiarong Chen*** [2], ***Dr. Matthew Williams*** [1]

1. *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust,* ***2.*** *Computational Oncology Laboratory, Institute of Global Health Innovation, Imperial College London*

Aims

Perform a limited systematic review of the literature on staged Stereotactic Radiotherapy.

Present our experience on staged Stereotactic Radiotherapy delivered using Linear Accelerator.

Method

Literature review:

Medline was searched using the criteria “brain metastasis” AND “radiosurgery” OR “gamma knife” and “staged”. Titles will be screened for full text extraction by JW and JC. Inclusion Criteria: Solid malignancy, Staged (1+wk separation with replanning), tumour size ≥2cm, SRS, Age 18+. Exclusion Criteria: Case reports, extracranial SRS. Full text articles will be reviewed with regard to the following outcomes: dose delivered, tumour size reduction, overall survival, local control and complication rate.

Case report:

We report the clinical details and radiotherapy technique for staged stereotactic radiotherapy (SRS) in a 3cm solitary met with extracranially controlled breast cancer on a Linear Accelerator, including clinical and radiological follow up through fractions and at 6 week post treatment.

Results

2453 titles were screened, yielding 14 full text articles. 8 were excluded and 2 added from references. 8 studies in total were included all using GK platform to deliver 10-14Gy over 2-3 fraction staged SRS. Median tumour shrinkage was 14.8-32.6% and median OS was 6.6-11.8m. 1 yr local control was 80.8-90.8% with 3.17-10.2% complication rates.

We delivered 10Gy in 3 fractions with a 4 week gap to 50% isodose line at PTV margin, where PTV = GTV + 1mm. Clinically patient tolerated the treatment course well although experienced three partial seizures in the 8 weeks that followed. Tumour volume initially increased by 11.2% but subsequently reduced by 35%. G1 neuropathic pain in the R lower limb necessitating analgesia was the only acute treatment-related toxicity.

Conclusion

Staged SRS has previously only been delivered on GK platforms to large mets with good local control and minimal toxicity.

Staged SRS can be safely delivered on Linac based platforms with tumour volume reduction seen after two fractions of treatment.

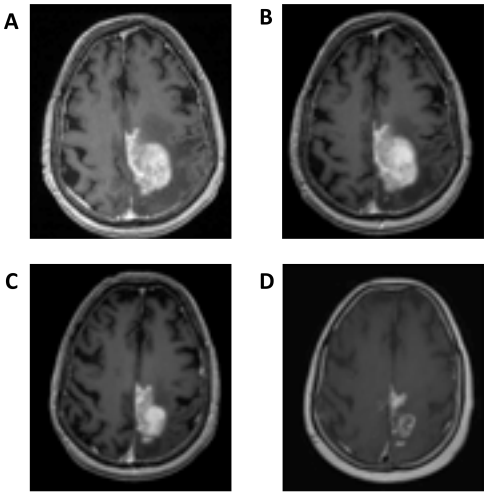


Image 1. Treatment evolution of target met. **A**: #1 Planning scan. **B**: increased size on #3 planning scan. **C**: partial response on #3 planning scan. **D**: 6 wk post-treatment scan.

Staged srs mri.png

Author, Year	Pts (Mets)	Largest GTV, Median cm^3	Interval days(#)	Dose (Gy)	Δ Size (%)	Median OS (m)	1 yr Control	Comp. Rate (%)
Ito 2020	178 (162)	12.9-24.4	15-22 (2)	10-14	26.6	6.6	80.8%	4.2 (9%)
Higuchi 2018	82 (N/A)	21	14, (3)	10	N/A	8.1	90%	4.9
Yamamoto 2018	78 (N/A)	21.5	14 (3)	10	20	8.3	90.8%	5.1
Dohm 2018	33 (39)	11.7	28 (2)	15 + 14	32.6		86.7%	6 (9% 10.2%)
Angelov 2017	54 (63)	10.5	28 (1-3)	11-12	17	10.8	88% (6m)	3.17 (6%)
Hasegawa 2017	56 (65)	21	14/7-28 (3/2)	10-13	28.6	7	80%	5.4
Yomo 2014	58 (61)	16.4	14-21 (2)	10-15	45.7	11.8	85% (6m)	5
Higuchi 2009	43 (46)	17.6 (mean)	14 (3)	10	14.8	8.8	75.9%	4.7

Summary of staged srs studies.png

Supratentorial glioblastoma with extensive spinal leptomeningeal spread and drop metastasis

Poster

Mr. Manoj Kumar [1], ***Mr. Salman Shaikh*** [2], ***Mr. Omar Shawki*** [1], ***Mr. Ronan Dardis*** [1]

1. *University Hospital Coventry and Warwickshire,* ***2.*** *university hospital*

Aims

The authors would like to present this case report of an insular glioblastoma who was diagnosed as having extensive holospinal leptomeningeal seeding alongwith drop metastasis to the conus and cauda equina within a month of his cranial biopsy. Metastasis of an intracranial glioblastoma via cerebrospinal fluid to the spine is an infrequent occurrence

Method

A 52 year male was referred to us with generalized tonic clonic seizures and dizzy spells. MRI was suggestive of a transforming left insular lesion favouring high grade glioma. He underwent a burr-hole biopsy of the lesion which was suggestive of IDH widltype, ATRX retained glioblastoma with an unmethylated MGMT. He was started on radical chemo-radiotherapy (Temozolamide). On complaining of severe neck pain, a spine screening was performed within a month of his surgery. This was suggestive of leptomeningeal spread extending through the whole spine alongwith thick conus and cauda spinal deposits. The patient then asked to be discharged from adjuvant treatment and was put on palliative care. Unfortunately, he passed away within 4 months of his presentation.

Results

Supratentorial glioblastoma can rarely show spinal seeding as described in various individual case reports in literature. However, extensive spinal spread within few months of presentation is even rarer. A strong index of suspicion must be kept for whole spine screening at initial presentation itself if there are any spinal symptoms or if radiologically there is ependymal enhancement favouring CSF spread.

Conclusion

Leptomeningeal metastasis in glioblastoma always results in a fatal outcome. IT has been postulated that CSF spread may be the cause of this metastasis. There is significant need for improved reporting methods for spinal metastases, either through enrollment of these patients in clinical trials or through increased granularity of coding for metastatic central nervous system diseases in cancer databases. The authors suggest that earlier detection of spinal spread would help in better patient care and advocate for increased inclusion in research.

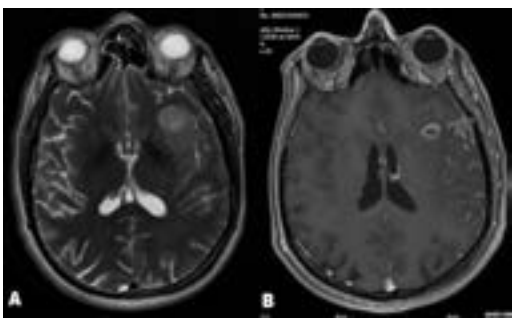


Figure 1.jpg

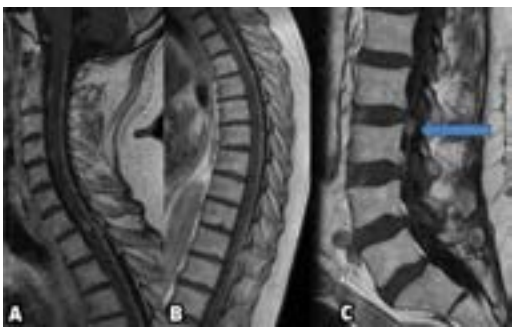


Figure 2.jpg

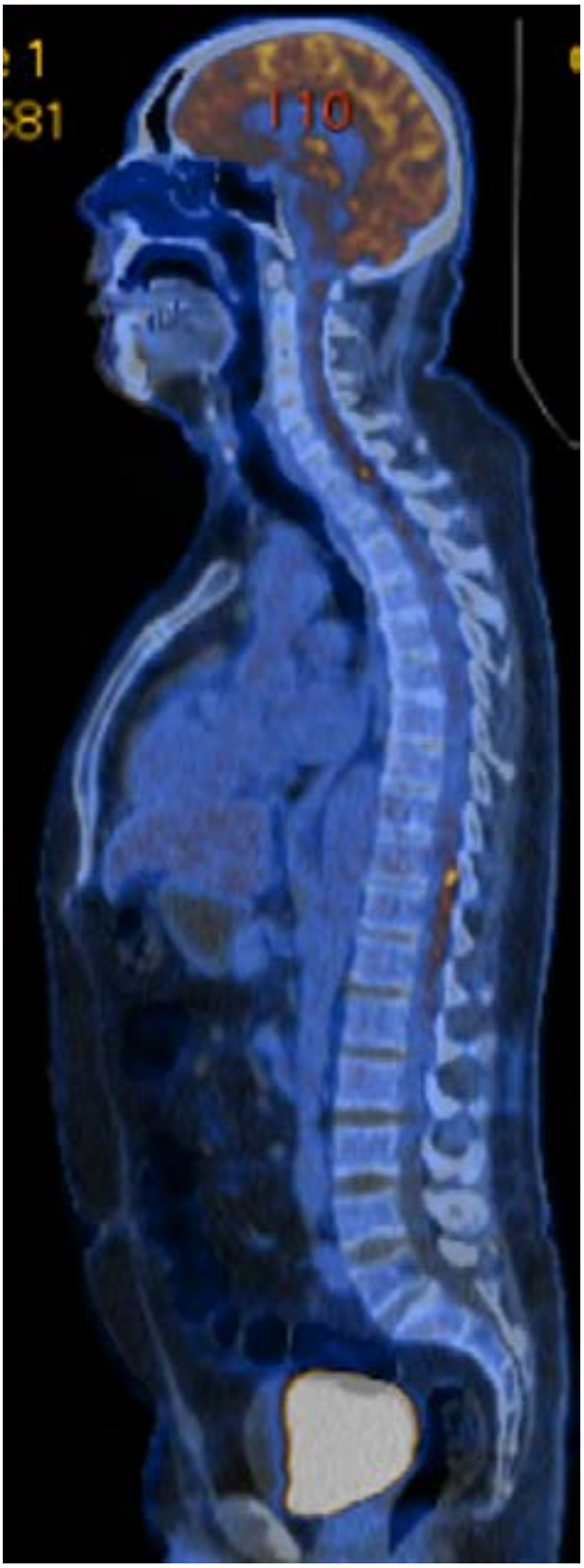


Figure 3.jpg

Tonsillar carcinoma spreading metastases to central nervous system – Case report and literature review

Poster

Dr. Shujhat Khan [1]

1. *Department of Radiotherapy, Charing Cross Hospital, Imperial College NHS Trust*

Aims

We present a case report of a 51-year-old left-handed gentleman with a background of HPV 16-positive tonsil squamous cell carcinoma presenting with tonic-clonic seizure and a radiological diagnosis of secondary metastatic deposits.

Method

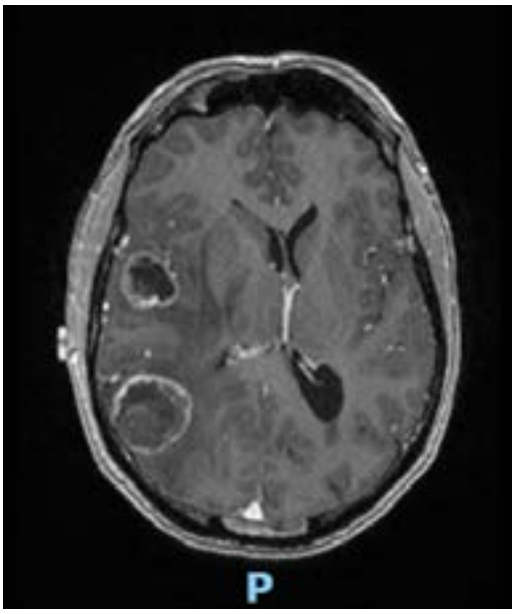
Metastasis was initially treated with Stereotactic RadioSurgery (SRS), and subsequently with surgery. Surgical resection was performed under general anaesthesia with right-sided temporal and parietal approaches. Both the parietal and temporal deposits were removed, while the intraventricular mass was intentionally left to avoid post-op deficits. Adjuvant radiotherapy and chemotherapy were administered post-op. The patient experienced a satisfactory recovery post-op and was re-operated for recurrence 4 months later. We additionally performed a literature review on PubMed using key words, “metastasis”, “squamous cell carcinoma”, “brain tumour”, and “HPV” to look for similar cases in the literature.

Results

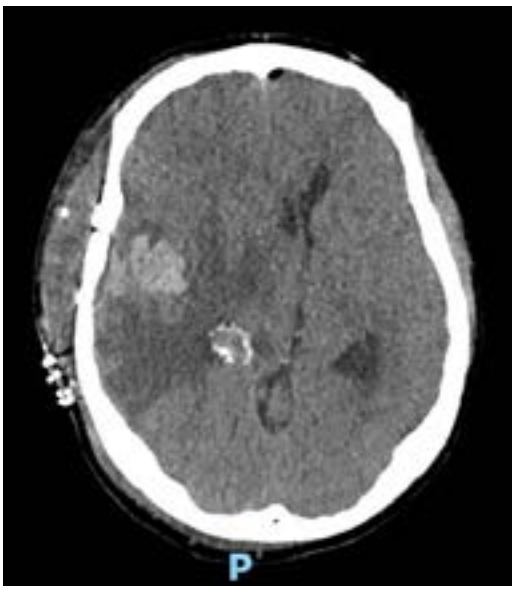
The CNS is a very rare site for DM of tonsillar carcinoma, with only a few cases reported in literature. Current guidelines recommend using surgical excision along with chemotherapy such as florouracil with or without cetuximab for metastatic oropharyngeal carcinoma. Early stage oropharyngeal carcinomas treated with surgery or radiation alone are equally successful. In more late stage disease, a combination of surgery and postoperative radiotherapy provides a superior outcome compared to chemoradiation therapy.

Conclusion

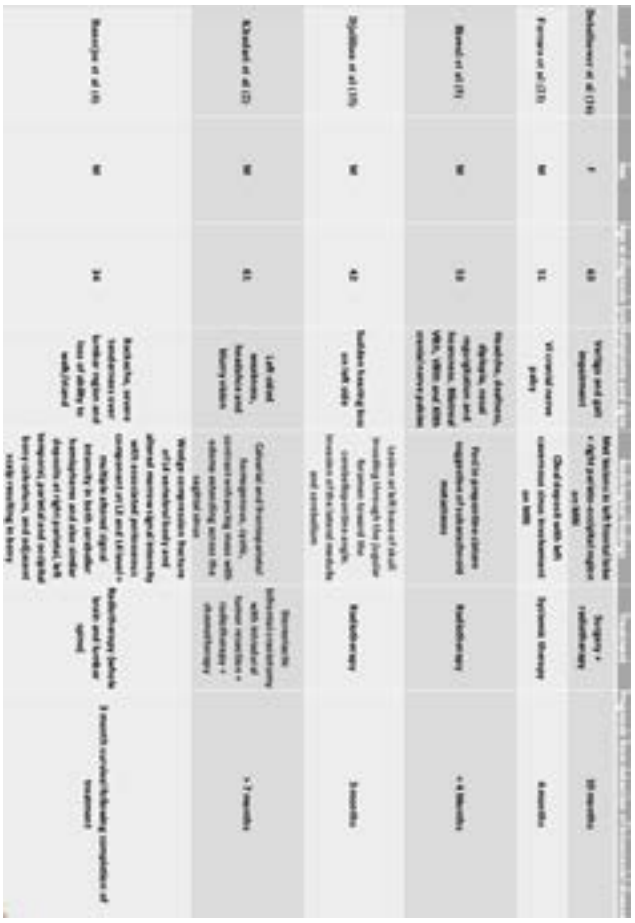
With limited data and treatment outcomes, there is no treatment guideline for patients with this rare presentation. More data is thus desirable in order to better define treatment guidelines and protocols when SCC brain metastases are present.



Picture 1.png



Picture 2.png



Picture 3.png

Authors Index

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